CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761355Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date:

1. Application/Product Information

BLA number	BLA 761355
Submission Type	Complete Response (Resubmission)
Regulatory Pathway	351(a)
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Neovascular "wet" Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** Eylea HD **Non-proprietary Name/Code Name:** aflibercept **OBP Naming:** FUS: MABFRAG HUMAN (IGG1 FC); RPROTFRAG P17948 (VGFR1_HUMAN); RPROTFRAG P35968 (VGFR2_HUMAN) [VEGFTRAP]
Drug Product Description	Aflibercept is recombinant protein that contains human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). It is supplied as an 8 mg/70 µl solution formulated in (b) (4) (b) (4) arginine (b) (4) hydrochloride, (b) (4) (b) (4) histidine, (b) (4)% (w/v) sucrose, (b) (4)% (w/v) polysorbate 20, at pH 5.8.
Dosage Form	Solution for injection
Strength	8 mg/70 µl (114.3 mg/mL aflibercept)
Route of Administration	Intravitreal injection

Primary Container Closure System	2 mL (b) (4) glass vial with an (b) (4) stopper, and sealed with an aluminum seal cap with a flip-off button		
Co-packaged Product Information	Optional convenience kit containing sterile and individually packaged, including a 1mL plastic syringe, 1 ½ inch filter needle, and ½ inch delivery needle, packaged with the DP vial.		
OPQ Review Team	**Discipline**	**Primary**	**Secondary/Tertiary**
	Drug product	Chringma Sherpa	Anshu Rastogi, Rachel Novak
	Facility	Melissa Ray	Zhong Li, Thuy Nguyen, Chris Downey
	RBPM	Andrew Shiber, Hannah Lee	
	ATL	Anshu Rastogi	

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761355 for Eylea HD manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in the Complete Response are adequate to support the conclusion that the manufacture of Eylea HD is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Regeneron Pharmaceuticals, Inc (81 Columbia Turnpike, Rensselaer, NY, 12144, USA) FEI: 1000514603
- **Drug Product:** (b) (4)

b. Fill size and dosage form: Eylea HD is supplied as 8 mg/70 µl solution in a 2 mL glass vial

c. Dating Period:

- **Drug Product:** 24 months at 2 – 8°C; (b) (4)
- **Drug Substance:** (b) (4) months (b) (4) C, (b) (4)
- **For packaged products:** Optional convenience kit
  - **Component:** Sterile, individually packaged, 1mL plastic syringe
  - **Component:** 1 ½ inch filter needle
  - **Component:** ½ inch delivery needle
- **Stability Option:**
  - Limited stability data [3 full scale lots available, but not through the dating period (and the applicant is committed to continue stability testing)]
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Eylea HD is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

- PMC 4496-1: Postmarketing commitment to perform (b) (4) (b) (4)
- PMC 4496-2: Postmarketing commitment for real-world shipping studies, covering worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final DP in the proposed container closure system to ensure there is no impact to product quality and sterility of the DP.

4. Basis for Recommendation

a. Summary:

Refer to the OPQ Executive Summary under the original BLA, uploaded to CDER Informatics Platform June 25, 2023 by Anshu Rastogi for background information.

The pre-license inspections at the DP manufacturing site, (b) (4) identified a 3-item form FDA-483,

Inspectional Observations and the firm did not provide adequate responses to address these observations during the original review cycle, leading to a withhold decision for the facility and a Complete Response was issued. The information and data provided in the Resubmission and responses to information requests support that any residual issues/concerns have been addressed and the DP manufacturing facility is compliant. Overall, the manufacturing control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Eylea HD (aflibercept) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for at Regeneron Pharmaceuticals, Inc., (IOPS Rensselaer; Rensselaer, NY; FEI: 1000514603) and (b) (4) proposed for aflibercept DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with PMCs/PMRs**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate with PMCs/PMRs**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for Eylea HD (i.e., there is no specific test method described in regulation for Eylea HD that establishes an official standard of potency). We next considered whether potency is a factor for Eylea HD within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Eylea HD for purposes of § 610.61(r) because lot variability is not a

concern for Eylea HD as Eylea HD's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:
   1. (b) (4) Protocol
   2. (b) (4) Protocol
   3. (b) (4) Protocol
   4. Protocol (b) (4)
   5. Drug substance post-approval stability protocol and stability commitment

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
   1. Drug product post-approval stability protocol and stability commitment

ii. Residual risk: None

iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANSHU RASTOGI
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BLA Executive Summary
Assessment Date: June 23, 2023

1. Application/Product Information

BLA number	BLA 761355
Submission Type	Original Submission
Regulatory Pathway	351(a); Fast-track
Associated IND/BLA	IND 012462; BLA 125387
Review Designation	Priority review
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Neovascular "wet" Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR)
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** Eylea HD **Non-proprietary Name/Code Name:** aflibercept **OBP Naming:** FUS: MABFRAG HUMAN (IGG1 FC); RPROTFRAG P17948 (VGFR1_HUMAN); RPROTFRAG P35968 (VGFR2_HUMAN) [VEGFTRAP]
Drug Product Description	Aflibercept is supplied as an 8 mg/70 µl solution formulated in (b) (4) (b) (4) arginine (b) (4) hydrochloride, (b) (4) (b) (4) histidine, (b) (4)% (w/v) sucrose, (b) (4)% (w/v) polysorbate 20, at pH 5.8. Aflibercept is recombinant protein that contains human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1).
Dosage Form	Solution for injection

Strength	8 mg/70 µl (114.3 mg/mL aflibercept)		
Route of Administration	Intravitreal injection		
Primary Container Closure System	2 mL (b) (4) glass vial with an (b) (4) stopper, and sealed with an aluminum seal cap with a flip-off button		
Device Information	None		
Co-packaged Product Information	Optional convenience kit containing sterile and individually packaged, including a 1mL plastic syringe, 1 ½ inch filter needle, and ½ inch delivery needle, packaged with the DP vial.		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Chringma Sherpa	Anshu Rastogi
	Drug product	Chringma Sherpa	Anshu Rastogi
	Immunogenicity Assay	Chringma Sherpa	Anshu Rastogi
	Facility	Ekaterina Allen (DS), Hyung Yul Lee (DP)	Zhong Li
	Microbiology	Ekaterina Allen (DS), Hyung Yul Lee (DP)	Maxwell Van Tassell
	RBPM	Andrew Shiber	
	ATL	Anshu Rastogi	
OPQ Issued Consults	CDRH consult for co-packaged vial kit		

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761355 for Eylea HD manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Eylea HD is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Regeneron Pharmaceuticals, Inc., to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

Facility Inspections Complete Response Comments (provided by OPMA):
Following a pre-license inspection of the (b) (4) the drug product manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this BLA submission may be approved.

Additional Product Quality Comments (provided by OBP):
Perform real-world shipping studies, covering worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final DP in the proposed container closure system to ensure there is no impact to product quality and sterility of the DP (i.e., comparison of pre-shipment to post-shipment data, assessed against pre-defined acceptance criteria).

4. Basis for Recommendation

a. Summary:

Aflibercept (Eylea high dose [HD]) is for the treatment of neovascular [wet] age-related macular degeneration [nAMD], diabetic macular edema [DME], diabetic retinopathy [DR]). Aflibercept is a recombinant dimeric fusion glycoprotein consisting of human vascular endothelial growth factor receptor (VEGFR)-derived peptide domains fused to the Fc portion of human IgG1. It is an inhibitor of VEGF pathway. It is manufactured from a (b) (4) (b) (4), for the same presentations (single-dose vial and single-dose vial kit) and route of administration (intravitreal injection) for which Eylea is currently approved. The Eylea HD product is a sterile aqueous buffered solution, pH 5.8, containing 114.3 mg/mL aflibercept, (b) (4) (b) (4) arginine (b) (4) hydrochloride, (b) (4) L-histidine, (b) (4)% (w/v) sucrose, and (b) (4)% (w/v) polysorbate 20. The DP is filled into a (b) (4) glass vial with an (b) (4)

stopper, and sealed with an aluminum seal cap. Each vial has a 0.07 mL withdrawable volume providing a dose of 8 mg, which allows for extended dosing intervals (up to 16 weeks).

The potency of aflibercept is evaluated though a bioassay that measures the ability of aflibercept to bind recombinant human VEGF121 (rhVEGF121) ligand and inhibit the effect of VEGF receptor activity in a transfected (b) (4) clonal cell line. The transfected (b) (4) cells express two chimeric receptors incorporating the VEGFR1 extracellular domain fused to the cytoplasmic domain of either IL18Rα or IL18Rβ, and an integrated NFκB luciferase-IRES-eGFP reporter gene. Upon rhVEGF121 binding, the extracellular VEGFR1 dimerizes and the IL18Rα or IL18Rβ intracellular domains interact and can signal through the NFκB driven luciferase reporter gene. Potency results are reported as percentage relative to a qualified reference material.

The drug substance (DS) manufacturing process consists of (b) (4) (b) (4) (b) (4) The drug product (DP) is manufactured at (b) (4) (b) (4)

The overall manufacturing control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Eylea HD (aflibercept) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from a product quality perspective.

However, while adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the DS manufacturing facility, Regeneron Pharmaceuticals, Inc., (IOPS Rensselaer; Rensselaer, NY; FEI: 1000514603; pre-license inspection waived due to recent

inspection history), the pre-license inspections at the DP manufacturing site, (b) (4) identified a 3-item form FDA-483, Inspectional Observations and the firm did not provide adequate responses to address these observations. A withhold decision is recommended for (b) (4) facility and satisfactory resolution of the observations is required before this facility can be approved.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Inadequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/s/

ANSHU RASTOGI
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