CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761181Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA/NDA Number: **761181**
Review Number: **1**
Review Date: **1/1/2021**

Drug Name/Dosage Form	EVKEEZA (evinacumab-dgnb)
Strength/Potency	345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	As an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).
Applicant/Sponsor	Regeneron Pharmaceuticals, Inc.

Product Overview

Evinacumab-dgnb is a recombinant human IgG4 monoclonal antibody produced in CHO cells. The heavy chains of evinacumab-dgnb are engineered with a serine to proline substitution at amino acid residue 234 within the hinge region of the Fc domain to promote stabilization of interchain disulfide bonds and to minimize half-antibody formation. Each heavy chain contains the consensus glycosylation site on asparagine residue 303.

Evinacumab specifically binds to the soluble angiopoietin-like protein 3 (ANGPTL3) and blocks ANGPTL3 from inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL) activities, thereby reducing LDL-C, triglyceride, and high density lipoprotein-cholesterol (HDL-C) concentrations.

Evinacumab is a colorless to pale yellow liquid solution. The drug product is supplied in two presentations of 150 mg/mL evinacumab, a 345 mg/vial solution and a 1200 mg/vial solution, as sterile single-dose vials to be used for intravenous infusion. The recommended dose is 15mg/kg.

Evkeeza is proposed as treatment for patients age 12 years and older, with homozygous familial hypercholesterolemia (HoFH).

Quality Review Team

Discipline	Reviewer	Branch/Division
RPBM	Kristine Leahy	OPQ/OPRO
Drug Substance	Jee Chung	OPQ/OBP/DBRRIV
Drug Product	Jee Chung	OPQ/OBP/DBRRIV
Immunogenicity	Jee Chung	OPQ/OBP/DBRRIV
Labeling - OBP	Vicky Borders-Hemphill	OPQ/OBP
Facility	Wayne Seifert	OPQ/OPMA/DBM/B1
Microbiology- drug substance (DS)	Zhong Li	OPQ/OPMA/DBM/B1
Microbiology- drug product (DP)	Wayne Seifert	OPQ/OPMA/DBM/B1
Team Lead - OBP	Chana Fuchs	OPQ/OBP/DBRRIV
Team Lead - Microbiology	Candace Gomez-Broughton	OPQ/OPMA/DBM/B2
Team Lead – Facilities	Thuy Thanh Nguyen	OPQ/OPMA/DBM/B1
Application Team Lead	Chana Fuchs	OPQ/OBP/DBRRIV

Core Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Kati Johnson	CDER/OND/ORO/DROCHEN
Cross-disciplinary Team Lead	John Sharrets	CDER/OND/OCHEN/DDLO
Medical Officer	Laura Higginbotham	CDER/OND/OCHEN/DDLO
Non-clinical	Lydia Haile	CDER/OND/OCHEN/DPTCHEN
Clinical Pharmacology	Johnny Lau	CDER/OTS/OCP/DCEP
Statistics	Kyunghee Song	CDER/OTS/OB/DBII

1. Names:

a. Proprietary Name: Evkeeza
b. Trade Name: Evkeeza
c. Non-Proprietary Name/USAN: evinacumab-dgnb
d. CAS Name: 1446419-85-7
e. Common Name: REGN1500
f. INN Name: evinacumab
h. OBP systematic name: MAB HUMAN (IGG4) ANTI A0JLS0 (ANGPTL3_HUMAN) [REGN1500]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
0001	2/28/2020
0002	3/27/2020
0004	5/20/2020
0005	6/11/2020
0012	7/30/2020
0015	8/28/2020
0016	9/8/2020
0019	10/6/2020
0020	10/16/2020
0025	11/25/2020
0027	12/4/2020
0029	12/15/2020
0030	12/16/2020
0032	12/23/2020
0034	1/19/2021
0035	1/29/2021

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	V		(b) (4)	1	adequate	
	III			3	N/A	
	III			3	N/A	
	V			1	adequate	

1. Action codes for DMF Table:
1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application: NONE

3. Consults: NONE

4. Environmental Assessment of Claim of Categorical Exclusion:

The sponsor is claiming a categorical exclusion from the requirement to prepare an environmental assessment as listed in 21 CFR Part 25.31(c)

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of BLA 761181 for Evkeeza (evinacumab-dgnb), manufactured by Regeneron Pharmaceuticals Inc. The Office of Biotechnology Products (OBP) found the manufacture and control of the (b) (4) drug substance and drug product well controlled in a manner that will lead to a product that is pure and potent for the duration of its shelf-life. The drug substance (DS) and drug product (DP) sections of the BLA, as amended, are recommended for approval from a product quality, microbiology and a sterility assurance perspective. The data submitted in this application are sufficient to support the conclusion that the manufacture of evinacumab-dgnb DS and Evkeeza DP is well-controlled and leads to a product that is pure and potent. It is recommended that Evkeeza be approved for human use under conditions specified in the package insert.

B. Action Letter Language:

- Manufacturing locations:
  - Drug Substance:
    - (b) (4) drug substance is manufactured at : Regeneron Pharmaceuticals Inc. 81 Columbia Turnpike, Rensselaer, NY.
    - Release and stability testing of the (b) (4) drug substance will be performed at : Regeneron Pharmaceuticals Inc. 81 Columbia Turnpike, Rensselaer, NY.
    - Storage of (b) (4) drug substance will be at : (b) (4) °C
  - Drug Product:
    - Vialed DP is manufactured at: (b) (4) .
    - Release and stability testing of the DP will be performed at:
      - Regeneron Pharmaceuticals, Inc, Rensselaer, NY
      - (b) (4) sterility and endotoxin tests
      - (b) (4): sterility and container closer integrity testing (CCIT)
      - Regeneron Ireland, Raheen Business Park, Limerick, Ireland. identity testing (immunoassay)
    - Vial labeling and packaging will be performed at: (b) (4)
  - Fill size and dosage form
    - 345 mg/2.3 mL (150 mg/mL) single-dose vial, injection
    - 1200 mg/8 mL (150 mg/mL) single-dose vial, injection

- Dating period:
  - Drug Product: 24 months at 2°C–8°C
  - Drug Substance (b) (4): (b) (4) months at (b) (4) °C
  - Stability Option (select one below):

    We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your (b) (4) drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes. Evkeeza is a specified product exempt from lot release in accordance with 21 CFR 601.2a.

C. Benefit/Risk Considerations:

The OPQ review of manufacturing has identified that the methodologies and processes used in manufacturing of (b) (4) drug substance and drug product, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The overall control strategy for Evkeeza manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, release of the (b) (4) drug substance and drug product, and stability of these materials. Any issues with the (b) (4) control strategy were resolved during the review cycle through communication with the applicant and updates to the BLA. The BLA is also recommended for approval from a sterility assurance and microbiology product quality perspective. The technical assessments for OBP drug substance and drug product quality and immunogenicity assay, DBM microbiological drug substance and drug product and facility, and OBP labeling are located as separate documents in Panorama.

Evkeeza vials are intended to deliver evinacumab-dgnb for intravenous infusion in treatment of adults and pediatric patients 12 years of age and older with homozygous familial hypercholesterolemia (HoFH). The recommended dose for evinacumab DP is 15 mg/kg administered by intravenous infusion over 1 hour every 4 weeks. The required volume from vials of Evkeeza is transferred into an IV infusion bag consisting of 0.9 NaCl injection, USP or 5% Dextrose Injection, USP. The final concentration of the diluted solution should be between 0.5 mg/mL and 20 mg/mL. Based on the endotoxin specification for the Evkeeza drug product, the diluent should be limited to 250 mL per dose in order to achieve a two-fold safety factor for the infused solution. This information was updated in the final version of the package insert.

Clinical immunogenicity data identifies that treatment emergent antibodies to Evkeeza were detected in patients following 24 weeks of therapy. Based on the validation data, our assessment of the screening, confirmatory, titer, and a neutralizing activity assays that were used to screen patient samples for the development of anti-drug-antibodies identifies that the assays and assay parameters (including assay sensitivities, drug tolerance levels, and titer cut-points) are suitable for the evaluation of the clinical samples.

4. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

PMC: Provide data from one media fill using the product-specific container closure system and product specific setup equipment to demonstrate adequate evinacumab drug product (b) (4) manufacture. Results will be submitted by May 2021

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Tables 1 and 2, below, summarize the critical quality attributes and their control strategy that are relevant specifically to the API and Drug Substance. Table 1 specifically identifies critical quality attributes intrinsic to the API in the (b) (4) drug substance.
For additional information, see the OBP quality technical assessment and the Drug Substance Microbiology technical assessment in Panorama.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
ANGPTL3 Binding (Potency)	Impact on safety and efficacy	Intrinsic to the molecule. Impacted by conditions of fermentation, purification, and storage (stability)	(b) (4)	Acceptance criteria were narrowed from proposed range based on clinical relevance.
High Molecular Weight species (HMWS) (Product Variant)	immunogenicity, safety	Manufacturing process, including exposure to heat, acidic pH, agitation, and light . (b) (4)		(b) (4)
Low Molecular Weight species (LMWS) (Product Variants)	Impact on efficacy, PK	Manufacturing process: increased during harvest. Increase with exposure to heat, oxidizing conditions, acidic pH (b) (4) and basic pH (b) (4)		
Charge variants: Basic region (Product Variants)	Impact on efficacy, immunogenicity.	Manufacturing process: Exposure to heat, oxidizing conditions, acidic pH (b) (4)		
Charge variants: Acidic region (Product Variants)	Impact on efficacy, immunogenicity	Manufacturing process, (b) (4) Increases upon exposure to oxidizing conditions, basic pH (b) (4)		

				(b) (4)
Oxidized species	Impact on efficacy	Evinacumab degradation during manufacturing.	(b) (4)	
Deamidation (product variant)	Potential to impact efficacy of IgG's, but there was no difference in potency for stressed deamidation therefore not a CQA for this molecule.	Deamidation from cell culture as well as evinacumab degradation during manufacturing		
(b) (4)	PK	Upstream manufacturing process.		
(b) (4)	Efficacy, PK	Upstream manufacturing process (b) (4)		
Identity	Impact on safety and efficacy	Intrinsic to molecule.		

B. Drug Substance evinacumab-dgnb Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other notes
Bioburden (contaminant)	Safety, purity, and efficacy (degradation or modification of the	Raw materials or contamination during manufacturing	(b) (4)	(b) (4) No further growth of bioburden

	product by microbial contamination)		present is anticipated during storage (b) (4)
Endotoxin (contaminant)	Impact on safety and purity	Raw materials or contamination during manufacturing process	
Host Cell Proteins – general. (Process-related impurity)	Safety, Immunogenicity efficacy	Process-related impurity from the production cell line.	Overall process clearance was (b) (4) fold for all validation lots.
Host Cell Proteins – (b) (4) (Process-related impurity)	Purity, efficacy	Component of CHO HCP with (b) (4)	
Specific HCPs: (b) (4)	Purity, efficacy	Components of CHO HCP (b) (4)	
Host Cell DNA (Process-related impurity)	Safety	Process-related impurity from the production cell line	Not tested at release, acceptable based on process validation.
Impurities from the WCB vial (b) (4)	Safety	Process related impurities from generation of the WCB	(b) (4)
(b) (4)	safety	Additive in the fermentation steps	
	safety	Lysed cells – (b) (4)	
	Safety	Media component in production bioreactor	

(b) (4)	Safety	Upstream manufacturing	(b) (4)	(b) (4)
(Process-related impurity)	Safety, PK, Immunogenicity	(b) (4)		
Viruses (Contaminant)	Safety	Contamination during manufacture from raw material and personnel.		
Mycoplasma (Contaminant)	Safety	Mycoplasma introduced during cell culture operations		
Visual appearance: Color and opalescence (general)	Impact on Safety and immunogenicity	Manufacturing process and formulation		
Protein content (general)	Impact on efficacy	DS manufacture at (b) (4)		
pH (general)	Safety, efficacy	Manufacturing process (b) (4)		

(b) (4)	Impact on efficacy through product stability	Manufacture at the formulation stage	(b) (4)	

- **Description:**

Evinacumab-dgnb is a recombinant human IgG4 monoclonal antibody of the kappa light chain isotype. It is a heterodimeric glycoprotein consisting of two 214-amino acid light chains and two 453-amino acid heavy chains covalently linked through inter- and intra-chain disulfide bonds. A total of 32 cysteine residues are present in evinacumab which forms 16 disulfide bonds (four intrachain disulfide bonds per heavy chain, two intrachain disulfide bonds per light chain, and four interchain disulfide bonds). The heavy chains of evinacumab-dgnb are engineered with a serine to proline substitution at amino acid residue 234 within the hinge region of the Fc domain to promote stabilization of interchain disulfide bonds and to minimize half-antibody formation. Evinacumab is produced in CHO cells and each heavy chain is glycosylate at the consensus glycosylation site on asparagine residue 303. The molecular weight of evinacumab is 146.08 kDa.

- **Mechanism of Action (MoA):**

Evinacumab binds to angiopoietin-like 3 (ANGPTL3) and blocks ANGPTL3 from inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL) activities, thereby reducing LDL-C, HDL-C, and triglycerides. ANGPTL3, is a soluble protein[1] that is almost exclusively expressed in the liver and belongs to a subfamily of angiopoietin-like proteins that regulate plasma lipid metabolism along with ANGPTL4 and ANGPTL8[2]. The N-terminal domain of ANGPTL3 was identified as regulating lipid metabolism[3]. LPL and EL help degrade triglyceride rich lipoproteins and high-density lipoprotein phospholipids in the plasma, respectively. Specific residues, Asn47, Gln52, and His55 in the N-terminal coiled-coil domain of ANGPTL3 are responsible for binding to LPL.
Evinacumab has no effector function as part of the Mechanism of action.

- **Potency Assay**:

The potency of evinacumab drug substance and drug product is measured using a cell-free enzymatic bioassay that measures the ability of evinacumab to bind to a recombinant N-terminal fragment of ANGPTL3 and prevent its ability to inhibit LPL. The inhibition of rhANGPTL3 is measured by fluorescence as LPL hydrolyzes a fluorescently-tagged synthetic triglyceride substrate and in the process removes the fluorescence quencher. The potency is defined as the percent activity relative to the reference standard in this assay. The relative potency is calculated by dividing the EC50 constrained value for reference standard by the constrained EC50 value of the test article.

- **Reference Materials:**

A Two-tiered approach is applied to the commercial reference material. Primary reference standard ((b) (4) and working reference standard ((b) (4)) were derived from drug substance lots manufactured using the (b) (4) process and used in the clinical trials. The primary reference standard (b) (4) was used for in process, release and stability testing of the pivotal trial

[1] Conklin, D. et al, Identification of a Mammalian Angiopoietin-Related Protein Expressed Specifically in Liver. 1999 Genomics 62: 477-482.
[2] Kersten, S., Angiopoietin-like 3 in Lipoprotein Metabolism. 2017 Nat Rev Endocrinol 13: 731-739
[3] Ono, M., T. et.al, Protein region important for regulation of lipid metabolism in angiopoietin-like 3 (ANGPTL3): ANGPTL3 is cleaved and activated in vivo. 2003, J Biol Chem 278: 41804-41809.

material, as well as for some of the characterization data. The primary and secondary RMs are stored at (b) (4)°C. The reference materials are suitable for their intended uses in evinacumab testing. The stability of the reference materials is monitored through a protocol and is tested annually. The criteria used to evaluate the stability of the RM are acceptable. The procedures and criteria proposed in order to establish and qualify new reference materials are suitable to ensure consistency of evinacumab product quality.

- **Manufacturing process summary:**

Evinacumab (b) (4) drug substance (b) (4) is manufactured at Regeneron Pharmaceuticals, Rensselaer, NY using standard monoclonal antibody manufacturing processes. (b) (4)

- **Container closure:**

The DS container closure system (CCS) consist of (b) (4) A leachables study is currently ongoing on the DS PPQ lots under a protocol through a minimum of the DS shelf-life, with 12 months available data submitted to the BLA. The container closure system is suitable for evinacumab based on stability data and maintenance of closure integrity.

- **Dating period and storage conditions:**

The dating period for evinacumab (b) (4) drug substance stability is (b) (4) months when stored at (b) (4) . A stability protocol was included in the BLA to extend the shelf life of the (b) (4) drug substance up to (b) (4) months.

C. Drug Product EVKEEZA Quality Summary:

Table 3, below, provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information, see the OBP quality technical assessment and the Drug Product Microbiology technical assessment in Panorama.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety (infection), purity, and efficacy via degradation or modification of products by microbial contamination	Manufacturing process or failure of container closure integrity	(b) (4)	Long term stability testing at 5 ± 3°C according to schedule includes container closure integrity at time 0 and at 12 month intervals until expiry
Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Raw materials, manufacturing process or failure of container closure integrity		
Container closure integrity	Safety (maintenance of sterility during shelf life)	Storage conditions and CCS quality.		
Appearance Visible Particulate Matter (product or process related impurities)	Safety and immunogenicity	DS and DP Manufacturing processes, formulation, interaction with the container closure system		
Subvisible Particulate Matter (product or process related impurities)	Safety and Immunogenicity	Manufacturing process (product and contact material) and container closure system. Could be product or foreign particles.		
Appearance: Color of solution (general)	Safety and Efficacy	Formulation, contamination or degradation		
pH (general)	Safety	Formulation		
Extractable Volume (general)	Efficacy/Dosing	DP manufacturing process		
Protein Concentration	Efficacy and Safety	(b) (4) . Can		Protein concentration is set

(general)		be impacted by DP process e.g (b) (4)	(b) (4)	(b) (4)
Identity (general)	Safety and Efficacy	Intrinsic to molecule		
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS		Extractables and leachable studies were conducted on the CCS and as part of an ongoing product stability study.
DP homogeneity	Efficacy	Manufacturing		

- **Potency and Strength :**

Evkeeza is supplied as a 150mg/mL solution, injection, for intravenous infusion, as a (i) 345 mg/2.3 mL single dose 3 mL glass vial and (ii) 1200 mg/8.0 mL single dose 20 mL glass vial.

Potency is defined as the percent activity relative to the reference standard using a Cell-free enzymatic bioassay. The potency assay is a proprietary cell-free enzymatic bioassay that measures the ability of evinacumab-dgnb to bind to ANGPTL3 and prevent its ability to inhibit lipoprotein lipase (LPL) activity. The inhibition of rhANGPTL3 is measured by fluorescence as LPL hydrolyzes a fluorescently-tagged synthetic triglyceride substrate.

- **Summary of Product Design:**

Evkeeza is supplied as a single-dose, sterile, preservative-free solution for IV infusion in two presentations: a 345 mg/vial and a 1200 mg/vial presentation. Both presentations contain 150mg/mL evinacumab (b) (4). The formulation has not changed from that used in the efficacy supporting clinical trials. The recommended dose is 15mg/kg, so multiple vials may be needed to make a single dose. The extractable volume for the 345mg/(b) (4)mL fill vial is 2.3 mL minimum withdrawable volume, and for the 1200mg/(b) (4)mL fill the minimum withdrawable volume is 8.0 mL. (b) (4) . There is sufficient uncovered area on the vial to enable visual the end-user to visually inspect the solution for cloudiness, discoloration or particulate matter prior to administration.

- **List of Excipients:**

Both Evkeeza drug product presentations use the same evinacumab (b) (4)

- **Reference Materials:**

The reference material used for testing drug product is the same one as used for drug substance. See description in the drug substance section above.

- **Manufacturing process summary:**

Evkeeza DP is manufactured at (b) (4) The manufacturing process includes (b) (4)

(b) (4)

The vialed DP lot is sent to (b) (4) for vial labeling and secondary packaging. Identity testing is performed on labeled and packaged DP samples collected from the beginning, middle, and end the labeling and packaging process per 21 CFR 610.14.

- **Container closure:**

The drug product container closure systems consist of a 3 mL or 20 mL (b) (4) glass vial and a 13 mm or 20 mm (b) (4) stopper (b) (4) Vials are supplied from (b) (4) . (b) (4)
The seal cap for the 13 mm and 20 mm stopper is sourced from (b) (4) and consist of aluminum seal with clear lacquered finish and flip-off button. The color of the seal cap is white. The suitability of the DP CCS for (b) (4) loss, gas and water vapor permeation, and microbial contamination is demonstrated through long-term and accelerated stability studies.

- **Dating period:**

The shelf life for Evkeeza drug product is 24 months when stored at 2-8°C. A protocol for the extension of the drug product expiration dating was included in the BLA.

D. Biopharmaceutics Considerations: N/A

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations:

Store refrigerated at 2-8°C.
Protect from light.
Do not freeze.
Single-Dose Vial.
Discard Unused Portion.

G. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of MCB, WCB and (b) (4) DS. In-process testing, release	Regeneron Pharmaceuticals, Inc.,	FEI: 1000514603	PLI Required	704 (a) (4) assessment conducted with a conclusion of adequate.	Approval

and stability testing.					
In-process DS testing. Mycoplasma 8 and 28 day indicator cell culture method.	(b) (4)		Approve based on profile	Not applicable	Approval
In-process DS testing. 14 day in-vitro test for adventitious viruses and minute virus of mice PCR assay.			Approve based on file review	Not applicable	Approval
In-process DS testing. Mycoplasma 8 and 28 day indicator cell culture method.			Approve based on profile	Not applicable	Approval
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP release and stability testing excluding sterility.	Regeneron Pharmaceuticals, Inc.	FEI: 1000514603	See Drug Substance	Not applicable	Approval
DP manufacturer, release testing for endotoxin and sterility.	(b) (4)		Approve based on profile	Not applicable	Approval
DP. Identity by Immunoassay.			Approve based on file review	Not applicable	Approval
DP. Sterility and CCI.			Approve based on profile	Not applicable	Approval
Labeling and packaging of DP.			Approve based on profile	Not applicable	Approval

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Regeneron Pharmaceuticals, Inc. (FEI: 1000514603) the DS manufacturing facility. The Regeneron facility, and specifically the suites used for manufacturing of evinacumab have recently been inspected on pre-license inspections. The proposed manufacturing process for evinacumab DS is similar to that of other licensed products. Due to COVID19, these points where considered and it was decided that the inspection will occur through a 704(a)(4) review.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4)), the site for the DP manufacture. The inspection at (b) (4) was waived

based on (b) (4) compliance history, current acceptable cGMP status, the (b) (4) manufacture of other licensed sterile liquid biologic products on the same vial filling line (b) (4) and the relatively simple and similar DP manufacturing process.

All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage, and the 704(a)(4) process. This submission is recommended for approval from a facility standpoint.

I. Lifecycle Knowledge Management:

a. Drug Substance (DS):

i. Protocols approved:

1. Protocol for construction of a new working cell bank
2. (b) (4)
3.
4.
5. New Reference standard qualification protocols for primary and working reference standards.
6. Primary and working reference standards stability protocol
7. DS Post approval stability protocol and stability commitment - (b) (4)
8. Primary stability program – continuation of stability under protocol of stability lots in the BLA
9. Master Cell Bank stability protocol
10. Working Cell Bank Stability protocol
11. DS leachables study - continuation of current protocol
12. (b) (4) Validation - At scale (b) (4) protocol

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product (DP)

i. Protocols approved:

1. Primary stability program – continuation of stability under protocol for the stability lots in the BLA
2. DP Post-approval stability protocol and stability commitment – up to 36 months at 5°C
3. DP container closure leachables stability study – continuation of current protocol

ii. Outstanding review issues/residual risk:

Outstanding issue is identified in a PMC: to provide data from one media fill using the product-specific container closure system and product specific setup

equipment to demonstrate adequate evinacumab drug product (b) (4) manufacture.

(b) (4)

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		x		
2.	Naturally Derived Product			x	
3.	Botanical			x	
4.	Human Cell Substrate/source material			x	
5.	Non-Human Primate Cell Substrate/Source Material			x	
6.	Non-Primate Mammalian Cell Substrate/source material		x		
7.	Non-Mammalian Cell Substrate/Source Material			x	
8.	Transgenic Animal source			x	
9.	Transgenic Plant source			x	
10.	New Molecular Entity		x		
11.	PEPFAR drug			x	
12.	PET drug			x	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements		x		
18.	SPOTS (special products on-line tracking system)			x	
19.	USAN assigned name		x		
20.	Other [fill in]				
	Quality Considerations				
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements		x		
27.	Real Time release testing (RTRT)			x	
28.	Parametric release in lieu of Sterility testing			x	
29.	Alternative Microbiological test methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial analytical procedures	Drug Product	x		
32.		Excipients		x	
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other {fill-in}				

Thuy Thanh Nguyen

Digitally signed by Thuy Thanh Nguyen
Date: 2/05/2021 01:56:22PM
GUID: 5256cce70002b21dd4c17f3ef09b075c

Chana Fuchs

Digitally signed by Chana Fuchs
Date: 2/05/2021 01:57:20PM
GUID: 508da6d600026258356a161aa9f68f8a

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/

KRISTINE F LEAHY
02/05/2021 02:30:33 PM

CHANA FUCHS
02/05/2021 02:38:25 PM

THUY T NGUYEN
02/05/2021 03:41:54 PM