CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

CHEMISTRY REVIEW(S)

OBP Review Cover Sheet

BLA STN 125387
Addendum 2

Eylea™ (Aflibercept)

Sponsor: Regeneron Pharmaceuticals, Inc.

Sarah Kennett, Ph.D.
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

(Includes only information updated since the initial review finalized on July 22, 2011)

1. **BLA#** STN 125387-0

2. **REVIEW #:** 3

3. **REVIEW DATE:** November 15, 2011

4. **REVIEWER(s):** Sarah Kennett, Ph.D.
   Chana Fuchs, Ph.D., Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS SINCE THE FINALIZATION OF THE INITIAL REVIEW:**

Communication/Documents	Date
Information Request	8-3-2011
Teleconference	8-4-2011
Teleconference	8-10-2011
Pre-meeting Document	9-2-2011
Sponsor Meeting	9-2-2011
Pre-meeting Document	9-9-2011
Teleconference	9-13-2011
Pre-meeting Document	9-26-2011
Teleconference	9-27-2011
Pre-meeting Document	10-6-2011
Teleconference	10-6-2011
Pre-meeting Document	10-17-2011
Teleconference	10-18-2011
Pre-meeting Document	10-21-2011
Teleconference	10-25-2011
PMC Agreements	11-8-2011
Information Requests	11-9-2011

6. **SUBMISSION(S) REVIEWED UNDER THIS ADDENDUM:**

Submission(s) Reviewed	Document Date
125387/0.23	7-1-2011
125387/0.24	7-6-2011
125387/0.25	7-8-2011
125387/0.27	7-19-2011
125387/0.28	7-21-2011
125387/0.29	8-1-2011
125387/0.30	8-5-2011
125387/0.31	8-10-2011
125387/0.32	8-12-2011
125387/0.33	9-1-2011
125387/0.34	9-1-2011

125387/0.36	9-12-2011
125387/0.37	9-20-2011
125387/0.38	9-27-2011
125387/0.39	10-7-2011
125387/0.40	10-21-2011
125387/0.42	10-27-2011
125387/0.44	11-9-2011
125387.1.0	11-11-2011

11. **STRENGTH/POTENCY:**

a) The concentration of Eylea (aflibercept) Drug Product is 40 mg/ml.
b) Potency is defined as IC_{50} of the sample relative to IC_{50} of the reference standard in a proprietary VEGF-stimulated reporter gene assay and an ELISA-based binding assay.
c) Potency specification is (b) (4) of reference standard as measured by the cell-based assay and (b) (4) of reference standard as measured by the binding assay.
d) Dating period for vialed drug product is 15 months when stored at 2-8°C.
e) 11.12 mg of aflibercept is filled into (b) (4) glass vials for a 2 mg dose.

16. **CONSULT STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
DMA Carton and vial labeling	Approve	11/4/11	Kimberly Rains
BMAB- memo for Drug Substance micro and facilities review	Approve (based on 10/27/11 email from Michael Puglisi)		Kalavati Suvarna/Patricia Hughes
BMAB- memo for Drug Product micro and facilities review	Approve (based on 10/27/11 email from Michael Puglisi)		Colleen Thomas/Patricia Hughes

18. **Recommendations on Approvability:** The data submitted in this Biologics License Application support the conclusion that the manufacture of Eylea™ (aflibercept) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Eylea™ (aflibercept) be approved for human use (under conditions specified in the package insert).

QUALITY UNIT ASSESSMENT

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The initial review of module 3.2 is provided in the original review document. Review of additional information received since the time of finalization of the initial review is found below.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY MODULE 1

a. **ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION**

As specified in 21 CFR 25.15(b), Regeneron states that this Biologic License Application (BLA) qualifies for a categorical exclusion to the environmental assessment (EA) requirement based on the estimated concentration of the substance at the point of entry into the aquatic environment being below 1 ppb. The expected introduction concentration (EIC) was calculated according to the 1998 "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application." Regeneron states that to their knowledge, no extraordinary circumstances exist and request exclusion from the requirement of the environmental assessment.

b. **PACKAGE INSERT**

CMC Review and comments on package insert were provided directly to the team to be incorporated into the package insert.

c. **DRUG PRODUCT LABEL**

CMC review of DP label will be generated under a separate consult to Kimberley Rains, OBP.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are no CMC-related deficiencies precluding approval of this BLA.

A list of PMC's can be found at the end of this document and in the quality team leader's executive summary.

IV. ADMINISTRATIVE

A. Reviewer's Signature

Product Quality Reviewer: Sarah Kennett, Ph.D. Sarah Kennett 11/15/2011

B. Endorsement Block

Product Division Team Leader: Chana Fuchs, Ph.D. 11/15/11

Product Division Deputy Director: Patrick Swann, Ph.D. Patrick Swann 11-15-11

Product Division Director: Kathleen Clouse, Ph.D. Kathleen Clouse 11/15/2011

C. cc Block

OBP Office Director: Steven Kozlowski, M.D.
Clinical Division Director (DTOP): Renata Albrecht, M.D.
Division of Monoclonal Antibodies File: BLA STN 125387

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies

The Quality Team Leader's Executive Summary - addendum

From: **Chana Fuchs, PhD**
Division of Monoclonal Antibodies (DMA),
CDER, FDA

Through: **Patrick Swann, PhD**
Deputy Director DMA

Kathleen A. Clouse, PhD
Director, DMA

BLA Number: **125387/0**
Product: **aflibercept (Eylea™)**
Sponsor: **Regeneron Pharmaceuticals, Inc.**

Date of Review: **8-November-2011**
Due Date of TL Memo: **10-November-2011**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, has completed review of BLA 125387/0 for aflibercept (Eylea™) manufactured by Regeneron Pharmaceuticals. The data submitted in this application are adequate to support the conclusion that the manufacture of Eylea (aflibercept) is well controlled, and will lead to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated and a consistent product was produced form the multiple production runs presented. We recommend that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

The following should be communicated to sponsor in the approval letter:

The dating period for aflibercept injection shall be 15 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture shall be defined as the (b) (4)

The expiration date for the packaged product, (aflibercept single-use vials, syringe, needle and filter needle) shall be dependent on the shortest expiration date of any component.

(b) (4)

(b) (4)

III. POST MARKETING COMMITMENTS AND REQUIREMENTS

DMA CMC PMCs

Post Marketing Commitments:

1. To conduct three drug product hold time studies for the 40 mg/mL vial presentation filled at the (b) (4) 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 (b) (4)

2. To confirm [redacted] (b) (4) by the aflibercept [redacted] (b) (4) process. The clearance study will be performed under protocol on three lots of drug substance produced at the commercial scale. [redacted] (b) (4) will be measured with a validated analytical test method for determining [redacted] (b) (4). The completed method validation and study reports will be submitted in the 2012 annual report by January, 2013.
3. 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.
4. 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 within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.
5. 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.
6. 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.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

V. EXECUTIVE SUMMARY

The original Quality Team Leader's Executive Summary from 7/22/11 recommended a CR and delineated significant deficiencies found during the initial review cycle. Following these recommendations, it was decided to extend the review clock based on a major amendment submitted within the last 90 days of the review cycle. During this timeline the CMC reviewers worked closely with Regeneron to help resolve apparent deficiencies found during the initial BLA review. The deficiencies and discrepancies originally identified can be grouped into the following overarching topics:

- Data supporting release methods and acceptance criteria for Drug Substance and Drug Substance Intermediate.
- Data supporting stability of Drug Substance and Drug Substance Intermediate.
- Drug substance (DS) and drug Substance intermediate (DSI) manufacturing process, process controls and process validation.
- Data supporting release methods and acceptance criteria for Formulated Bulk Drug Product and Drug Product.
- Data supporting stability of Formulated Bulk Drug Product and Drug Product
- Formulated Bulk Drug Product (FB) and Drug Product (DP) manufacturing process controls and process validation.
- immunogenicity assay validation

All the issues identified were sufficiently addressed in the additional data provided by Regeneron.

Also updated since the original review and PQTL memo, (b) (4) (b) (4) Therefore, the proposed approval covers only the 40 mg/mL vial filled at (b) (4)

(b) (4)

(b) (4) The BLA currently contains a protocol that is consistent with the manufacturing process and controls section of the BLA, as well as a FMEA to evaluate risks and control strategies documents with triggers for extended evaluation of product quality and cell culture performance. Results of studies performed for any trigger (or statement that no triggers were identified) will be reported yearly in the Annual Report. The BLA does not contain protocols for qualification of new cell banks (Master or Working Cell Banks); these would need to be implemented under a PAS.

A. Description of Aflibercept (Eylea) Drug Product and Drug Substance

Aflibercept is a genetically engineered homodimeric protein that is generated by the in-line fusion of Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2, which in turn are fused to the Fc region of human IgG.

Aflibercept acts as a soluble decoy receptor that binds vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these receptors.

Eylea (aflibercept) Drug Product is supplied as a sterile, preservative free liquid formulation of 2 mg/0.05mL (40 mg/mL) aflibercept in sterile, single use vial (b) (4) of 0.278 mL and intended to deliver 0.05 mL (50 microliters) of aflibercept (40 mg/mL) aqueous solution.

Formulation: Eylea drug product is a sterile solution of 40 mg/ml aflibercept in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% (w/v) polysorbate 20, and 5% sucrose, pH 6.2.

There is no preservative in the formulation so any unused portion of vial contents must be discarded.

Each carton of Eylea contains one single-use 3-mL glass vial of EYLEA, one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents (filter needle not to be used for intravitreal injection), one 30-gauge x ½-inch needle for intravitreal injection, one 1-mL plastic syringe for administration, and one package insert.

Storage: Eylea should be refrigerated at 2°C to 8°C, protected from light. Eylea should not be frozen.

Container Closure information: Vials consists of a (b) (4) type I glass vial, a (b) (4) rubber (b) (4) stopper (b) (4) and an aluminum seal. According to section 3.2.P.5.5.1 Table 1, (b) vials and (b) (4) (b) (4) stoppers are used.

The extinction coefficient for aflibercept was determined experimentally to be 1.15 AU/mg/ml.

B. Clinical Trial Information

Indication: EYLEA™ (aflibercept) is proposed for the treatment of patients with neovascular (Wet) Age-Related Macular Degeneration (AMD).

Route of Administration: ophthalmic intravitreal injection

The proposed dosage regimen is 2 mg (50 microliters) administered by intravitreal injection once every 2 months following 3 initial monthly injections of 2 mg (50 microliters).

Clinical efficacy and safety data are from studies VIEW1 and VIEW2, two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD, form the basis of the application. The primary efficacy endpoint was the proportion of patients in the Per-Protocol Set who maintained vision, defined as losing fewer than 15 letters of

visual acuity at week 52 compared to baseline. Four randomly assigned dosing regimens were (A) Eylea 2 mg administered every 8 weeks following 3 initial monthly doses; (B) Eylea 2 mg administered every 4 weeks; (C) Eylea 0.5 mg administered every 4 weeks; and (D) ranibizumab 0.5 mg administered every 4 weeks. Arms A and B were shown to have efficacy that was non-inferior and clinically equivalent to arm D.

C. Stability

Drug Product:

- Drug product is intended to be stored at 2-8°C.
- Expiration dating for the Drug Product, aflibercept injection, is 15 months from the date of manufacture when stored at 2 - 8°C, protected from light. The date of manufacture is defined as (b) (4)
- Aflibercept is light sensitive and should not be exposed to excessive light. A photostability study identified impacts to size variants, charge variants, and particulates.
- The expiration date for the packaged product, (aflibercept single-use vials, syringe, needle and filter needle) shall be no longer than the shortest expiration date of any component.
- Eylea drug product formulation does not contain a preservative; vials are intended for single use only.

The manufacturing process of aflibercept is (b) (4)

(b) (4)

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E. **Mechanism of Action**

Aflibercept acts as a soluble decoy receptor that binds Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (KD) for aflibercept binding to human VEGF-A_{165} is 0.55 pM and to human VEGF-A_{121} is 0.36 pM. The KD for binding to human PlGF-2 is 39 pM.

VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability.

(b) (4)

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Although this would not normally be required in other BLAs, these types of changes would have required supplements for this BLA due to cell bank clonality issues, if the risk mitigation protocol would not have been included in the BLA.

VI. SIGNATURE BLOCK

Name and Title	Signature and Date
Patrick Swann, Ph.D,, Deputy Director Division of Monoclonal Antibodies Kathleen A. Clouse, Ph.D., Director, Division of Monoclonal Antibodies	Patrick Swann 11-15-11 Kathleen A. Clouse 11/15/2011
Chana Fuchs, PhD Product Quality Team Leader Division of Monoclonal Antibodies	11/15/11
Sarah Kennett, PhD Product Reviewer Division of Monoclonal Antibodies	Sarah Kennett 11/15/2011

OBP Review Cover Sheet

BLA STN 125387

Eylea™ (Aflibercept ophthalmic solution)

Sponsor: Regeneron Pharmaceuticals, Inc.

Sarah Kennett, Ph.D.
Sang Bong Lee, Ph. D.
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

1. **BLA#** STN 125387-0

2. **REVIEW #:** **1**

3. **REVIEW DATE:** July 21, 2011

4. **REVIEWER(s):** Sarah Kennett, Ph.D.
Sang Bong Lee, Ph.D.
Chana Fuchs, Ph.D., Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS TO DATE:**

Communication/Documents	Date
Pre-BLA meeting	9-15-2009
Pre-BLA meeting	9-27-2010
Information Request	3-18-2011
Filing Review	4-20-2011
Regeneron Rensselaer 483	5-20-2011
Information Request	6-20-2011

6. **SUBMISSION(S) REVIEWED TO DATE:**

Submission(s) Reviewed	Document Date
125387/0.0	2-18-2011
125387/0.1	3-1-2011
125387/0.2	3-10-2011
125387/0.4	3-25-2011
125387/0.6	4-4-2011
125387/0.7	4-8-2011
125387/0.8	4-11-2011
125387/0.9	4-12-2011
125387/0.10	4-14-2011
125387/0.11	4-14-2011
125387/0.12	5-2-2011
125387/0.15	5-23-2011
125387/0.18	6-7-2011
125387/0.19	6-9-2011
125387/0.21	6-21-2011
125387/0.22	6-28-2011
125387/0.23	7-1-2011
125387/0.24	7-6-2011
125387/0.25	7-8-2011

Amendments in red have been received but were not included in the current review as they were submitted late in the review cycle. These were not reviewed during the current review cycle to allow the reviewers to meet the review deadlines.

7. **NAME & ADDRESS OF APPLICANT:**
Name: Regeneron Pharmaceuticals, Inc.
Address: 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707
Representative: Laura Pologe, Associate Director, Regulatory Affairs
Telephone: (914) 345-7926
Fax: (914) 345-7688

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name:	Eylea™
Non-proprietary/USAN:	Aflibercept ophthalmic solution
Code name:	VEGF Trap-EYE, BAY 86-5321
Common name:	Vascular endothelial growth factor receptor type VEGFR (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer
Drug Review Status:	Priority
Chemical Type:	recombinant fusion protein of human VEGFR1 Ig domain 2, human VEGFR2 Ig domain 3, and human IgG1 Fc

9. **PHARMACOLOGIC CATEGORY:** Therapeutic recombinant fusion protein of human VEGFR1 Ig domain 2, human VEGFR2 Ig domain 3, and human IgG1 Fc

10. **DOSAGE FORM:** Solution for intravitreal injection (vial)
(b) (4)

11. **STRENGTH/POTENCY:**
a) The concentration of Eylea (aflibercept) Drug Product is 40 mg/ml.
b) Potency is defined as IC_{50} of the sample relative to IC_{50} of the reference standard in a proprietary VEGF-stimulated reporter gene assay.
c) Proposed potency specification is (b) (4) of reference standard.
d) Proposed dating period for vialed drug product is (b) (4) when stored at 2-8°C.
e) 11.12 mg of aflibercept is filled into (b) (4) glass vials or (b) (4) glass vials for a 2 mg dose.
(b) (4)

12. **ROUTE OF ADMINISTRATION:** Intravitreal Injection

13. **ACID (Animal Component Information Database)**
This section lists starting materials of biological origin. No materials of direct animal origin are used in the current manufacturing process.

Raw Material:	(b) (4)
Vendor:	
Source:	

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Raw Material: (b) (4)
Vendor:
Source:

14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**

Aflibercept is a dimeric IgG1 fusion protein. The Fc portion of human IgG1 is fused to human vascular endothelial growth factor receptor (VEGFR)-derived peptide domains. VEGFR2 extracellular Ig domain 3 is fused to the Fc region, and VEGFR1 extracellular Ig domain 2 is fused to the VEGFR2 domain. (b) (4) The theoretical (unglycosylated) molecular weight is 96.9 kD, and the experimental molecular weight is 115 kD. The isoelectric point is 5.8-8.3.

15. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]
(b) (4)	III	(b) (4)	(b) (4)	4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	V			4	N/A

[1] Action codes for DMF Table:
4 – Sufficient information in application

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
510(k)	K941562	1 ml (b) (4) Syringe
510(k)	K021475	30G x ½" (b) (4) Needle
Class I exempt (letter from manufacturer)	N/A	19G x 1 ½" (b) (4) Filter Needle

16. **CONSULT STATUS:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
(b) (5)			
Environmental Assessment	Approve	7/12/11	Sarah Kennett
DMA Carton and vial labeling	Review not yet completed		Kimberly Rains
BMAB- memo for Drug Substance review	Review not yet received		Kalavati Suvarna/Patricia Hughes
BMAB- memo for Drug Product review	Review not yet received		Colleen Thomas/Patricia Hughes
EIR for Regeneron Rensselaer	Approve	6/27/11	Kalavati Suvarna/ Lakshmi Narasimhan/Kennett

17. **Inspectional Activities**

A pre-approval inspection (PAI) for aflibercept drug substance production at the (b) (4) facility was conducted (b) (4) by BMAB reviewers Kalavati Suvarna and Lakshmi Narasimhan and product reviewer Sarah Kennett. (b) (4) for manufacture of denosumab drug substance intermediate, drug substance, and formulated bulk and for QC testing. A form 483 was issued at the end of this inspection. Observations made during the inspection pertain to inadequate microbial control strategy for downstream manufacture of aflibercept drug substance and QA documents that do not assure appropriate production record review and release of commercial material. This inspection was initially classified VAI; however, final classification is pending finalization of the review by CDER OC.

18. **Recommendations on Approvability:** We recommend a Complete Response be issued to Regeneron to outline the deficiencies noted.

QUALITY UNIT ASSESSMENT

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is provided below. A review of the product immunogenicity assays is included at the end of the primary review document.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

a. **ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION**

As specified in 21 CFR 25.15(b), Regeneron states that this Biologic License Application (BLA) qualifies for a categorical exclusion to the environmental assessment (EA) requirement based on the estimated concentration of the substance at the point of entry into the aquatic environment being below 1 ppb. The expected introduction concentration (EIC) was calculated according to the 1998 "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application." Regeneron states that to their knowledge, no extraordinary circumstances exist and request exclusion from the requirement of the environmental assessment.

b. **PACKAGE INSERT**

CMC Review and comments on package insert were provided directly to the team to be incorporated into the package insert.

c. **DRUG PRODUCT LABEL**

CMC review of DP label will be generated under a separate consult to Kimberley Rains, OBP.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

A. The following deficiencies were sent to Regeneron in a communication dated June 20, 2011. Regeneron submitted replies to these deficiencies in 3 amendments to the BLA, however, these were not reviewed during the first review cycle to allow FDA staff to meet the review deadlines. Deficiencies that need to be addressed to support approval are copied here:

1. Regarding the cell banks:

(b) (4)

[redacted]

(b) (4)

(b) (4)

2. As currently presented, it is not possible to assess the appropriateness of most of the in process controls (IPCs) identified in section 3.2.S.2.2.

a. Provide data to support the IPCs. For each IPC, historical data for each lot that was used for calculating mean should be presented; the IPC historical range, mean, and standard deviation (SD) should also be included.

b. For those IPC limits set using historical mean (b) (4) SD, provide justification for setting IPC limits based on (b) (4) SDs.

c. Describe the actions taken for out-of-trend excursions (IPC values that fall outside the internal action limits). Identify any IPC that would not follow the general OOT actions and the action(s) that would be taken. For example, excursions past the limit of in vitro cell age (LIVCA), which is based on LIVCA validation data in the BLA, would require submission of a supplement supporting a new LIVCA prior to product release and should not be administered only through a general established deviation procedure and Regeneron's QA release process.

d. Section 3.2.S.2.4.1 (p. 11) states that "IPCs with limited predictive power will be removed from consideration." The IPCs identified in section 3.2.S.2.2 should not be removed without the proper submissions to the BLA.

(b) (4)

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(b) (4) [redacted]

d. Regarding hold time:

i. Provide data supporting the hold time validation acceptance criteria.

ii. Submit results (raw data) from IEF testing for the samples that did not meet acceptance criteria for hold time validation.

(b) (4) [redacted]

v. Table 13 in section 2.3.S.2 lists the completion status of processing hold times as "concurrent validation." Please clarify your intentions. Until validation of hold times is complete and data are submitted to the BLA, the hold times may not be considered part of the approved BLA process.

vi. For (b) (4) [redacted] hold times, it is stated that microbial results met their acceptance criteria "demonstrating that the evaluated hold times are acceptable for this process" (section 3.2.S.2.5.7 p. 108). However, product quality assessment was included in the study design and testing is "currently in progress." Therefore, the hold time validations are not complete, and the hold times will not be acceptable as part of the approved BLA process.

vii. Regarding media hold times (Table 78, section 3.2.S.2.5.7, p. 109), bioburden acceptance criteria are presented; however, footnote "a" states that "a bioburden specification is not applicable." The media and media solution hold studies are performed to ensure that the hold times and conditions are appropriate with respect to the quality of the solutions for use in manufacture; bioburden is a critical parameter for media and solutions, and therefore should be included in these hold studies. Hold times should be based on materials prepared and stored as they would be for use in manufacturing. Therefore, the media and solutions should be filtered and stored under conditions comparable to those used during the manufacturing process, and appropriate bioburden criteria should be set and met. Provide appropriate media and solutions hold times and validation data to justify these times.

(b) (4) [redacted]

(b) (4)

[redacted]

f. The section on Leachates from Contact Surfaces (3.2.S.2.5.9) does not provide any information on the assessments made for the components used and gives the impression that this assessment has not yet been done for the current process. Identify whether assessment of leachates for contact surfaces has been finalized and include the evaluation results for those products/steps requiring further evaluation based on your decision process.

g. Regarding the production-scale conformance batches:

i. Provide the validation protocols, including acceptance criteria.

ii. Provide the genealogy for all batches from C07003 through C07006. (b) (4) [redacted]

iii. Provide data justifying the use of (b) (4) SD outside of the historical average for those situations where (b) (4) SD was used.

iv. Provide all the validation data, including all operating parameters, performance values, and quality assessments. Include a column containing the historical ranges for each.

v. The action limits for operation and performance values were not discussed; identify any results that were outside the action limits that were identified in section 3.2.S.2.4.

vi. Regeneron's conclusion of the performance results for DS intermediate (section 3.2.S.2.5.11.1, p. 125) is that "in total, the outlying performance results comprised less than (b) (4) of the total results evaluated. These data suggests that the performance of the aflibercept manufacturing process is highly consistent." This statement is not supported by the information provided as this is not the total of the outlying performance results but is the performance results with particular results excluded. Two paragraphs earlier, it is stated that "in total, 123 of 2472 performance results (72 of 616 performance parameters) fell outside the (b) (4) standard deviation historical limits." Therefore, the actual outlying performance results comprised (b) (4) of the total results evaluated. No data were provided to allow an assessment of the results that were excluded by Regeneron. In your response to item g(iii), identify those datapoints that were excluded. For each of these datapoints, provide a justification for the validity of its exclusion.

vii. Clarify why there is a minimum load requirement for the (b) (4) (b) (4) [redacted] (section 3.2.S.2.5.10.2, p. 133).

viii. Provide good quality reproductions of the IEF gels and individual band quantitation data for the conformance lots and any additional lots from which data will be used for setting specification acceptance criteria.

4. Regarding DS characterization:
   a. Provide data for characterization of higher order (secondary/tertiary) structure in addition to the disulfide bonding assessment obtained using peptide mapping.
   b. Regarding MALLS analyses:
      i. Provide justification of [redacted] (b) (4) for performing an assessment to detect high molecular weight species. Include any data identifying if there are HMW species that are no longer detected [redacted] (b) (4)
      ii. Provide enlargements of the entire chromatograph for SEC-MALLS rather than enlargement only for the region containing the dimer species.
   c. Regarding MS analysis:
      i. Provide results from a blank run.
      ii. Provide an enlarged view of the spectra surrounding the main aflibercept peaks and clarification of the "satellite" peaks/deconvolution artifacts.

[redacted] (b) (4)

   e. Provide relative percentage data for [redacted] (b) (4) for each of the lots assessed.
   f. Provide the complete integrated peak area analyses for [redacted] (b) (4). In addition, there are unidentified peaks with percent areas that appear to be greater than [redacted] (b) (4) (based on the apparent size of [redacted] (b) (4) identification of such peaks should have been determined. Submit data on all these peaks and the complete integrated peak area analysis to the BLA.
   g. Provide the VEGF165 binding stoichiometry data for lot C08001M440.
   h. [redacted] (b) (4) and [redacted] (b) (4) should be assessed as process related impurities; there is no discussion of either of these cell culture components in either the validation section or the impurities section. Provide data regarding the amount present in drug substance or validate clearance of these process related impurities by the purification process.

[redacted] (b) (4)

j. Regarding product size-related impurities:

i. It is stated in section 3.2.S.3.2.3.1.2 (p. 26) that al[redacted] (including [redacted] were "determined to possess the correct, predicted N-terminal sequence of aflibercept." However, Table 13 of that section states that the N-terminal sequence of [redacted] was "not determined." Clarify this discrepancy.

ii. Table 13 lists only 3 N-terminal sequences for the non-reduced [redacted] species [redacted] while an additional sequence with truncation at [redacted] is listed in Table 12. It is not clear which species corresponds to the structure depicted for the [redacted] species. Please clarify.

iii. Provide information regarding the locations of the truncations for species that initiate at the N-terminus.

iv. Provide to section 3.2.S.3.2.3.2 Table 14 the results for % aggregate for all lots, as these data should be available, and update the aggregation range to include the additional data.

[redacted] There appear to be HMW bands in the reduced SDS-PAGE gel shown in Figure 7 (section 3.2.S.3.2.3.1.2). However, in section 3.2.S.3.2.3.2 (p. 34), it is stated that "the lack of high molecular weight species in SDS-PAGE analysis suggests that aflibercept aggregates formed under stress conditions are reversible in SDS-PAGE and non-covalent in nature." It appears that there are discrepancies in the identification of the nature of the aflibercept aggregates; in addition, SDS-PAGE analyses of material stored under stress conditions are not described in this section. Clarify the apparent discrepancies and include data supporting the statements and conclusions made.

k. ISOQUANT analysis was used for the characterization of deamidation. Given that deamidation of asparagine can result in non-isomerized aspartate, and, therefore, that this assay would not monitor all potential deamidation reactions, provide information on non-isomerized forms of deamidated species that may be present.

5. Regarding specifications:

a. Provide justification for a proposed bioassay acceptance criterion of [redacted] for DS intermediate, when the proposed acceptance criterion for DS is [redacted]

b. Provide justification for a proposed charge heterogeneity acceptance criterion of [redacted] for DS intermediate, when the proposed acceptance criterion for DS is [redacted]

c. Provide justification for the proposed DS protein concentration acceptance criterion of [redacted]

d. Describe and justify the use of stability data for setting proposed acceptance criteria for release (section 3.2.S.4.5.1). Include an assessment of how release at extremes that are supported by stability data would not allow for failure of aflibercept by the expiration timeline.

6. Regarding analytical procedures:
   a. Clarify the statement that appearance and color and pH methods are "based on" USP and Ph. Eur. If different from the compendial method, provide information on the changes from compendia and the validation data where appropriate.
   b. Provide data supporting the use of [redacted] for the SEC assay that is intended to monitor levels of aggregate.

7. Provide batch analysis data for all DS intermediate lots and equivalent lots used as [redacted]

8. Regarding reference standard (RS):
   a. In section 3.2.S.5.1.2 Regeneron states that Qualification of future lots of reference standard will be performed using the commercial specifications. Please be aware that qualification of a RS based on the lot release acceptance criteria is not necessarily acceptable. Criteria must be in place to prevent drift in product quality. For example, assays that use RS as a comparator, such as the potency assay, would require a new RS to be very similar to the existing reference standard, and those requirements should be reflected in the protocol for qualification of a new RS. Please note that release of new RS would require submission of the protocol and data to the BLA for approval prior to use.
   b. Characterization results for the current RS lot [redacted] at qualification and data from earlier RS lots at the 24 month stability time point (section 3.2.S.5.1.3, Table 3) show that the molecular weights for HMW species and main species determined by SEC-MALLS were significantly lower for the 24 month stability samples than for the fresh qualification sample, indicating that there could have been an [redacted] change in each monomer during storage. Address the apparent instability of the RS under its storage condition of -80°C.

9. Regarding DS container closure:
   a. Regarding the microbial aerosol challenge (section 3.2.S.6.1.7.3), identify the manufacturing steps involving [redacted] and justify the use of [redacted] during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing [redacted] is the same as the [redacted]
   b. Justify the use of the [redacted] for the leachable/extractable testing (section 3.2.S.6.1.4, Table 2).
   c. Clarify the calculation of [redacted] (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than [redacted]
   d. Justify the methods used for concentration of samples from extractables testing, given that the concentration methods could lead to loss of some types of extractables.

10. Regarding DS stability:
    a. For SDS-PAGE and IEF testing, provide good quality reproductions of the gels containing the first and last available timepoints for all lots on stability.

b. Provide freeze-thaw stability data for DS intermediate and DS. Alternatively, provide the controls that are in place to prevent thawed DS intermediate or DS from being refrozen and thawed again for use in future manufacturing.

11. Regarding post-approval stability protocol and stability commitment:
a. Regeneron states in both section 3.2.S.7.2 and in the overall quality summary that one lot of drug substance will be [redacted] (b) (4) and that any failures will be reported. As drug substance intermediate may be stored for an extended time, it should also [redacted] (b) (4) Include all stability data for drug substance and drug substance intermediate in the AR.
b. We note that drug substance stability allows a [redacted] (b) (4) Identify the causes for this change in protein concentration. We also note that color and appearance are not tested to the same criteria at stability as at release. Please justify these differences.

12. Provide stability data for all formulated bulk lots tested. Include data for all timepoints available and provide good quality reproductions of SDS-PAGE and IEF gels for the first and last available timepoints for each of the lots.

13. Regeneron's formulation development studies to support upper and lower ranges and effect on product quality is ongoing. Very limited data were submitted to the BLA in section 3.2.P.2.1.4. Conclusions made based on these limited data need further justification:
a. Provide updated stability data and justification of conclusions made based on only 2 months of real time data. The submitted 1st and 2nd month timepoints for the "proven acceptable range" studies have no potency assessments for any of the completed portions of the study or for any available time point for the real time or accelerated portions of the study, no SDS-PAGE or IEF assessments for the real time or accelerated portions of the study, and no instron, imaged microscopy, FTIR assessments. Provide updated data to this section.
b. The studies for assessment of effects of [redacted] (b) (4) on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude [redacted] (b) (4)
c. Update the data from the studies assessing effects of [redacted] (b) (4) on product quality.
d. Update the data from the studies assessing the effects of manufacturing steps on product quality.
e. Regarding the assessment of effects of exposure to [redacted] (b) (4) on stability, section 3.2.P.2.2.1.7.3 states that the control was DP that was "not exposed to [redacted] (b) (4)" Clarify this statement; i.e. was DP manufactured without the use of [redacted] (b) (4)

14. Regarding manufacturing process development:

a. On the subject of comparability:

(b) (4)

Regarding the decay profiles, as no primary data were provided, the degradation profile of individual aspects (e.g. the identity of HMW variants, LMW variants, charge variants that are generated) cannot be assessed; provide appropriate data to the BLA for review.

iii. Provide assessments of rates of degradation for the stressed (45°C) stability comparability studies based on statistical analyses.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

15. There are inconsistencies among the quality overall summary (2.3.I) Table 1, the manufacturer information in sections 2.3.P and 3.2.P, and the attachment to FDA Form 356h regarding manufacturers and the activities occurring at each manufacturing site. Update all of the sections to reflect the correct manufacturing and testing activities occurring at each site for each of the drug product presentations.

16. Regarding the description of the manufacturing process:

(b) (4)

17. Regarding controls of critical steps and intermediates:
a. Submit formulated bulk stability data for all lots placed on stability. Include all time points available.

b. In sections 3.2.P.3.4, it is not clear what type(s) of limit are associated with the given parameters and criteria. The limits are listed as action limits in section 3.2.P.3.3. Clarify and discuss the action taken. (b) (4) [redacted]

18. Regarding process validation

a. Formulated bulk – (b) (4) [redacted]

b. Drug Product:

i. Provide the validation report for the manufacturing of the vial and (b) (4) [redacted]

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20. According to the container closure section for (b) (4) vials (3.2.P.7 p.5), the secondary packaging contains one vial, one filtration needle, and one package insert; there is no mention of a syringe or delivery needle. Clarify the contents of the final packaging.

(b) (4)

22. Regarding the post approval stability commitment:

(b) (4)

23. Regarding the adventitious agents safety evaluation:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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IV. ADMINISTRATIVE

A. Reviewers' Signatures

Product Quality Reviewer: Sarah Kennett, Ph.D. Sarah Kennett 7/21/11

Product Quality Reviewer: Sang Bong Lee, Ph.D. Sang Bong Lee 7/21/11

B. Endorsement Block

Product Division Team Leader: Chana Fuchs, Ph.D. 7/21/11

Product Division Deputy Director: Patrick Swann, Ph.D. Patrick Swann 7-21-11

Product Division Director: Kathleen Clouse, Ph.D. Kathleen Clouse 7/22/2011

C. cc Block

OBP Office Director: Steven Kozlowski, M.D.
Clinical Division Director (DTOP): Renata Albrecht, M.D.
Division of Monoclonal Antibodies File: BLA STN 125387

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies

The Quality Team Leader's Executive Summary

From: **Chana Fuchs, PhD**
Division of Monoclonal Antibodies (DMA),
CDER, FDA

Through: **Patrick Swann, PhD**
Deputy Director DMA

Kathleen Clouse, PhD
Director, DMA

BLA Number: **125387/0**
Product: **aflibercept (Eylea™)**
Sponsor:

Date of Review: **19-July-2011**
Due Date of TL Memo: **22-July-2011**

INDEX

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, has completed review of BLA 125387/0 for aflibercept (Eylea™) manufactured by Regeneron Pharmaceuticals. The data submitted in this application are not sufficient to support a conclusion that the manufacture of aflibercept is well controlled, and will lead to a product that is pure and potent for the duration of the product shelf life. From a CMC standpoint the division is recommending a Complete Response be issued to Regeneron to outline the deficiencies noted below and the information and data that will be required to support approval.

A list of deficiencies and requested information is provided in section IV of this TL summary. Some overarching topics include lack of required information regarding validation and control of the manufacturing process, insufficient data to support the comparability of the DP vial (b) (4) insufficient stability data to support the requested shelf life of the drug product, insufficient data regarding validation or qualification for some of the release and stability assays, and inconsistencies and discrepancies in the data provided.

Pending review of additional information being requested, final specifications and product shelf life have not been assigned. Final specifications and product shelf life can be finalized once the full data package is available for assessment.

II. APPROVAL LETTER INFORMATION

Not applicable as DMA is recommending a Complete Response be issued.

III. POST MARKETING COMMITMENTS AND REQUIREMENTS

DMA CMC PMCs

Not applicable as DMA is recommending a Complete Response be issued.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

A. The following deficiencies were sent to Regeneron in a communication dated June 20, 2011. Regeneron submitted replies to these deficiencies in 3 amendments to the BLA, however, these were not reviewed during the first review cycle to allow FDA staff to meet the review deadlines. Deficiencies that need to be addressed to support approval are copied here:

1. Regarding the cell banks:

(b) (4)

(b) (4)

2. As currently presented, it is not possible to assess the appropriateness of most of the in process controls (IPCs) identified in section 3.2.S.2.2.

a. Provide data to support the IPCs. For each IPC, historical data for each lot that was used for calculating mean should be presented; the IPC historical range, mean, and standard deviation (SD) should also be included.

b. For those IPC limits set using historical mean (b) (4) SD, provide justification for setting IPC limits based on (b) (4) SDs.

c. Describe the actions taken for out-of-trend excursions (IPC values that fall outside the internal action limits). Identify any IPC that would not follow the general OOT actions and the action(s) that would be taken. For example, excursions past the limit of in vitro cell age (LIVCA), which is based on LIVCA validation data in the BLA, would require submission of a supplement supporting a new LIVCA prior to product release and should not be administered only through a general established deviation procedure and Regeneron's QA release process.

d. Section 3.2.S.2.4.1 (p. 11) states that "IPCs with limited predictive power will be removed from consideration." The IPCs identified in section 3.2.S.2.2 should not be removed without the proper submissions to the BLA.

3. For DS process validation:

(b) (4)

(b) (4)

[redacted] (b) (4)

d. Regarding hold time:

i. Provide data supporting the hold time validation acceptance criteria.

ii. Submit results (raw data) from IEF testing for the samples that did not meet acceptance criteria for hold time validation.

[redacted] (b) (4)

v. Table 13 in section 2.3.S.2 lists the completion status of processing hold times as "concurrent validation." Please clarify your intentions. Until validation of hold times is complete and data are submitted to the BLA, the hold times may not be considered part of the approved BLA process.

vi. For [redacted] (b) (4) hold times, it is stated that microbial results met their acceptance criteria "demonstrating that the evaluated hold times are acceptable for this process" (section 3.2.S.2.5.7 p. 108). However, product quality assessment was included in the study design and testing is "currently in progress." Therefore, the hold time validations are not complete, and the hold times will not be acceptable as part of the approved BLA process.

vii. Regarding media hold times (Table 78, section 3.2.S.2.5.7, p. 109), bioburden acceptance criteria are presented; however, footnote "a" states that "a bioburden specification is not applicable." The media and media solution hold studies are performed to ensure that the hold times and conditions are appropriate with respect to the quality of the solutions for use in manufacture; bioburden is a critical parameter for media and solutions, and therefore should be included in these hold studies. Hold times should be based on materials prepared and stored as they would be for use in manufacturing. Therefore, the media and solutions should be filtered and stored under conditions comparable to those used during the manufacturing process, and appropriate bioburden criteria should be set and met. Provide appropriate media and solutions hold times and validation data to justify these times.

(b) (4)

[redacted]

f. The section on Leachates from Contact Surfaces (3.2.S.2.5.9) does not provide any information on the assessments made for the components used and gives the impression that this assessment has not yet been done for the current process. Identify whether assessment of leachates for contact surfaces has been finalized and include the evaluation results for those products/steps requiring further evaluation based on your decision process.

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i. Provide the validation protocols, including acceptance criteria.

ii. Provide the genealogy for all batches from C07003 through C07006 (b) (4)

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iii. Provide data justifying the use of (b) (4) SD outside of the historical average for those situations where (b) (4) SD was used.

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v. The action limits for operation and performance values were not discussed; identify any results that were outside the action limits that were identified in section 3.2.S.2.4.

vi. Regeneron's conclusion of the performance results for DS intermediate (section 3.2.S.2.5.11.1, p. 125) is that "in total, the outlying performance results comprised less than (b) (4) of the total results evaluated. These data suggests that the performance of the aflibercept manufacturing process is highly consistent." This statement is not supported by the information provided as this is not the total of the outlying performance results but is the performance results with particular results excluded. Two paragraphs earlier, it is stated that "in total, 123 of 2472 performance results (72 of 616 performance parameters) fell outside the (b) (4) standard deviation historical limits." Therefore, the actual outlying performance results comprised (b) (4) of the total results evaluated. No data were provided to allow an assessment of the results that were excluded by Regeneron. In your response to item g(iii), identify those datapoints that were excluded. For each of these datapoints, provide a justification for the validity of its exclusion.

vii. Clarify why there is a minimum load requirement for the (b) (4) (b) (4) section 3.2.S.2.5.10.2, p. 133).

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i. Provide justification of (b) (4) for performing an assessment to detect high molecular weight species. Include any data identifying if there are HMW species that are no longer detected (b) (4)

ii. Provide enlargements of the entire chromatograph for SEC-MALLS rather than enlargement only for the region containing the dimer species.

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i. Provide results from a blank run.

ii. Provide an enlarged view of the spectra surrounding the main aflibercept peaks and clarification of the "satellite" peaks/deconvolution artifacts.

(b) (4)

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g. Provide the VEGF165 binding stoichiometry data for lot C08001M440.

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(b) (4) (b) (4)

(b) (4)

j. Regarding product size-related impurities:

i. It is stated in section 3.2.S.3.2.3.1.2 (p. 26) that all (b) (4) (including (b) (4) were "determined to possess the correct, predicted N-terminal sequence of aflibercept." However, Table 13 of that section states that the N-terminal sequence of (b) (4) was "not determined." Clarify this discrepancy.

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b. Justify the use of the [redacted] leachable/extractable testing (section 3.2.S.6.1.4, Table 2).
c. Clarify the calculation of [redacted] (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than [redacted].
d. Justify the methods used for concentration of samples from extractables testing, given that the concentration methods could lead to loss of some types of extractables.

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b. The studies for assessment of effects of (b) (4) on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude (b) (4)

c. Update the data from the studies assessing effects of (b) (4) on product quality.

d. Update the data from the studies assessing the effects of manufacturing steps on product quality.

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14. Regarding manufacturing process development:

a. On the subject of comparability:

i. The comparative stability study was not complete at the time of BLA (b) (4) Regarding the decay profiles, as no primary data were provided, the degradation profile of individual aspects (e.g. the identity of HMW variants, LMW variants, charge variants that are generated) cannot be assessed; provide appropriate data to the BLA for review.

iii. Provide assessments of rates of degradation for the stressed (45°C) stability comparability studies based on statistical analyses.

iv. Provide data with respect to charge variants supporting the comparability of stability of DP in vials (b) (4) (b) (4)

(b) (4)

b. Regarding container closure:

(b) (4)

(b) (4)

15. There are inconsistencies among the quality overall summary (2.3.I) Table 1, the manufacturer information in sections 2.3.P and 3.2.P, and the attachment to FDA Form 356h regarding manufacturers and the activities occurring at each manufacturing site. Update all of the sections to reflect the correct manufacturing and testing activities occurring at each site for each of the drug product presentations.

16. Regarding the description of the manufacturing process:

(b) (4)

17. Regarding controls of critical steps and intermediates:
    a. Submit formulated bulk stability data for all lots placed on stability. Include all time points available.
    b. In sections 3.2.P.3.4, it is not clear what type(s) of limit are associated with the given parameters and criteria. The limits are listed as action limits in section 3.2.P.3.3. Clarify and discuss the action taken.

(b) (4)

18. Regarding process validation
    a. Formulated bulk – (b) (4):

(b) (4)

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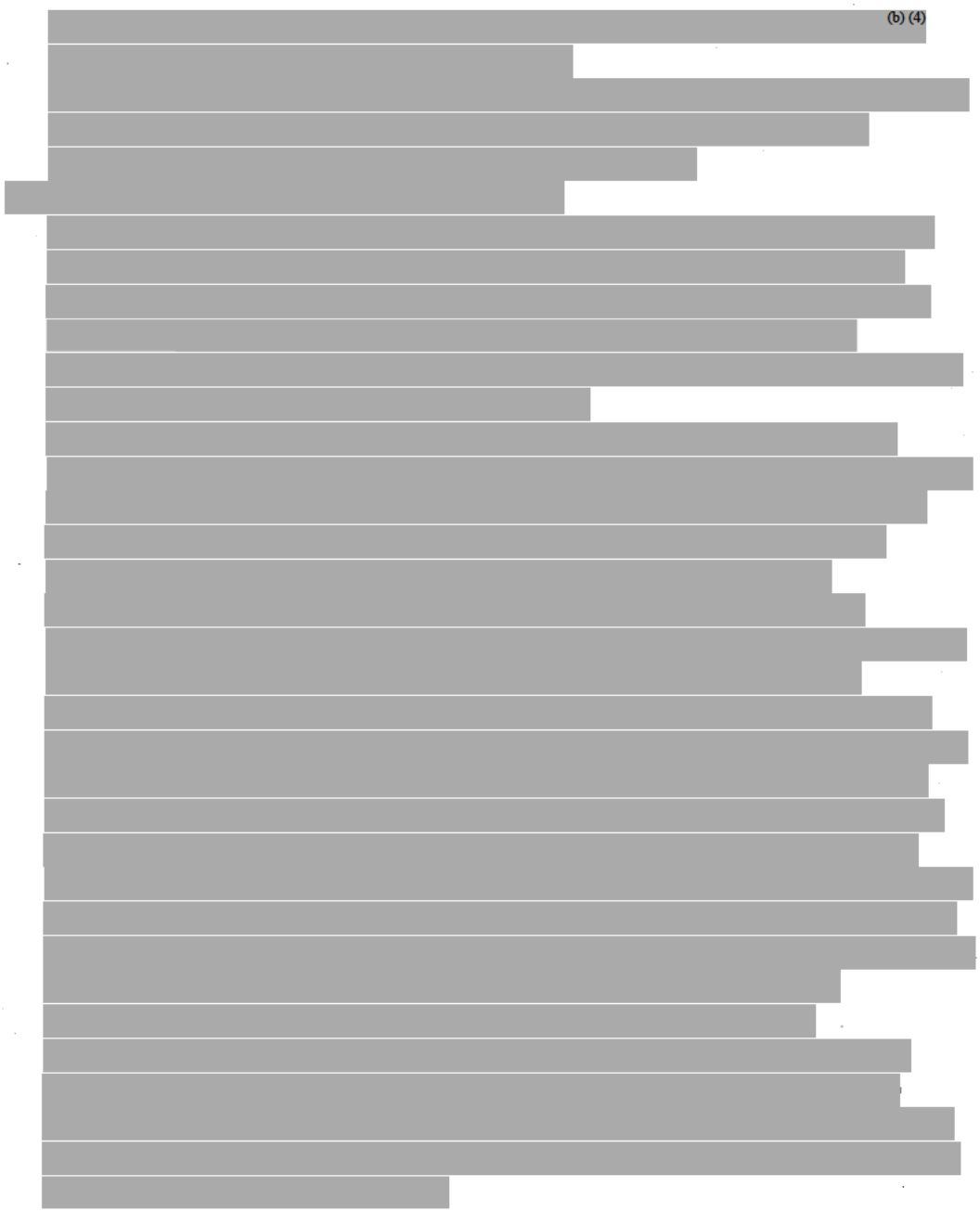
(b) (4)



20. According to the container closure section for (b) (4) vials (3.2.P.7 p.5), the secondary packaging contains one vial, one filtration needle, and one package insert; there is no mention of a syringe or delivery needle. Clarify the contents of the final packaging.

(b) (4)

22. Regarding the post approval stability commitment:
    a. Include a requirement for reporting stability data from every lot put on stability protocols in the annual report.

(b) (4)

23. Regarding the adventitious agents safety evaluation:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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V. EXECUTIVE SUMMARY

A list of deficiencies and requested information is provided in section IV, above. Some overarching topics include lack of required information regarding validation and control of the manufacturing process, insufficient data to support the comparability of the Drug product (DP) vials (b) (4) insufficient stability data to support the requested shelf life of the drug product, insufficient data regarding validation or qualification for some of the release and stability assays, and inconsistencies and discrepancies in the data provided.

Pending review of additional information being requested, final specifications and product shelf life have not been assigned. These should be finalized once the full data package is available for assessment.

A. Description of Aflibercept (Eylea) Drug Product and Drug Substance

Aflibercept is a genetically engineered homodimeric protein that is generated by the in-line fusion of Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2, which in turn are fused to the Fc region of human IgG.

Aflibercept acts as a soluble decoy receptor that binds Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) with higher affinity than their

natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Eylea (aflibercept ophthalmic solution) Drug Product is supplied as a sterile, preservative free liquid formulation of 2 mg/0.05mL (40 mg/mL) aflibercept in sterile, single use vials (b) (4) for intravitreal injection.

(b) (4)

Each carton of Eylea **vial** contains one single-use 3-mL glass vial of EYLEA, **one** 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents (filter needle not to be used for intravitreal injection), **one** 30-gauge x ½-inch needle for intravitreal injection, **one** 1-mL plastic syringe for administration, and one package insert

(b) (4) vial presentations are intended to deliver 0.05 mL (50 microliters) of Eylea (40 mg/mL) aqueous solution.

Formulation: Eylea drug product is a sterile solution of 40 mg/ml aflibercept in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% (w/v) polysorbate 20, and 5% sucrose, pH 6.2.

Storage: Eylea should be refrigerated at 2°C to 8°C, protected from light. Eylea should not be frozen.

There is no preservative in the formulation so any unused portion of the vial (b) (4) must be discarded.

Container Closure information:

(b) (4)

(b) (4)

(b) (4)

DS intermediate is (b) (4)

Aflibercept **Drug Substance** (DS) is (b) (4) aflibercept formulated in 10 mM sodium phosphate, pH 6.2.

Formulated Bulk: (b) (4)

(b) (4)

The proposed action is subject to the categorical exclusion from Environmental Assessment listed in 21 CFR Part 25.31(c).

B. Clinical Trial Information

Indication: EYLEA™ (aflibercept injection) is proposed for the treatment of patients with neovascular (Wet) Age-Related Macular Degeneration (AMD).

Route of Administration: ophthalmic intravitreal injection

The proposed dosage regimen is 2 mg (50 microliters) administered by intravitreal injection once every 2 months following 3 initial monthly injections of 2 mg (50 microliters).

Clinical efficacy and safety data are from studies VIEW1 and VIEW2, two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD, form the basis of the application. The primary efficacy endpoint was the proportion of patients in the Per-Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Four randomly assigned dosing regimens were (A) Eylea 2 mg administered every 8 weeks following 3 initial monthly doses; (B) Eylea 2 mg administered every 4 weeks; (C) Eylea 0.5 mg administered every 4 weeks; and (D) ranibizumab 0.5 mg administered every 4 weeks. Arms A and B were shown to have efficacy that was non-inferior and clinically equivalent to arm D.

C. Stability

Drug Product

Regeneron proposed a (b) (4) shelf life for DP vials and (b) (4) stored at 2-8°C, protected from light. Expiration dating of Eylea drug product has not yet been finalized as additional information is being requested from the sponsor.

Drug product is intended to be stored at 2-8°C

Aflibercept-Eylea is light sensitive and should not be exposed to excessive light. A photostability study identified impacts to size variants, charge variants, and particulates.

Eylea drug product formulation does not contain a preservative. Vials (b) (4) are single use.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

[redacted]

E. **Mechanism of Action**

Aflibercept acts as a soluble decoy receptor that binds Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (KD) for aflibercept binding to human VEGF-A_{165} is 0.55 pM and to human VEGF-A_{121} is 0.36 pM. The KD for binding to human PlGF-2 is 39 pM.

VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability.

(b) (4)

[redacted]

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VI. SIGNATURE BLOCK

Name and Title	Signature and Date
Patrick Swann, Ph.D,, Deputy Director Division of Monoclonal Antibodies Kathleen Clouse, Ph.D., Director, Division of Monoclonal Antibodies	7-21-11 07/22/2011
Chana Fuchs, PhD Product Quality Team Leader Division of Monoclonal Antibodies	7/21/11
Sarah Kennett, PhD Product Reviewer Division of Monoclonal Antibodies Sang Bong Lee, PhD Product Reviewer Division of Monoclonal Antibodies	7/21/11 7/21/11

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125387/0 | **Applicant:** Regeneron Pharmaceuticals, Inc. | **Stamp Date:** Feb. 18, 2011

Established/Proper Name: Aflibercept | **BLA/NDA Type:** Priority

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
❑ including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	N	Not necessary
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
❑ PI –non-annotated	Y	
❑ PI –annotated	Y	
❑ PI (electronic)	Y	
❑ Medication Guide	N	Not necessary for filing
❑ Patient Insert	N	Not necessary for filing
❑ package and container	Y	
❑ diluent	Y N	Not applicable
❑ other components	Y	
❑ established name (e.g. USAN)	Y	
❑ proprietary name (for review)	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
~~Overall CTD Table of Contents [2.1]~~	~~N~~	~~Not necessary~~
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	Y	
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	Not necessary
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y	
❑ control of critical steps and intermediates o justification of specifications o stability	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ ~~manufacturing process development~~ (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance		
❑ control of drug substance		
o specifications		
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation		
o batch analyses		
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	Y N	Not applicable
o container-closure integrity	Y Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation		
o Component, container, closure depyrogenation		

CTD Module 3 Contents	Present?	If not, justification, action & status
and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y	Cross-references for DMFs for a number of components were not included in the submission. These were requested and have been submitted to the BLA.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development o preservative effectiveness o container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through	Y N Y N Y N Y N Y N Y N Y **N**	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N	
❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer sterilization validation o Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part	Y N Y N	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y Y Y	
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	Y Y Y N	This section was originally incomplete. Complete records were requested and submitted to the BLA. Not applicable
Literature references and copies [3.3]	N	Not necessary

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
process, from material used in clinical trial to commercial production lots		
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	 Y Y Y	Rabbit pyrogen testing was not originally included. This was requested and has been submitted to the BLA.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Not applicable
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? (Yes) No

---

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sarah Kennett — 4/12/11

Product Quality Reviewer(s) — Date

[signature] — 4/12/11

Branch Chief/Team Leader/Supervisor — Date

Kathleen Clouse — 04/14/2011

Division Director — Date

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y		
Introduction to the summary documents (1 page) [2.2]	Y		
Quality overall summary [2.3]	Y		
❑ Drug Substance	Y		
❑ Drug Product	Y		
❑ Facilities and Equipment	Y		
❑ Adventitious Agents Safety Evaluation	Y		
❑ Novel Excipients		N	OBP Lead; no novel excipients
❑ Executed Batch Records	Y		OBP Lead
❑ Method Validation Package	Y		For drug substance and drug product endotoxin and bioburden methods (drug product in section P.3.5). Container closure integrity test validation not included in the BLA. OBP lead for other methods.
❑ Comparability Protocols	Y	N	OBP Lead

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	N	Defer to OBP
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y		
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y		
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y	N	Defer to OBP
❑ control of critical steps and intermediates o justification of specifications	Y		OBP Lead. Bioburden and endotoxin related information is included.

CTD Module 3 Contents	Present?		If not, justification, action & status
○ analytical method validation ○ reference standards ○ stability			
❑ process validation (prospective plan, results, analysis, and conclusions)	Y		Microbial control is discussed and data are presented
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	N	Defer to OBP
❑ characterization of drug substance	Y	N	Defer to OBP
❑ control of drug substance ○ specification ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses ○ consistency (3 consecutive lots) ○ justification of specs.	Y		Microbiology information included; OBP lead on other aspects.
❑ reference standards	Y	N	Defer to OBP
❑ container closure system	Y		Description, container-closure integrity, sterilization information included.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y		Bioburden testing; OBP lead on other stability test
Drug Product [3.2.P]			
❑ description and composition	Y		
❑ pharmaceutical development	Y		Microbial attributes section incomplete. No method validation for container closure integrity test.
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y		
❑ batch formula	Y	N	OBP lead.
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y		
❑ controls of critical steps and intermediates	Y		Microbial controls.

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y	Sterility assurance validation data is scant and incomplete.
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	OBP lead.
❑ control of drug product (justification of specifications; analytical method validation)	Y	Sterility and endotoxin.
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s)	Y	Incomplete description and information. LOAs not included for closure DMFs.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	Microbial tests and container closure integrity.
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent	Y N	Not applicable - no diluent supplied.
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y N	
❑ control of excipients (justification	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of	Y N	
specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N Y N Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	Not applicable.
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination	Y	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed	Y N	OBP lead.

CTD Module 3 Contents	Present?	If not, justification, action & status
bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y N	OBP lead.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	OBP lead.
Literature references and copies [3.3]	Y N	OBP lead.

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	N Y Y Y Y Y Y Y	See comments below.
includes appropriate process validation data for the manufacturing process at the commercial production facility?	N	Process validation data for sterility assurance is scant and incomplete.
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y	
includes data demonstrating consistency of manufacture	Y N	OBP lead.
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	OBP lead.
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	OBP lead.
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	OBP lead.

Examples of Filing Issues	Yes?	If not, justification, action & status
certification that all facilities are ready for inspection	Y	Facilities listed; certification that they are ready for inspection is included.
data establishing stability of the product through the proposed dating period and a ~~stability protocol describing the test~~ methods used and time intervals for product assessment.	Y N	OBP lead.
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	Y N N Y N Y	Rabbit pyrogen test data not included. OBP lead.
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	OBP lead.
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y	Sterility assurance validation data is scant and incomplete.
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	Not applicable; original BLA

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Fileable with reservations due to the extent of missing information for drug product. If the BLA is filed, the drug product quality sections (for each drug product presentation) will require extensive amendment.

Recommendation (circle one) File RTF

18 Mar 2011

Reviewer: Kalavati Suvarna; Colleen Thomas Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: 3/21/11
(signature/ date)

Division Director: for RF
(signature/ date) 3/21/11