

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125387Orig1s000

OTHER REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW-Amendment

Application Number: STN 125387/0
Name of Drug: EYLEA™ (aflibercept)
Sponsor: Regeneron Pharmaceuticals, Inc.
Material Reviewed: EYLEA™ (aflibercept)
Carton and Container Labels
Submission Dates: February 17, 2011, August 31, 2011, November 2, 2011,
and November 17, 2011

EXECUTIVE SUMMARY

The carton and container labels for EYLEA™ (aflibercept) were reviewed and found to comply with most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 8/1/11-11/30/11, USP 34/NF 29. Labeling deficiencies were identified and mitigated. A proper name decision was made communicated to the company on November 17, 2011 and subsequent labels were submitted, reviewed, and mitigated. Please see comments in the conclusions section. The carton and container labels submitted on November 17, 2011 are acceptable.

Background

STN 125387/0 for aflibercept is an original Biologic License Application (BLA) indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). The product was originally submitted as a solution in a 2 mg/ 0.05 mL concentration supplied in (b)(4) glass vial. The August 31, 2011 submission supports the vial configuration only. The November 17, 2011 submission also includes the vial and carton presentation only.

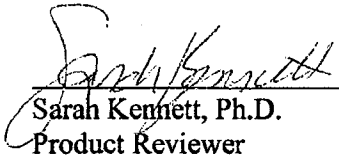
Labels Reviewed:
EYLEA™ (aflibercept) Container Labels
Vial and syringe label

7 Pages of Draft
Labeling have been
Withheld in Full as b4
(CCI/TS) immediately
following this page

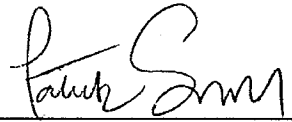
 11/18/11

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBP

Comment/Concurrence:

 11-18-11

Sarah Kennett, Ph.D.
Product Reviewer
Division of Monoclonal Antibodies
CDER/OPS/OBP

 11-18-11

Patrick Swann, Ph.D.
Deputy Director
Division of Monoclonal Antibodies
CDER/OPS/OBP



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
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Silver Spring, MD
Tel. 301-796-4242

Memorandum

Date: November 17, 2011

To: Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products

From: Kimberly Rains, Pharm.D. *Kimberly Rains 11/17/11*
Labeling Reviewer,
Office of Biotechnology Products

Through: Steven Kozlowski, M.D. *Steve Kozlowski 11/17/11*
Director
Office of Biotechnology Products

On November 9, 2011, a meeting was held to discuss Biologic License Application (BLA) 125387 for EYLEA™ (aflibercept) submitted by Regeneron Pharmaceuticals, Inc. (Regeneron, or the company). The question at issue was whether the proper name of the product

(b) (4)

(b) (4)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: BLA 125-387/ Eylea (aflibercept injection)

PMR/PMC Description: The applicant will be required to provide clinical information from a 1-year (minimum) clinical trial evaluating the adverse effects, if any, on the corneal endothelium following the intravitreal administration of aflibercept.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2012</u>
	Study/Trial Completion:	<u>11/30/2015</u>
	Final Report Submission:	<u>05/31/2016</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety concern
- Small subpopulation affected
- Theoretical concern
- Other

There is no clinical experience from the clinical trials performed to date that intravitreally administered aflibercept injections cause corneal endothelial cell decompensation, but this clinical experience regarding the endothelium is indirect from evaluation of the cornea as a whole and not from direct endothelial cell counts.

Direct evaluation of the corneal endothelium, while not required for NDA approval, is required for ocular safety reasons as a PMR for aflibercept injection.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Direct evaluation of the corneal endothelium is required to determine if intravitreally administered aflibercept injections cause corneal endothelial cell decompensation. There is a potential risk of corneal decompensation leading to a permanent decrease in vision if aflibercept injections cause damage to the corneal endothelium.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- Which regulation?

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Open-label, prospective, clinical trial of at least 1-year duration evaluating the corneal endothelium following the intravitreal administration of aflibercept. Will not be performed in a subpopulation.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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- Other
-

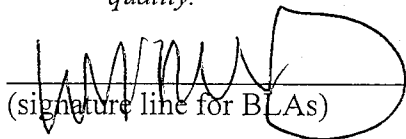
5. Is the PMR/PMC clear, feasible, and appropriate?

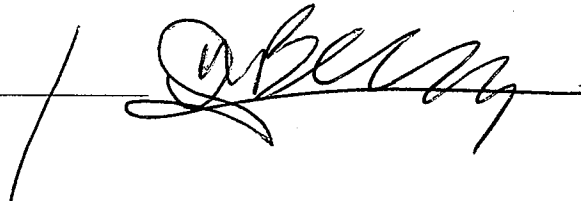
Does the study/clinical trial meet criteria for PMRs or PMCs?

- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*


(signature line for BLAs)



11.17.2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125387

PMR/PMC Description: To conduct three drug product hold time studies of the 40 mg/mL vial presentation filled at [REDACTED] ^{(b) (4)} site. Material will be held at commercial scale, and microbiological samples (total viable count, bacterial endotoxin) will be taken at the end of the hold times. The completed validation report will be submitted as a CBE-0 supplement.

Final Report Submission: CBE-0 in November 2012

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>11/30/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The study will be performed during routine manufacturing. Therefore, execution of the study protocol has to be coordinated with the manufacturing process. The study cannot be completed prior to BLA approval. The study is appropriate as a PMC because acceptable product quality has been demonstrated by other tests and studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to validate the maximum hold times for in-process material.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- Which regulation?

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To conduct three drug product hold time studies of the 40 mg/mL vial presentation filled at (b) (4) Material will be held at commercial scale, and microbiological samples (total viable count, bacterial endotoxin) will be taken at the end of the hold times.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

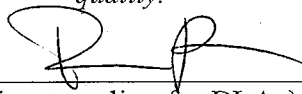
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*



(signature line for BLAs)

11/17/2011



11.17.11

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125387/Eylea

PMR/PMC Description: PMC #3 in AP letter
To conduct three drug product hold time studies for the 40 mg/mL vial presentation filled at the (b) (4) site. These studies will include t=0 and end of hold samples for product quality (pH, purity by size exclusion, purity by nrSDS-PAGE, charge variant distribution by IEF, isoaspartate, and potency of aflibercept) evaluation. The completed validation report will be provided as a CBE-0 supplement.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>06/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Limited hold time validation has already been performed for DP manufacture at (b) (4) these studies provide some assurance of the safety of the product when manufacturing includes a hold step.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Validation of hold times during manufacture of drug product was performed on only one lot each of the (b) (4) 40 mg/ml (commercial) presentations, and these studies were performed at the (b) (4)

(b) (4) In addition, product quality parameters were not directly addressed and can only be inferred from an evaluation of release data. This study will provide validation of the manufacturing hold times (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Quality manufacturing hold time validation study to include three lots of commercial drug product filled at the (b) (4) site. These studies will include t=0 and end of hold samples for product quality (pH, purity by size exclusion, purity by nrSDS-PAGE, charge variant distribution by IEF, isoaspartate, and potency of aflibercept) evaluation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
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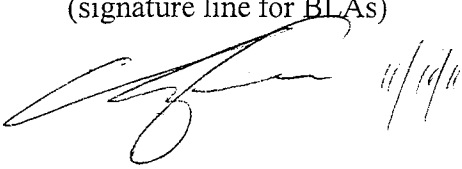
5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

A handwritten signature in black ink, appearing to be 'J. J. J.', written over a horizontal line.A handwritten signature in black ink, appearing to be 'B. M.', written over a horizontal line.

U. 17. 11

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125387/Eylea

PMR/PMC Description: PMC #4
To confirm (b) (4) by the aflibercept (b) (4) process. The (b) (4) study will be performed under protocol on three lots of drug substance produced at the commercial scale. (b) (4) will be measured with a validated analytical test method for determining (b) (4). The completed method validation and final reports will be submitted in the 2012 annual report by January 2013.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 01/2013
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical experience indicates there are no safety issues that would be related to (b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

(b) (4) Clinical studies to date have indicated that residual levels of (b) (4) are not a safety concern; however, this molecule has the potential to be a safety risk. Based on the clinical data and experience with similar manufacturing schemes, it is expected that there is sufficient (b) (4) This PMC would confirm that the process is capable of (b) (4) (b) (4) to acceptable levels.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Quality study assessing (b) (4) in three lots of drug substance produced at the commercial scale. (b) (4) will be measured with a validated analytical test method for determining (b) (4) concentration.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)



11/16/11



11.17.11

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125387/Eylea

PMR/PMC Description: **PMC #5**
To re-evaluate the release and shelf-life specifications for aflibercept drug product after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by December, 2014, whichever occurs first.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Drug Product release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of (b) (4) for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Eylea Drug Product release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Statistical analysis of release data acquired following manufacture of additional commercial lots

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

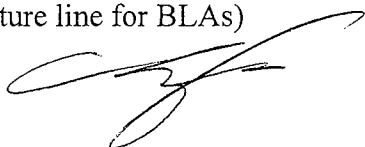
5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

 11/16/11

 11.17.11

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125387/Eylea

PMR/PMC Description: PMC #6
To re-evaluate the release and shelf-life specifications for aflibercept drug substance after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS by within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>06/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Drug Substance release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of (b) (4) for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Eylea Drug Substance release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Statistical analysis of release data acquired following manufacture of additional commercial lots

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition; different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

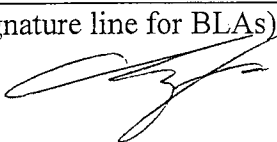
5. Is the PMR/PMC clear, feasible, and appropriate?

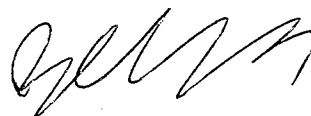
- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

 11/16/11



11.17.11

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125387/Eylea

PMR/PMC Description: PMC #7

To re-evaluate the release and shelf-life specifications for aflibercept drug substance intermediate after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2014, whichever occurs first.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>06/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Drug Substance Intermediate release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of (b) (4) for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Eylea Drug Substance Intermediate release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Statistical analysis of release data acquired following manufacture of additional commercial lots

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)



04/16/11



11.17.11

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 125387/Eylea

PMC #8

PMR/PMC Description: To re-evaluate the release and shelf-life specifications for aflibercept formulated bulk after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>06/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Formulated Bulk release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of (b) (4) for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Eylea Formulated Bulk release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Statistical analysis of release data acquired following manufacture of additional commercial lots

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?


PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)



11/16/11



11.17.11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Date: November 16, 2011

To: Edward Cox, M.D.
Director
Office of Antimicrobial Products

From: Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products

Subject: Established/Official/Proper Name of EYLEA

Regeneron Pharmaceuticals Inc. has submitted a **Biologic License Application (BLA)** 125387 for EYLEA™ in which the biologic aflibercept has been formulated into a preparation suitable for intraocular administration. The question addressed in this memo was whether the established/official/proper name of the product (b) (4)

(b) (4)



(b) (4)

W.A. Chambers MD 11/16/11

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology Products

MEMORANDUM

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

DATE: November 2, 2011

TO: Sonal D. Wadhwa, MD,
Medical Officer
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products

FROM: Kassa Ayalew, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Division Director (Acting)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Addendum to Evaluation of Clinical Inspections

NDA or BLA: BLA 125387

APPLICANT: Regeneron Pharmaceuticals, Inc.
Attn: Laura Pologe
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
Phone#: 914-345-7926
Email: laura.pologe@regeneron.com

DRUG: Proposed Eyelea™ (aflibercept ophthalmic solution)

NEW MOLECULAR ENTITY (NME): Yes

REVIEW PRIORITY (Standard or Priority): Priority

INDICATIONS:

BLA : 125387

PDUFA: November 18, 2011

I. BACKGROUND:

This CIS Addendum is submitted to update the CIS (finalized on July 18, 2011) for the BLA for aflibercept ophthalmic solution (Eyelea™).

BLA 125387 for aflibercept ophthalmic solution (Eyelea™) was submitted by Regeneron Pharmaceuticals, Inc. to support a labeling claim for the treatment of neovascular age-related macular degeneration (AMD). In support of the application, the sponsor submitted data from two well controlled clinical trials (1365 subjects enrolled) and two additional phase 2 studies in support of the application.

A consult from DAIOP (now DTOP) was received on March 15, 2011 for inspection of the clinical sites enrolling in the pivotal trials Protocol No. VGFT-OD-0605 (VIEW 1) and Protocol No. VGFT-OD-0702 in order to verify the quality of conduct of these studies for this BLA. The inspections were routine audits requested to assess data integrity and human subject protection for clinical trials submitted in support of a NME in this application. The PDUFA date for this NDA is November 18, 2011.

OSI requested foreign inspections of four sites (including the sponsor Regeneron Pharmaceuticals, Inc.). This CIS Addendum will provide information which has become available since finalization of the CIS on July 18, 2011 pertaining to the sponsor/monitor Regeneron Pharmaceuticals, Inc. Please see the original CIS for further background, including outlines of the protocols audited and a brief summary of study results. There is no change in the previous conclusion regarding data integrity for the three clinical investigator sites.

II. RESULTS (by Site):

Name of CI or Sponsor	Protocol # & # of Subjects:	Inspection Date	Preliminary Classification	Final Classification
Jeffrey S. Heier, M.D. Ophthalmic Consultants of Boston 50 Staniford Street, Suite 600 Boston, MA 02114	Study VGFT-OD-0605/ n=53	April 26 to May 9, 2011	VAI	VAI
Prema Abraham, M.D. Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701	Study VGFT-OD-702/ n=11	April 24 to 29, 2011	NAI	NAI
For Cause Inspection: Mark Michels, M.D. Retina Care Specialists LLP 3399 PGA Boulevard, Suite 220 Palm Beach Gardens, FL 33410	Study VGFT-OD-0605/ n=15	April 28 to May 12, 2011	OAI	VAI
Sponsor: Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707	Study VGFT-OD-0605 With focus on Dr. Jeffrey S. Heier, M.D. and *Dr. Mark Michels, M.D. Study VGFT-OD-702 With focus on Dr. Prema Abraham, M.D.	July 25 to 29, 2011	NAI	NAI

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 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

*Dr. Mark Michels, MD: the site was included because of the preliminary inspection findings from for-cause inspection as results of the complaint received by OSI, in regards to recruitment material for the subject study.

**PLEASE SEE FULL SUMMARY IN THE CIS FINALIZED JULY 18, 2011
UPDATED INFORMATION IS PROVIDED BELOW**

1. Dr. Jeffrey S. Heier, M.D.
Ophthalmic Consultants of Boston
50 Staniford Street, Suite 600
Boston, MA 02114

There is no change in the previous conclusion regarding data integrity. Please see full summary in the CIS finalized July 18, 2011.

2. **Dr. Prema Abraham, M.D.**
Black Hills Regional Eye Institute
2800 Third Street
Rapid City, South Dakota 57701

There is no change in the previous conclusion regarding data integrity. Please see full summary in the CIS finalized July 18, 2011.

3. **For Cause Inspection: Mark Michels, M.D.**
Retina Care Specialists LLP
3399 PGA Boulevard, Suite 220
Palm Beach Gardens, FL 33410
(561) 624-0099

There is no change in the previous conclusion regarding data integrity. Please see full summary in the CIS finalized July 18, 2011.

4. **Sponsor: Regeneron Pharmaceuticals, Inc.**
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

- a. **What was inspected?**

This inspection was conducted in accordance with Compliance Program 7348.811, between July 25, 2011 and July 29, 2011. This inspection covered Study #VGFT-OD-0605 (VIEW 1) and Study #VGFT-OD-0702.

- b. **General observations/commentary:**

The inspection audited Regeneron Pharmaceuticals, Inc., and focused on two studies; Protocol #VGFT-OD-0605 (VIEW 1) entitled "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Relapsed Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration", and Protocol #VGFT-OD-0702 entitled "A Randomized, Single-Masked, Long-Term, Safety, and Tolerability Study of Intravitreal VEGF Trap-Eye in Subjects with Neovascular Age-Related Macular Degeneration". During the inspection, the Sponsor's role in the evaluation of data from the following clinical investigator sites was focused on: Dr. Jeffrey S. Heier, (Site #146), Dr. Prema Abraham (Site #028), and Dr. Mark Michels (Site #114).

The inspection covered adherence to the protocol, review of the firm's organization and personnel, training and qualification records, transfer of responsibilities to a CRO,

financial disclosures, subject records/source documents, practices for training the clinical sites, media receipts, handling and transferring of data to the sponsor, and data assessment and validation for the primary endpoint. Regulatory violations were not identified, and a Form FDA 483 was not issued. However, the following observations were discussed:

1. Transfer of responsibilities to a CRO was not reported to the FDA for Protocol VGFT-OD-0702.

OSI Reviewer Comments: The sponsor acknowledged the above concern and provided a new approved SOP pending an effective date, titled "Conducting a Clinical Study with a Vendor/CRO", which detailed procedures on transfer of responsibilities to a CRO.

2. Two non-compliant clinical investigators under Protocol VGFT-OD-0605 were not reported to the FDA.

- (b) (4) Sponsor decided to close this site because they lacked adequate resources and study personnel did not have adequate training.
- Dr. Tongalp Tezel (Louisville, KY): This site was closed due to excessive protocol violations, improper enrollment of subjects, and inadequate training of study personnel. This site randomized 4 subjects. After site was closed, these subjects were transferred to a new site under Dr. Steven Bloom.

(b) (4) site never randomized subjects. The sponsor also made a new Regeneron SOP effective April 26, 2011, titled "Suspected Serious Non-compliance", that details better procedures on the handling of non-compliant CIs.

3. There was non-IRB approved recruitment material on Dr. Micheles' website which was not noted during monitoring. Regeneron later became aware of the presence of non-IRB approved recruitment material, and it was removed from the website.

4. Inappropriate administration of ICFs was not properly addressed during monitoring of investigator sites. The inappropriate administration of ICFs involved failure to update subject informed consent in a timely fashion when a new ICF version was approved.

OSI Reviewer Comments: The updated versions of the ICF did not contain significant changes that would impact on subject safety.

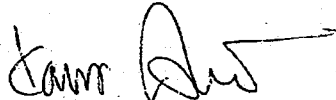
c. Assessment of data integrity:

Based on the review of the EIR, the observations at Sponsor's site are isolated findings and minor in nature, and they do not appear to significantly impact data integrity or subject protection. The above observations are not likely to significantly impact data reliability, and the data may be used in support of the application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites and the sponsor/monitor were inspected in support of this application. Please see full summary in the CIS finalized July 18, 2011. There is no change in the previous conclusion regarding data integrity for the three clinical investigator sites. The overall assessment of findings and recommendation in this addendum pertain to the sponsor/monitor Regeneron Pharmaceuticals, Inc.

The inspection of the sponsor, Regeneron Pharmaceuticals, Inc. revealed that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of this application. The final classification for the inspection of Regeneron Pharmaceuticals, Inc. is No Action Indicated (NAI).



/Kassas Ayalew, M.D./

Kassa Ayalew, M.D.

Medical Officer

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

CONCURRENCE:

/Susan Thompson, M.D./

Susan Thompson, M.D.

Acting Team Leader

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations



/Tejashri Purohit-Sheth, M.D./

Tejashri Purohit-Sheth, M.D.

Acting Division Director

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

**Determining When Pre-License / Pre-Approval Inspections are
Necessary**

Inspection Waiver Memorandum

Date: 11 October 2011
From: Colleen Thomas, Ph.D.
CDER/OC/OMPQ/DGMPA/BMAB
To: BLA File – STN 125387
Subject: Recommendation to waive a pre-approval inspection
Sponsor: Regeneron Pharmaceuticals, Inc. (U.S. license 1760)
Contract Facility: [REDACTED] (b) (4)
Product: Eylea® (aflibercept ophthalmic solution)
Indication: Neovascular (wet) age-related macular degeneration
Through: Patricia Hughes, Ph.D., Acting Branch Chief
CDER/OC/OMPQ/DGMPA/BMAB

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that [REDACTED] (b) (4) has been approved to manufacture multiple CDER and CBER products using a similar manufacturing process, we recommend that the pre-approval inspection of the [REDACTED] (b) (4) be waived for STN 125387 submitted 18-Feb-2011.

Clearance Routing

David Doleski CONCUR / DO NOT CONCUR DATE 10/20/2011
David Doleski / Acting for
Barry Rothman, Acting Director
Division of Good Manufacturing Practice Assessment, OC/CDER

Kathleen Clouse CONCUR / DO NOT CONCUR DATE 10/18/2011
PH.D.
Kathleen Clouse, Director
Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS/CDER

Summary

BLA 125387 is a new biologics license application for Eylea® (aflibercept ophthalmic solution). Eylea® is a sterile, 40 mg/ml preservative-free aqueous solution for intravitreal injection. Eylea® is packaged in a single-use (b) (4) glass tubing vial sealed with a (b) (4) rubber stopper and an aluminum crimp seal. Each vial contains 0.278 ml of drug product. The proposed shelf life is (b) (4)



Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4) is a contract manufacturer that produces multiple CDER and CBER approved products using aseptic processing.

2. *FDA has not inspected the establishment in the past 2 years.*

A compliance check of the (b) (4) indicates that it has been inspected in the past 2 years. A GMP inspection was conducted by the (b) (4) from (b) (4). The inspection covered drug product manufacturing operations and found the (b) (4) profiles acceptable. The inspection was classified VAI.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

There were no serious deficiencies or systemic problems identified during the last inspection.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change).*

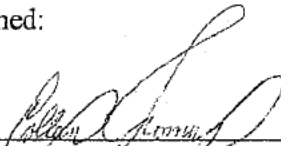
This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.

_____ (b) (4) is
approved to manufacture multiple drug and biologic products using _____ (b) (4)

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

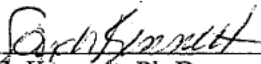
There are no significant differences between the _____ (b) (4)
_____ used for Eylea® (aflibercept ophthalmic solution).

Signed:



Colleen Thomas, Ph.D.
Microbiologist, CDER/OC/OMPQ/DGMPA/BMAB

DATE 13 Oct 2011



Sarah Kennett, Ph.D.
Biologist, OPS/OBP/DMA

DATE Oct-17, 2011

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

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

Memorandum

Date: October 13, 2011

To: Mike Puglisi, Regulatory Project Manager
Division of Transplant and Ophthalmic Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Promotion (DPP)

Subject: BLA 125387
(b) (4) (b) (4) intravitreal injection

Christine Corser
10/13/11

As requested in your consult dated September 8, 2011, the Office of Prescription Drug Promotion (OPDP) has reviewed the draft labeling for (b) (4) (b) (4) (b) (4) intravitreal injection.

OPDP's comments are based on the substantially complete version of the labeling titled, (b) (4) July 19 2011 submission.doc" which was sent via email from Mike Puglisi on September 8, 2011. The carton and container labeling used for this consult review is in a submission dated, August 5, 2011 located at the following EDR location:

<\\cher-fs3\m\eCTD Submissions\STN125387\125387.enx>.

OPDP's comments on the PI are attached in the substantially complete version of the labeling. Please note that the Division of Professional Promotion (DPP) reviewed the PI and carton and container labeling.

DPP has the following comment regarding the proposed carton and container labeling:

- We note that the carton and container include an image of an eye, thus making a representation about the drugs indication. This logo can be used in promotional materials, if it is included in the approved labeling for this product.

If you have any questions about DPP's comments on the PI or carton and container labeling, please contact Christine Corser at 6-2653 or at christine.corser@fda.hhs.gov.

Thank you for the opportunity to provide comments.

15 Pages of Draft Labeling
have been Withheld in Full
as b4 (CCI/TS)
immediately following this
page



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125387/0
Name of Drug: EYLEA™ (aflibercept)
Sponsor: Regeneron Pharmaceuticals, Inc.
Material Reviewed: EYLEA™ (aflibercept)
Carton and Container Labels
Submission Date: February 17, 2011

EXECUTIVE SUMMARY

The carton and container labels for EYLEA™ (aflibercept) were reviewed and found to comply with most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 8/1/11-11/30/11, USP 34/NF 29. Labeling deficiencies were identified. Please see comments in the conclusions section.

Background

STN 125387/0 for aflibercept is an original Biologic License Application (BLA) indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). The product is available as a solution in a 2 mg/ 0.05 mL concentration supplied in (b) (4) a glass vial.

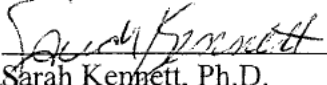
Labels Reviewed:

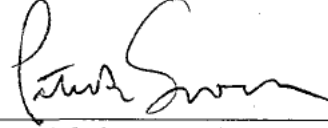
EYLEA™ (aflibercept) Container Labels
Vial and syringe label
EYLEA™ (aflibercept) Carton Labels
Vial Carton, (b) (4)

Start of Sponsor Material

9 Pages of Draft Labeling
have been Withheld in
Full as b4 (CCI/TS)
immediately following
this page

Comment/Concurrence:

 5/15/11
Sarah Kennett, Ph.D.
Product Reviewer
Division of Monoclonal Antibodies
CDER/OPS/OBP

 8/22/11
Patrick Swann, Ph.D.
Deputy Director
Division of Monoclonal Antibodies
CDER/OPS/OBP

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: August 05, 2011

To: Renata Albrecht, MD, Director
Division of Transplant and Ophthalmology Products

Reviewer(s): Walter Fava, RPh, MSED, Safety Evaluator *Walter Fava 8-5-11*
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh, Team Leader *Clleena 8/5/11*
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Product Name/Strength: Eylea (Aflibercept) Injection, 2 mg/0.05 mL

Application Type/Number: BLA 125387

Applicant/sponsor: Regeneron Pharmaceuticals, Inc.

OSE RCM #: 2011-539

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling of Eylea (Aflibercept) Injection for BLA 125387 for areas of vulnerability that can lead to medication errors. The review responds to a request from the Division of Transplant and Ophthalmology Products (DTOP) to review the container labels, carton and insert labeling for this Application.

1.1 PRODUCT INFORMATION

Eylea (Aflibercept) Injection is indicated for treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) and is administered as an intravitreal injection. The recommended dose is 2 mg (0.05 mL) once per month for the first three months, followed by 2 mg once every two months. It is available in a single-use vial containing 0.278 mL Aflibercept and is packaged with one 19-gauge x 1 and ½ inch, 5-micron, filter needle for withdrawal of the vial contents, one 30-gauge x ½ inch injection needle for intravitreal injection, and one 1 mL syringe for administration. (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted on February 18, 2011 to identify vulnerabilities that may lead to medication errors. See Appendix A for samples of the draft container label and carton labeling.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentations of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to product approval, and thus we provide the recommendations in section 3.1 to be communicated to the Sponsor prior to approval of this BLA.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

(b) (4)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

MEMORANDUM

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

DATE: July 18, 2011

TO: Sonal D. Wadhwa, MD,
Medical Officer
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products

FROM: Kassa Ayalew, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Branch Chief (Acting)
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: BLA 125387

APPLICANT: Regeneron Pharmaceuticals, Inc.
Attn: Laura Pologe
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
Phone#: 914-345-7926
Email: laura.pologe@regeneron.com

DRUG: Proposed (b) (4) (aflibercept ophthalmic solution)

NEW MOLECULAR ENTITY (NME): Yes

REVIEW PRIORITY (Standard or Priority): Priority

INDICATIONS: (b) (4)

BLA : 125387

PDUFA: August 20, 2011

ACTION GOAL DATE: August 20, 2011

I. BACKGROUND:

Regeneron Pharmaceuticals, Inc, submitted a new biologic application (BLA) for aflibercept ophthalmic solution (b) (4) for the treatment of neovascular age-related macular degeneration (AMD).

The sponsor made reference to IND 12,462 for Vascular Endothelial Growth Factor (VEGF) Trap-Eye (aflibercept ophthalmic solution), which has been developed as a therapeutic for ocular vascular diseases characterized by the over-expression of VEGF and consequent neovascularization and vascular leakage into the retina. The sponsor proposes that aflibercept ophthalmic solution be indicated for the treatment of neovascular "wet" age-related macular degeneration (AMD). The proposed route of administration is intravitreal (IVT) injection. VEGF Trap (aflibercept) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc.

The sponsor submitted data from two well controlled clinical trials (1365 subjects enrolled) and two additional phase 2 studies in support of the application. A priority review has been requested because the sponsor believes that the clinical evidence presented supports that a once every two month IVT treatment regimen for VEGF Trap-Eye (after three initial monthly doses) provides adequate evidence of efficacy that is non-inferior to the approved, once monthly IVT ranibizumab.

This was a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of a NME in this application.

To support the approval, the Applicant provided data from two studies: Protocol No. VGFT-OD-0605 (VIEW 1) and Protocol No. VGFT-OD-0702.

VGFT-OD-0605: A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration

This is an ongoing study designed to assess whether VEGF Trap-Eye has efficacy on VA (Visual Acuity) that is non-inferior to ranibizumab. The study is a randomized, double-masked, active controlled, multi-center, phase 3 study conducted in the United States and Canada. Approximately 1200 subjects were to be enrolled with a target enrollment of 300 subjects per treatment arm. Approximately 220 study sites in the USA and Canada were planned to participate in this study.

The findings presented are the results based on the data obtained between the start of enrollment and the data cut-off point for each individual subject at the week 52 visit when the primary endpoints of this study were reached. The period covered is 02 August 2007 (first subject's first dose) to 14 September 2010 (last subject's last visit for the primary endpoint) for year 1. The studies are continuing for the second year as planned while masking is maintained for subjects and personnel involved in the study.

This study was designed to determine whether VEGF Trap-Eye at any of 3 dose regimens is non-inferior to an approved dosing regimen in the U.S. of ranibizumab 0.5 mg given once every 4 weeks with respect to prevention of moderate vision loss at 52 weeks.

Subjects in this study were to be randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:

- 1) 2 mg VEGF Trap-Eye administered every 4 weeks (2Q4),
- 2) 0.5 mg VEGF Trap-Eye administered every 4 weeks (0.5Q4),
- 3) 2 mg VEGF Trap-Eye administered every 8 weeks (2Q8), and
- 4) 0.5 mg ranibizumab administered every 4 weeks (RQ4)

During the dosing phase, AEs and concomitant medications (ie, interval history) information was to be collected, vital signs were to be measured, ocular assessments were to be performed and an IVT injection of study drug (or sham) was to be administered. Only one eye per subject was to be enrolled in the study.

Study Prot. VGFT-OD-0702: A Randomized, Single-Masked, Long-Term, Safety, and Tolerability Study of Intravitreal VEGF Trap-Eye in Subjects with Neovascular Age-Related Macular Degeneration

VGFT-OD-0702 is a phase 2, single-masked (to the subject), randomized, multi-center clinical study. Subjects were eligible if they had neovascular AMD and completed dosing in VGFT-OD-0502 (an exploratory study of the safety, tolerability and biological effect of intravitreal administration of VEGF Trap in patients with neovascular age-related macular degeneration), -0508 (a double-masked, prospective, randomized, controlled study, in which 5 groups of approximately 30 patients were randomly assigned in a balanced ratio to receive IVT injections of 0.5 mg or 2 mg at 4- or 12-week intervals, or 4 mg VEGF Trap-Eye at 12-week intervals for

(b) (4) (afibercept ophthalmic solution)

12 weeks, followed by prn dosing through week 52, or -0603 (a multi-center, double-masked study designed to assess the safety and tolerability of 3 monthly ITV injections of 2 formulations of VEGF Trap-Eye in 12 patients with AM). Approximately 165 subjects at 35 sites in the US who completed the required portions of VGFT-OD-0502, -0508, or -0603 were planned for enrollment into this study. The main objectives of the study were to allow subjects previously enrolled in VGFT-OD-0502, -0508, and -0603 to continue to receive vascular endothelial growth factor (VEGF) Trap-Eye after completion of dosing in those studies and assess the long-term safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD for periods of up to three years

Subjects were to receive injection of VEGF Trap-Eye in one of two forms:

- 2 mg VEGF Trap-Eye PRN in a 50 µL injection volume from a PFS
- 2 mg VEGF Trap-Eye PRN in a 50 µL injection volume from a Vial

Each subject was to have only one eye be designated as the study eye and was to be treated in one of the two treatment arms after enrollment. The other eye was designated as the fellow (non-study) eye and was to be treated if the investigator deemed treatment necessary.

A consult from DAIOP to DSI (now OSI) was received on March 15, 2011. The above studies were considered pivotal and inspection of the below sites (Drs Heier and Abraham) was requested to verify the data generated and the quality of conduct of these studies for this BLA. In addition, during the review cycle the results of a related "for cause" inspection of Dr. Mark Michels became available and the results of this inspection are also provided.

II. RESULTS (by Site):

Name of CI or Sponsor	Protocol # & # of Subjects:	Inspection Date	Preliminary Classification	Final Classification
Jeffrey S. Heier, M.D. Ophthalmic Consultants of Boston 50 Staniford Street, Suite 600 Boston, MA 02114	Study VGFT-OD-0605/ n=53	April 26 to May 9, 2011	VAI	Pending
Prema Abraham, M.D. Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701	Study VGFT-OD-702/ n=11	April 24 to 29, 2011	NAI	NAI
For Cause Inspection: Mark Michels, M.D. Retina Care Specialists LLP 3399 PGA Boulevard, Suite 220 Palm Beach Gardens, FL 33410	Study VGFT-OD-0605/ n=15	April 28 to May 12, 2001	VAI	Pending
Sponsor: Regeneron	Study VGFT-OD-0605	Pending	Pending	Pending

(b) (4) (afibercept ophthalmic solution)

Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707	With focus on Dr. Jeffrey S. Heier, M.D. and *Dr. Mark Michels, M.D. Study VGFT-OD-702 With focus on Dr. Prema Abraham, M.D.			
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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 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

*Dr. Mark Michels, MD: the site was included because of the preliminary inspection findings from for-cause inspection as results of the complaint received by OSI, in regards to recruitment material for the subject study.

1. **Dr. Jeffrey S. Heier, M.D.**
Ophthalmic Consultants of Boston
50 Staniford Street, Suite 600
Boston, MA 02114

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811, and it was conducted from April 26 to May 9, 2011. The observations noted are based on the review of the EIR and the Form FDA 483.

At this site, a total of 53 subjects were screened, 32 subjects were enrolled, and 25 subjects completed the study. Three (3) subjects discontinued: Subject # 016 died due to a cerebral vascular accident and Subjects #012 and #032 withdrew consent. Four subjects are still actively enrolled pending the completion of the study. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequate 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.

During the inspection, records of all subjects were evaluated adequacy of informed consent process, SAE's, and deaths. In addition the inspection evaluated 12 subjects for verification of randomization, inclusion/exclusion criteria, primary efficacy endpoint, concomitant medications, and compared source documents, CRFs, and data listings.

b. General observations/commentary:

There was no evidence of underreporting of AE's at this site and primary efficacy endpoint data were verifiable. The inspection of Dr. Heier's site did, however, reveal that the study

(b) (4) (affibercept ophthalmic solution)

was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

- i. Failure to ensure, in accordance with the signed statement of investigator, the requirements relating to obtaining informed consent and institutional review board approval are met, and failure to ensure that study personnel performed only their designated responsibilities as required by the protocol. In addition, Dr. Heier did not ensure that all employees assisting in the conduct of the study were trained prior to performing study related activities.

Section 4.1 of the protocol, "Informed Consent Process" states "No person other than those indicated may be involved in the informed consent process without first submitting a CV to (b) (4) IRB for review and approval." Employee (b) (6) obtained informed consent prior to receiving approval from (b) (6) from Subjects 146-001, 146-002, 146-003, 146-004, 146-005, 146-006, 146-007, 146-008, 146-009, 146-010, and 146-011. In addition, Employee (b) (6) printed, signed, and dated the legally authorized representative area of informed consent for Subject 146-001 as well as printed, signed, and dated the witness area of the informed consent for Subjects 146-002 through 146-011.

OSI Reviewer Comment: The employee (b) (6) should have not been involved in the informed consent process without first submitting a CV to CCRI's IRB for review and approval. The clinical investigator failed to ensure that study personnel obtaining informed consent were approved by the IRB as required by the protocol.

In addition, the clinical investigator did not ensure that study personnel performed only the designated responsibilities as required by the protocol. Employee (b) (6) printed, signed, and dated the legally authorized representative area of informed consent for Subject 146-001 as well as printed, signed, and dated the witness area of the informed consent for Subjects 146-002 through 146-011. Except for Subject 146-001, all participants in the study signed informed consent document before participating in the study indicating they understand the benefits and risks. The CI also replaced employee (b) (6) with a new study coordinator after the matter was brought to his attention in February 2008, and irregularities of the above nature have not been identified since then.

Although the clinical investigator failed to ensure that the study personnel performed only their designated responsibilities and sign informed consents properly, the observed regulatory violations were isolated and do not appear to significantly affect data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

In Dr. Heier's written response (submitted on May 23, 2011) to the Form FDA 483, he acknowledged the findings identified above and stated that he has implemented corrective actions for the appropriate administration of informed consent and developed SOPs concerning IRB approval.

(b) (4) (aflibercept ophthalmic)

- ii. Failure to ensure the investigation was conducted in accordance with the investigational plan. Specifically, Employee (b) (6) changed roles from Unmasked to Masked during the course of the study prior to completion and approval of a "ROLE CHANGE IVRS FORM". Each study site must have had a masked investigator responsible for all medical and ophthalmic assessments pre-injection and for the overall safety evaluation of all subjects in the study and an unmasked investigator responsible for the preparation and injection of the study drug and for the immediate (30-60 minute) post-injection exam. This should have been conducted according to page 11 of Section 7.6 of the protocol "Study Site Personnel Roles" that states "Masked and Unmasked roles will be assumed for the entire study and switching roles during the course of the study is not permitted."

OSI Reviewer Comments: Employee (b) (6) (sub-investigator) was assigned to perform unmasked procedures (treating role) for Subject # 1, 3, 6, 8, 11, 13, and 15 in the first phase of the study (8/25/2007-5/7/2008). Later, the CI switched Employee (b) (6) unmasked role and designated her to perform duties and procedures as a masked (evaluating role) sub-investigator. Employee (b) (6) who was unmasked in managing Subject # 1, 3, 6, and 8 should not have been assigned to perform the masked duties such as evaluation of safety and efficacy for Subject # 1, 3, 6, 8 as a masked investigator. According to the protocol, a separate masked physician (evaluating) should have been assigned to perform the masked duties such as evaluation of safety and efficacy for all subjects to avoid problems with blinding.

Unblinding of treatment is evident for 4 of the 12 (33%) subjects enrolled at this site. We recommend that the review division determines the potential impact, if any, that unblinding of data from the four subjects (Subject # 1, #3, #6, and #8) has on overall efficacy and safety analyses and conclusions.

Dr. Heier's written response (submitted on May 23, 2011) to the Form FDA 483 acknowledged the findings identified above and stated that he had implemented corrective actions to SOPs to prevent similar recurrences in future studies.

c. Assessment of data integrity:

Although the above regulatory violations were noted at this site, it is unlikely that these findings would affect subject data reliability or integrity. The review division will need to determine the potential impact, if any, that unblinding of data from the four subjects (Subject # 1, 3, 6, and 8) has on efficacy and safety analyses and conclusions, and consider excluding their data from analyses. As the above observations were relatively isolated, the findings are unlikely to impact data reliability. In general, based on the Establishment Inspection Report (EIR) for this site, data derived from Dr. Heier's site is considered reliable.

- 2. Dr. Prema Abraham, M.D.**
Black Hills Regional Eye Institute
2800 Third Street
Rapid City, South Dakota 57701

a. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between April 24 and 29, 2011. At this site, 15 study subjects were screened and 15 enrolled into the study. Eleven subjects completed the study. Four Subjects discontinued the study (Subject # 2706, 2807 and 2813 terminated the study early, and Subject # 2806 died due to a pulmonary condition). The observations noted are based on the review of the EIR and the Form FDA 483. There were no limitations to the inspection.

An in depth audit of the study records for all 15 subjects was conducted. Records reviewed included, but were not limited to, source documents, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. General observations/commentary:

The study appears to have been executed appropriately at this site. No regulatory violations were noted and a Form FDA 483 was not issued.

c. Assessment of data integrity:

Based on inspectional findings and the observations noted, efficacy and safety data obtained from this site are considered reliable.

- 3. For Cause Inspection: Mark Michels, M.D.**
Retina Care Specialists LLP
3399 PGA Boulevard, Suite 220
Palm Beach Gardens, FL 33410
(561) 624-0099

a. What was inspected?

The inspection of Dr. Mark Michels's site was conducted on the basis of a complaint received by OSI, in regards to online subject recruitment material regarding the pivotal Study VGFT-OD-0605 for this application. The inspection was conducted from 4/28 – 5/12/2011.

At this site 22 study subjects were screened and 15 were enrolled into the study. Twelve subjects completed the study. The observations noted are based on the review of the EIR and the Form FDA 483. There were no limitations to the inspection. A review of the records of all of the 12 subjects in the study was conducted. A limited audit of records for protocol adherence, documentation practices, protocol deviations, adverse events, study drug administration and accountability, adherence to inclusion/exclusion criteria, contraindicated medication usage, and informed consent procedures was also done.

Records reviewed included, but were not limited to, source documents, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

b. General observations/commentary:

There was no evidence of underreporting of AE's at this site and primary efficacy endpoint data were verifiable. The inspection of Dr. Michels site did, however, reveal that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

Failure to conduct the study in accordance with the signed statement of investigator and investigational plan. For example:

- i. The CI failed to maintain proof of evidence to show that subjects who failed (b) (4) at screening had met the study eligibility criteria. There was no objective evidence such as total lesion or scar size as determined by angiogram in any of the subject's source documents proving the subjects met exclusion criteria 4 and 6.

OSI Reviewer Comments: Dr. Michels provided a written response to the Form FDA 483 received on June 28, 2011. The protocol specified that these angiographic characteristics are to be measured /confirmed by the central reading center prior to study drug administration. However, the CI's equipment did not have the capability of determining the ocular angiographic conclusions required for study inclusion. He was dependent on the (b) (4) to confirm suitability for enrollment, and he was not able to retain this source data at the site. Dr. Michels stated that he awaited confirmation by the outside reading center before any patients were randomized or treated in the study.

Dr. Michels also acknowledged the concerns about including subjects into the study without verification that they fulfilled the inclusion and exclusion criteria. He stated that he has implemented corrective actions to modify inclusion and

exclusion documents to specifically reflect pending verifications by including a hand written note on the inclusion/exclusion criteria page.

OSI requested that the sponsor provide documentation that the subjects enrolled at Dr. Michel's site were eligible for study entry. This information was provided in a submission dated July 11, 2011. This information confirms that of 20 enrolled subjects, 13 subjects were randomized and 7 subjects failed screening. Included in the submission were the parameters assessed from the fluorescein angiogram for all 20 subjects, which confirms that subjects were appropriately enrolled into the study.

- ii. The CI included Subject 001 (b) (6) although the subject had branch retinal vein occlusion in the non-study eye which should have resulted in exclusion from the study.

OSI Reviewer Comments: The clinical investigator should have excluded the above subject from participation in this study based on Exclusion Criterion #11. Based on the review of the EIR, the above-mentioned protocol deviation was identified and described by the study monitor. The CI reported the deviation to the sponsor and later received a waiver from the sponsor. In addition, Dr. Michels acknowledged the he did incorrectly include this patient in the study. He plans to correct the problem in the future by double checking all available records in his possession prior to considering patients for clinical trials, since relevant historical information was available but overlooked for Subject 001 (b) (6). This finding was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.

- iii. The CI used non-IRB approved study recruitment material on his website such as subject testimonials and physician statements promoting the investigational drugs for studies he was conducting, including the. VGFT-OD-0605 (VIEW 1), (b) (4) studies.

OSI Reviewer Comments: The EIR shows the CI's medical practice's website (www.retinacarespecialists.com) included non IRB approved subject testimonials and physician's statements promoting the investigational drug. These recruitment materials should have been approved by IRB before being posted on the website.

Dr. Michels acknowledged the above concerns and stated that all press releases and news stories were ordered removed from the website. He also stated that he has developed a process by which any research related materials must be approved by the IRB prior to posting on the website. In addition, he plans to post materials only about approved drugs and "on label" indications.

(b) (4) (afibercept ophthalmic solution)

- iv. There was no documentation of what changes were made to revised informed consent documents to determine how the changes affected the subjects and whether re-consenting was necessary for the following informed consent documents: Version v071207 was approved on 07/20/2007; v021108 was approved on 02/11/2008; v033009 was approved on 03/30/09; version 30Mar2009 rev 05May2010 was approved on 05May2010; v0905201 was approved on 05Sep10; and v09052010 revised 10042010 was approved on 10/04/2010.

OSI Reviewer Comments: *Although the CI should have properly documented what changes were made to revised informed consent documents and determined whether the changes that were made affected the subjects and whether re-consenting was necessary, the observed modifications to the Informed Consent Forms do not appear to significantly affect the safety of subjects in the study.*

Dr. Michels' written response (received on June 28, 2011) to the Form FDA 483, acknowledges the findings identified above and stated that he has implemented corrective actions in which he instituted a new document control spreadsheet for Informed Consent Form (ICF) specific changes.

- v. Subject 005 (b) (6) failed to sign the 02/11/08 IRB approved consent form on Visits 2,3,4, and 5 which occurred on 02/29/08, 03/07/08, 03/26/08 and 04/23/08.

OSI Reviewer Comments: *The clinical investigator failed to ensure that Subject 005 (b) (6) signed the 02/11/08 IRB approved informed consent document at 4 subsequent visits. However, the finding was isolated in nature and unlikely to impact subject protection.*

- vi. There was a Spanish IRB approved consent form that was approved before it was created. The consent form is dated 02/26/08 and the IRB approved it on 02/11/08 which is 15 days before the creation of the document.

OSI Reviewer Comments: *Dr. Michels' written response (received on June 28, 2011) to the Form FDA 483, acknowledges the findings identified above, and states that there is some "ambiguity" in how documents are dated by the IRB. He does note that the informed consent document in Spanish was not used at his site. He notes that a form letter has been created to query regarding unclear regulatory issues.*

c. Assessment of data integrity:

Several regulatory violations were noted at Dr. Michels' site including lack of source documents that subjects met inclusion and exclusion criteria, use of non-IRB approved promotional material for subject recruitment, and lack of documentation of use of the appropriate version of the informed consent document.

At OSI's request, the Applicant provided the angiographic data measurements and description of eligibility based on (b) (4) assessment and enrollment for Site 114 (Dr. Michels) in an email dated July 11, 2011. Based on the angiographic measurements and documentation by the Applicant that show subjects at Dr. Michels' site were eligible for enrollment, the observations at Dr. Michels' site do not appear to significantly impact data integrity or subject protection. The other regulatory violations are not likely to significantly impact data reliability, and the data may be used in support of the application.

4. Sponsor: Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

a. What was inspected?

This inspection is pending, and the Establishment Inspection Report was not available at the time this CIS was written.

b. General observations/commentary:

This inspection is pending.

c. Assessment of data integrity:

This inspection is pending.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

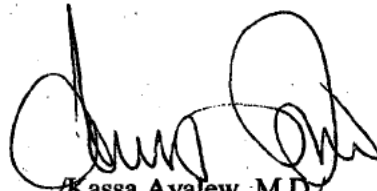
Three clinical site inspections were conducted in support of this application. The sponsor inspection is pending. No significant regulatory violations were noted at Dr. Abraham's site, and although regulatory violations were noted at Drs. Heier's and Michels' sites, the findings are unlikely to significantly impact data reliability.

Inspection of Dr. Heier's site documented regulatory violations including failure to ensure the investigation was conducted in accordance with the investigational plan. Informed consent was obtained by a non-IRB approved employee, and this employee erroneously completed the legally authorized representative area of the informed consent. Although these regulatory violations were noted at this site, it is unlikely that these findings would affect subject data reliability or integrity. In addition, a subinvestigator switched roles in violation of the protocol from masked to unmasked resulting in unblinding of Subjects #1, 3, 6, and 8. The review division will need to assess the impact of the unblinding of these subjects on the efficacy results, and consider exclusion from analyses. The final classification for the inspection of Dr. Heier's site is Voluntary Action Indicated (VAI).

In general, inspection of Dr. Abraham's site revealed that the study appears to have been conducted adequately and the data appear reliable in support of the BLA. The final classification for the inspection of Dr. Abraham is No Action Indicated (NAI).

Regulatory violations documented at Dr. Michels' site initially raised concerns regarding the lack of documentation that subjects met inclusion and exclusion criteria, use of non-IRB approved promotional material for subject recruitment, and lack of documentation of use of the appropriate informed consent document. OSI submitted an Information Request to the Applicant requesting that they provide angiographic measurements to determine eligibility. In an email dated July 11, 2011, the Applicant provided the angiographic data measurements and description of eligibility based on (b) (4) assessment and enrollment at Dr. Michel's site. Although several significant regulatory violations were noted during the inspection including lack of documentation that subjects met inclusion and exclusion criteria at Dr. Michels' site, the sponsor has provided adequate information and documentations showing that subjects at Dr. Michels' site were eligible for enrollment. Given the additional information provided by the applicant and review of Exhibits in the EIR, the observations at Dr. Michels' site do not appear to significantly impact data integrity or subject protection. The preliminary classification for this inspection is VAI.

Follow-Up Actions: The inspection of the sponsor, Regeneron Pharmaceuticals, Inc., is pending. A CIS addendum will be generated when the Regeneron Pharmaceuticals, Inc. EIR is received.



/Kassa Ayalew, M.D./

Kassa Ayalew, M.D.

Medical Officer

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

CONCURRENCE:



/ Susan Thompson, M.D./

Susan Thompson, M.D.

Acting Team Leader

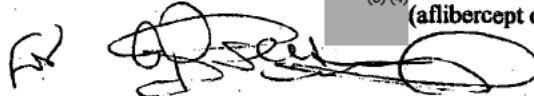
Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

(b) (4)

(afibercept ophthalmic solution)



/ Jean Mulinde, M.D. /

Jean Mulinde, M.D.

Acting Branch Chief

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations

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 # BLA# 125387	NDA Supplement #:S- BLA STN # 0	Efficacy Supplement Type SE-
Proprietary Name: Eylea Established/Proper Name: aflibercept injection Dosage Form: ophthalmic injection Strengths: (b)(4), 40 mg/mL		
Applicant: Regeneron Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: February 17, 2011 Date of Receipt: February 18, 2011 Date clock started after UN: n/a		
PDUFA Goal Date: August 18, 2011		Action Goal Date (if different):
Filing Date: April 20, 2011		Date of Filing Meeting: March 23, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): treatment of neovascular (wet) age-related macular degeneration		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input 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 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"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<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 12,462				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
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)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p>User Fee Status</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 Unacceptable for Filing (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>
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<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 checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>
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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)]?				
<i>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 (b)(2) review staff in the Immediate Office of New Drugs</i>				
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.accessdata.fda.gov/scripts/cder/ob/default.cfm				

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

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		X		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>				
<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 type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
<p>Overall Format/Content</p>	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ 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/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain:				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<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>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
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)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p>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].</p> <p><i>Note: Debarment Certification should use wording in FDCA 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></p>				
<p>Field Copy Certification (NDAs/NDA efficacy supplements only)</p> <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>	YES	NO	NA	Comment

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</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)²</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			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

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? <i>If no, request in 74-day letter</i>				
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)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
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 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? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Consult to be sent after filing date
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input 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?				
Other 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): <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/8/10 & 9/27/10 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): 1/18/07, 5/31/07 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

Completed by: Michael Puglisi
 Regulatory Project Manager

MP 3/18/11