CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review #2

Date	November 16, 2011
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	125387
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Submission	February 18, 2011
PDUFA Goal Date	November 18, 2011
Proprietary Name / Established (USAN) names	Eylea (aflibercept)
Dosage forms / Strength	40 mg/mL solution for intravitreal injection
Proposed Indication(s)	treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD)
Recommended:	Approval

1. Introduction

VEGF Trap (aflibercept injection) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc. VEGF Trap is a specific antagonist that binds and inactivates circulating VEGF and PlGF (placental growth factor 1) in the blood stream and in the extravascular space. In comparison, pegaptanib (Macugen) is an inhibitor of the VEGF165 isomer and ranibizumab (Lucentis) and bevacizumab (Avastin) are inhibitors of all VEGF-A isomers.

Throughout this review, Eylea (aflibercept) may be alternately referred to by some disciplines as VEGF Trap.

2. Background

The review clock for this BLA was extended to November 18, 2011, based on a major amendment (August 12, 2011, amendment) submitted within the last 90 days of the review cycle.

The original Quality Team Leader's Executive Summary and the original Product Quality Review recommended a CR and delineated significant deficiencies found during the initial review cycle. All the issues identified were sufficiently addressed in the additional data provided by Regeneron. Since the original Product Quality Review and original Quality Team Leader memo, (b) (4) (b) (4)

[redacted] Any proposed approval would cover [redacted] the 40 mg/mL vial filled at [redacted]

3. Product Quality

From the Product Quality Review dated 11-15-11:

DRUG PRODUCT SPECIFICATIONS:

Table 1: 40 mg/mL Filled Drug Product Release Specification

Filled Unlabeled Container Test	Analytical Method	Acceptance Criterion
Appearance	Ph.Eur. 2.2.1. Ph.Eur. 2.9.20	a. Not greater than turbidity standard III b. Essentially free from visible particulates
Color	Ph. Eur. 2.2.2	Not greater than reference standard BY6
pH	USP <791>. Ph. Eur. 2.2.3	5.9 – 6.5
Identity by Western Blot (αR2)	Immunoblotting	Conforms to reference standard
Total Protein Content (A_{280})	UV Spectrophotometry	[redacted] mg/mL
Potency by Cell-based Bioassay	Cell-based assay	[redacted] %
Potency by Binding Assay	ELISA	[redacted]
Purity by SDS-PAGE		
Reduced, Coomassie	Slab gel electrophoresis	Aflibercept main band [redacted] total band area
Non-Reduced, Coomassie a. % main band b. % non-reduced band 1 (NR1)	Slab-gel electrophoresis	a. Aflibercept main band [redacted] total band area b. [redacted]
Purity by Size Exclusion HPLC a. % main peak b. % aggregate	Size exclusion HPLC/UV	a. Aflibercept main peak [redacted] total peak area b. [redacted]
[redacted]	[redacted]	[redacted]

Oligosaccharide Profile %0SA %1SA %2SA %3SA	Normal-phase HPLC/fluorescence	(b) (4)
Isoelectric Focusing a. Profile b. Total area of bands 3 – 9	Slab gel electrophoresis	a. Principal bands (b) (4) of test article correspond in position to principal bands (b) (4) of reference standard. b. Total area of bands (b) (4)
Isoaspartate Assay	Enzyme-linked detection of isoaspartate with reversed phase HPLC/UV	(b) (4) mol isoaspartate/mol aflibercept
Endotoxin content	USP <85>, Ph. Eur. 2.6.14 Limulus Amebocyte Lysate Kinetic Turbidimetric Assay	< 0.4 EU/mL
Particulate Matter	USP <789>, Ph. Eur. 2.9.19	(b) (4)
Sterility	USP <71>, Ph. Eur. 2.6.1	Meets USP, EP requirements
Volume in Container	USP <1> Ph. Eur. 2.9.17	(b) (4) minimum withdrawable content

[a] Only required if the microscopic method is used.

Table 2: 40 mg/mL Finished Drug Product Release Specification

Finished Container Test	Analytical Method	Acceptance Criterion
Appearance	Ph.Eur. 2.2.1. Ph.Eur. 2.9.20	a. Not greater than turbidity standard III b. Essentially free form visible particulates
Color	Ph. Eur. 2.2.2	Not greater than reference standard BY6
Identity by Western Blot (αR2)	Immunoblotting	Conforms to reference standard.
Total Protein Content (A_{280})	UV Spectrophotometry	36 – 44 mg/mL
Labeling	Visual inspection	Labeling matches label masters

Regarding Table 1 and Table 2, above, the difference between filled DP and finished DP is labeling and packaging.

CONTAINER CLOSURE

For US distribution, the carton will contain the vial, syringe, filter needle, delivery needle, and physician package insert.

INSPECTIONS

Per a November 14, 2001, email communication from CDER, Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment, New Drug Manufacturing Assessment Branch, there are no pending or ongoing compliance actions that prevent approval of this supplement:

Drug Substance manufacturing
Regeneron Pharmaceuticals, Inc.
(b) (4)

Inspected by CDER-DMPQ from (b) (4) and classified VAI. This was pre-licensing inspection for this BLA that found operations acceptable.

Drug Substance (b) (4) Testing Laboratory
(b) (4)

Inspected by (b) (4) from (b) (4) and classified VAI. This GMP inspection found the CTL profile updated and acceptable.

Drug Substance (b) (4) Testing Laboratory
(b) (4)

Inspected by (b) (4) from (b) (4) and classified NAI. This inspection found the CTL profile updated and acceptable.

Drug product manufacturing (vials) and sterility testing
(b) (4)

Inspected by (b) (4) from (b) (4) and classified VAI. This was routine GMP inspection that found the (b) (4) and (b) (4) profile acceptable.

Drug product manufacturing (vials) and sterility testing

(b) (4)

(b) (4)

(b) (4)

DATING PERIOD

From the Quality Team Leader's Executive Summary addendum dated November 15, 2011:

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) (b) (4)

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

(b) (4)

DEFICIENCIES/POSTMARKETING COMMITMENTS

From the Quality Team Leader's Executive Summary addendum dated November 15, 2011:

The following are Product Quality Postmarketing 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 by June 1, 2012.

2. To confirm (b) (4) by the aflibercept (b) (4). 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 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.

There are no other deficiencies to be communicated.

4. Nonclinical Pharmacology/Toxicology

See original Clinical Team Leader Review dated August 12, 2011.

5. Clinical Pharmacology/Biopharmaceutics

See original Clinical Team Leader Review dated August 12, 2011.

6. Sterility Assurance

I. DRUG SUBSTANCE

From the original drug substance Product Quality Microbiology Review:

Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective.

II. DRUG PRODUCT

From the drug product Product Quality Microbiology Review finalized October 17, 2011:

The BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval. There is one product quality microbiology PMC which has been incorporated into the Product Quality Postmarketing Commitments:

> Perform at-scale hold time validation studies with three lots of 40 mg/ml aflibercept manufactured at the (b) (4) vial site. Include bioburden and endotoxin data from samples taken at the end of the hold times. Provide the results in a CBE-O supplement within one year of BLA approval.

7. Clinical/Statistical - Efficacy

See original Clinical Team Leader Review dated August 12, 2011.

8. Safety

See original Clinical Team Leader Review dated August 12, 2011.

See Section 13 of this review regarding recommendation for postmarketing risk management activities.

9. Advisory Committee Meeting

See original Clinical Team Leader Review dated August 12, 2011.

10. Pediatrics

See original Clinical Team Leader Review dated August 12, 2011.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
See original Clinical Team Leader Review dated August 12, 2011.

CDRH CONSULTATION
See original Clinical Team Leader Review dated August 12, 2011.

DDMAC
See original Clinical Team Leader Review dated August 12, 2011.

DMEPA
See original Clinical Team Leader Review dated August 12, 2011.

FINANCIAL DISCLOSURE
See original Clinical Team Leader Review dated August 12, 2011.

OSI
See original Clinical Team Leader Review dated August 12, 2011.

12. Labeling

BLA 125-387 for Eylea (aflibercept) is recommended for approval with the submitted labeling (November 17, 2011) attached in Appendix 1 of this review.

There was disagreement within the review team (Division of Transplant and Ophthalmology Products, Office of Antimicrobial Products, Office of Biotechnology Products) whether the established/official/proper name of the product should include the dosage form, which is "injection."

In this reviewer's opinion, the established/official/proper name of the product should include the dosage form, which is "injection." The use of a different name would treat this product differently than a similarly situated product, namely ranibizumab injection. Use of the name aflibercept injection for the product would make the product consistent with other ophthalmologic products including the only other products approved for use in the treatment of age-related macular degeneration.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
BLA 125-387 for Eylea (aflibercept) is recommended for approval. The clinical studies contained in this submission support the use of aflibercept injection for the treatment of neovascular AMD.

RISK BENEFIT ASSESSMENT:
Adequate and well controlled studies (VIEW #1, VIEW #2, and VGFT-OD-0702) support the efficacy of aflibercept for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). When compared to ranibizumab, all 3 doses of aflibercept were non-inferior when comparing the proportion of subjects who maintained vision (lost less than 15 letters lost in the ETDRS letter score). However, none of the doses were superior to ranibizumab. The current analysis of VIEW #1 and VIEW #2 examined the efficacy of aflibercept at Week 52.

The 2 mg Q 8 weeks dose is recommended for inclusion in the labeling for the aflibercept product. Since the 2 mg Q 8 weeks dose has fewer injections than the other 2 studied doses (2 mg Q 4 weeks and 0.5 mg Q 4 weeks), this regimen is recommended based on the theoretical benefit of less injection related risks (i.e. endophthalmitis).

The 12-Month Clinical Study Reports submitted within this BLA 125387 for VIEW #1, VIEW #2, and VGFT-OD-0702 support the safety of aflibercept injection in the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD). The most common adverse reactions (≥5%) reported in patients receiving aflibercept injection were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Product Quality and Drug Product Microbiology Reviewers now recommend approval for this product.

Clinical, Pharmacology/Toxicology, Clinical Pharmacology, and Drug Substance Product Quality Microbiology have recommended approval for this application.

The Biostatistics consultative review states that the efficacy of aflibercept compared to 0.5 mg ranibizumab has been adequately demonstrated for treatment of neovascular AMD in the Phase-3 studies included in this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
In a Postmarketing Requirement, the applicant should:

1. Provide clinical information from a 1-year (minimum) clinical trial evaluating the adverse effects, if any, on the corneal endothelium following administration of aflibercept.

The timetable submitted by the applicant on October 24, 2011, stated that the applicant will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2012
Trial Completion:	November 2015
Final Report Submission:	May 2016.

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Appendix 1

Vial Label

Vial Carton

(b) (4)

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

Signatures:

Reviewer Signature _____ 11/18/11
William Boyd, MD

Supervisor Signature _____ MD 11/18/11 Concurrence Yes ✓ No ___
Wiley Chambers, M.D.