CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761083Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Acting Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.

BLA:	761083/0
Applicant:	Genentech
US License Number:	1048
Submission Reviewed:	Original BLA
Product:	Hemlibra (emicizumab)
Indication:	hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
Dosage Form:	Sterile solution for subcutaneous injection supplied in a (b) (4) vial at 150 mg/mL or 30 mg/mL
Manufacturing Sites:	Chugai Pharma Manufacturing Co. (FEI: 3006942691)
FDA Receipt Date:	5/31/2017
Action Date:	11/15/2017

Conclusion and Approvability Recommendation

The drug product section of this BLA is recommended for approval from a sterility assurance and quality microbiology standpoint.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0023	10/12/2017	Response to IR
0019	10/06/2017	Response to IR
0007	08/28/2017	Response to IR
0001	05/31/2017	Original BLA

Module 3.2

P.1 Description and Composition of the Drug Product

Emicizumab is a sterile liquid that is transparent to slightly yellow in color. It is intended for (b) (4), contains no preservatives, and is administered by subcutaneous injection. Emicizumab is produced in two dosages: 150 mg/mL or 30 mg/mL, and 4 presentations: 150 mg (1 mL at 150 mg/mL), 105 mg (0.7 mL at 150 mg/mL), 60 mg (0.4 mL at 150 mg/mL), and 30 mg (1mL at 30 mg/mL). The table below was adapted from the submission and shows the composition of each of the 4 vial presentations.

Ingredient	Function	Concentration				Specification
		150 mg	105 mg	60 mg	30 mg	
Emicizumab	Active ingredient	150 mg/mL			30 mg/mL	S.4.1
L-histidine	(b) (4)	(b) (4)				USP-NF / Ph. Eur. / JP
L-aspartic acid	pH adjusting agent					
L-arginine	(b) (4)					
Poloxamer 188						
(b) (4)		1 mL	0.7 mL	0.4 mL	1 mL	

SATISFACTORY

P.2 Pharmaceutical Development

P.2.4 Container Closure System

Primary container closure for emicizumab is comprised of a 3 mL Type I glass vial, 14 mm (b) (4) rubber stopper, and 15 mm aluminum cap with a plastic flip-off disk. It is described in 3.2.P.7. Vials and stoppers meet USP / Ph. Eur. / JP standards.

SATISFACTORY

P.2.5 Microbiological Attributes

General Overview

Emicizumab DP is presented without preservatives in (b) (4) vials. Microbial control of DP during manufacturing includes: (b) (4)

(b) (4)

Container Closure Integrity Testing (CCIT)

CCI for emicizumab was validated throughout the life cycle of the drug: initial validation of capping and crimping, in-process testing of physical CCI, and stability assessments annually and at the end of the shelf life of DP. Genentech uses the (b) (4) test for assessment of CCI on stability; the method and its validation are described within section 3.2.P.8.3.1.

(b) (4)

The (b) (4) is used as an in-process test for CCI to validate capping and crimping. A (b) (4) precisely monitors the atmosphere surrounding a crimped vial within the

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Aimee Cunningham

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Reyes Candau-Chacon

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First Approval for Indication
Breakthrough Designation with Priority Review
Orphan Drug

Recommendation: Approval

BLA Number: 761083
Review Number: First round
Review Date: November 9, 2017

Drug Name/Dosage Form	Hemlibra™ (emicizumab-kxwh), injection
Strength/Potency	60 mg/0.4 mL, 105 mg/0.7 mL, 150 mg/1.0 mL (150 mg/mL concentration); 30 mg/1.0 mL (30 mg/mL concentration)
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.
Applicant/Sponsor	Genentech, Inc.

Product Overview

Emicizumab-kxwh is a humanized modified immunoglobulin G4 (IgG4) monoclonal antibody with a bispecific antibody structure of which one Fab arm binds to activated Factor IX (FIXa) and its precursor form (FIX) and the other Fab arm binds to Factor X (FX) and its activated form (FXa). Emicizumab mimics activated Factor VIII (FVIIIa) activity by bridging FIXa and FX thus promoting the activation of FX by FIXa and downstream hemostasis at the site of bleeding in patients with hemophilia A who have decreased or no circulating levels of FVIII.
Emicizumab was designed by humanization and further amino acid substitutions to optimize mimetic cofactor activity (functional properties of FVIII) and other properties (isoelectric point of each chain, stability, solubility, immunogenicity). The CDRs of the anti-FIXa heavy chain (Q chain), the anti-FX heavy chain (J chain), and the light chains were derived from rats immunized with human FIXa, mice immunized with human FX, and both, respectively. Emicizumab molecule contains two different heavy chains and two identical light chains. The Fc regions of the heavy chains were engineered to preferentially heterodimerize by electrostatic steering mutations.
Emicizumab is produced in genetically engineered CHO cells. Emicizumab drug product, Hemlibra, is supplied as a sterile, preservative-free, colorless to slightly yellow solution for subcutaneous injection in single-dose vials containing emicizumab at 30 mg/1.0 mL, 60 mg/0.4 mL, 105 mg/0.7 mL, or 150 mg/1.0 mL.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Leslie Rivera-Rosado	OPQ/OBP/DBRRIV
Drug Product	Nina Brahme	OPQ/OBP/DBRRIV
Immunogenicity	Haoheng Yan	OPQ/OBP/DBRRIV
Labeling	Vicky Borders Hemphill	OPQ/OBP

Facility	Marion Michaelis	OPQ/OPF/DIA
Microbiology	Maxwell Van Tassell (Drug Substance) Aimee Cunningham (Drug Product)	OPQ/OPF/DMA IV
Team Leads	Bazarragchaa Damdinsuren (Product quality) Peter Qiu (Facility) Reyes Candau-Chacon (Microbiology)	OPQ/OBP/DBRRIV OPQ/OPF/DIA OPQ/OPF/DMA IV
CMC RPBM	Andrew Shiber	OPQ/OPRO
Application Team Lead	Bazarragchaa Damdinsuren	OPQ/OBP/DBRRIV

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Laura Wall	OHOP/DHP
Cross-disciplinary Team Lead	R. Angelo De Claro	OHOP/DHP
Medical Officer	Lori Ehrlich	OHOP/DHP
Pharm/Tox	Shwu-Luan Lee	OHOP/DHP
Clinical Pharmacology	Yuhong Chen	OHOP/DHP
Statistics	Xin Gao	OHOP/DHP

Names:

- Proprietary Name: Hemlibra
- Non-Proprietary/USAN/INN: Emicizumab-kxwh/emicizumab
- CAS Registry number: 1610943-06-0
- Company/Laboratory code: RO5534262
- OBP systematic name: MAB HUMANIZED BISPECIFIC (IGG4) ANTI P00740 (FA9_HUMAN) & ANTI P00742 (FA10_HUMAN) [RO5534262]
- Other Names: ACE-910, CH5534262, hBS910

Submissions Reviewed:

Submission(s) Reviewed /sequence number	**Document Date**
STN 761083/1	5/31/2017
STN 761083/2	6/23/2017
STN 761083 /7 (response to IR #1) STN 761083 /9 (response to IR #1)	8/28/2017 9/6/2017
STN 761083 /8 (response to IR #2)	9/1/2017
STN 761083 /16 (response to IR #3) STN 761083 /17 (response to IR #3)	9/28/2017 10/4/2017
STN 761083 /19 (response to IR #4)	10/6/2017
STN 761083 /22 (response to IR #5)	10/11/2017
STN 761083 /23 (response to IR #6)	10/12/2017
STN 761083 /28 (response to IR #3)	10/16/2017

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]	Date Review Completed	Comments
(b) (4)	III	(b) (4)		3	N/A	N/A	Not reviewed. Sufficient information related to compatibility with the product is in the BLA.
	III			3	N/A	N/A	

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 122954

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The OPQ, CDER, recommends approval of BLA STN 761083 for Hemlibra (emicizumab-kxwh) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Hemlibra 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.

B. Approval Action Letter Language:

- Manufacturing locations:
  - Drug Substance:
    - Manufacturing: Chugai Pharma Manufacturing Co., Ltd., Kita-ku, Tokyo, Japan
  - Drug Product:
    - Manufacturing and fill: Chugai Pharma Manufacturing Co., Ltd., Utsunomiya City, Tochigi, Japan
    - Labeling and packaging: F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland
- Fill sizes and dosage forms:
  - 30 mg/mL single dose vial, injection
  - 60 mg/0.4 mL single dose vial, injection
  - 105 mg/0.7 mL single dose vial, injection
  - 150 mg/mL single dose vial, injection
- Dating period:
  - Drug Product: 24 months when stored at 2-8 °C
  - Drug Substance: (b) (4) months when stored at below (b) (4) °C
  - Stability Option:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release:
  - Yes. Hemlibra is a specified product exempted according to 21 CFR 601.2a.

D. Benefit/Risk Considerations:

Hemlibra (emicizumab-kxwh) is indicated for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. Emicizumab received Orphan drug designation on January 10, 2014 and Breakthrough therapy designation on September 2, 2015 under IND 122954, and the BLA was granted a priority review (with expedited action). The pivotal clinical studies supporting the BLA showed 87% reduction of annualized bleed rate (ABR) with Hemlibra prophylaxis versus no prophylaxis (ABR 2.9 vs 23.3) in patients ≥ 12 years of age, and 87% of pediatric patients (< 12 years of age) achieved zero ABR with Hemlibra prophylaxis. Some serious adverse reactions, including thrombotic microangiopathy and thromboembolism, are described in the labeling.

The OPQ review of manufacturing has identified that the methodologies and processes used for drug substance and drug product manufacturing, 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 BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of emicizumab drug substance at Chugai Pharma Manufacturing Co., Ltd. (Chugai Ukima) and of drug product at Chugai Pharma Manufacturing Co., Ltd. (Chugai Utsunomiya) and F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland (labeling and packaging).
The immunogenicity assays are not sufficiently sensitive to detect anti-drug antibodies in presence of emicizumab at plasma concentrations. The review team agrees that the potential under-reported ADA and NAb rates do not preclude the approval of the BLA as the overall treatment benefits outweigh the risk and the immunogenicity studies (including the assay re-development) should be conducted as PMCs.
The technical assessments for OBP drug substance and drug product quality and immunogenicity assay, DMA microbiological drug substance and drug product, DIA facility, and OBP labeling are located as separate documents in Panorama (see list in the end of this review).

- **Recommendation on Phase 4 (Post-Marketing) Commitments:**

1. Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include screening, confirmation, and titer assay validation reports and assay standard operating procedures.
2. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.
3. Re-evaluate the action limit and acceptance criterion for (b) (4) testing by validated (b) (4) method after data from 30 drug substance batches are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results, action limit and acceptance criterion, and any proposed changes to the approved limit or criterion.
4. Re-evaluate the drug substance stability acceptance criteria for stability samples held at the (b) (4)C condition after data from 5 drug substance lots stored at (b) (4)C for (b) (4) months are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results and acceptance criteria and any proposed changes to the approved criteria.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA type	CQA	Risk[1]	Origin and process linkage/QbD (manufacturing experience)	Control Strategy
Potency	* Function of binding to FIXa and FX and subsequent hemostatic potential in vitro (by chromogenic assay)	**Bioactivity**, Safety	Intrinsic to the molecule.	(b) (4)
Identity	* Identity by peptide mapping	Bioactivity, Safety	Intrinsic to the molecule.	
Size-Related Variants	HMWS (by SE-HPLC)	**Bioactivity**, PK (**FcRn**), Immunogenicity, Safety	No source is identified (≤ (b) (4)%). QbD studies show impact by (b) (4) (b) (4) (b) (4)	
	LMWS (pre-peaks by non-reduced CE-SDS)	Bioactivity, PK	Manufacturing process and DP storage. ((b) (4) (b) (4)%). QbD studies show impact by (b) (4) rocess.	
Charge-Related Variants: Acidic Variants	Deamidation in CDRs	Bioactivity	Not detected (< (b) (4)%)	
	Deamidation in Non-CDRs	PK	Not detected (< (b) (4)%)	
	Glycation in CDRs	Bioactivity	Not detected (< (b) (4)%). QbD studies show impact by (b) (4) process.	
	Q-CDR Clipped Variant (by CE-HPLC)	**Bioactivity,** Immunogenicity	(b) (4) , and DP storage. (b) (4) (b) (4)%) QbD studies show impact by (b) (4) (b) (4)	
	Pre-Peaks (by CE-HPLC)	**Bioactivity**	(b) (4) ((b) (4)%). QbD studies show impact by (b) (4)	
Charge-Related Variants: Basic Variants	Asp Isomerization in CDRs	Bioactivity	No source is identified, *possibl* (b) (4) (≤ (b) (4)%)	

	Asp Isomerization in Non-CDRs	PK	No source is identified, *possibl* (≤ (b) (4)%)	(b) (4)
	Protected Disulfide Isoform	**Bioactivity**	No source is identified, *possibly* ((b) (4) area%)	
	Sum of Post-Peaks	**Bioactivity**	QbD studies show impact by (b) (4). (≤ (b) (4)%)	
Oxidation Variants	Met/Trp Oxidation in CDRs	**Bioactivity**	(b) (4) and (b) (4). ((4)%)	
	Met Oxidation in Non-CDRs for Homodimer	PK (**FcRn**)	No source is identified. (b) (4)) *Theoretically by* (b) (4)	
Glycosylation	High-Mannose Type Glycans	PK	(b) (4) (b) (4)– (4)%). QbD studies show impact by (b) (4) .	
	Hybrid Type Glycans	PK	(b) (4). No source is identified. (b) (4)– (b) (4)%)	
Homo Variants	Q-Homo Main (by CE-HPLC)	**Bioactivity**, PK (**FcRn**), immunogenicity, Safety	(b) (4) QbD studies show impact by (b) (4) process.	
	J-Homo Main (by CE-HPLC)	**Bioactivity**, PK, Immunogenicity, Safety	(b) (4)	
Structural Variants	Q277H Sequence Variant	Immunogenicity, Safety	Genomic mutation (≤ (b) (4)%)	
	Cysteine Forms (Free Thiol)	Bioactivity, PK	No source is identified. *Possible due to light exposure during* (b) (4)	

DS - drug substance, DP - drug product, DL - detection limit
* Sponsor did not name potency and identity as CQA, however these are always tested as part of core control system.
[1]The potential impact of the attribute to bioactivity (in vitro potency), PK (based mainly on FcRn binding, but also PK studies in mice, and literature), immunogenicity (prior knowledge, literature), and safety (literature, clinical observations) was assessed. **Bold** define the effects shown experimentally.

B. Drug Substance, emicizumab, Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA type	CQA	Risk[1]	Origin and process linkage/QbD	Control Strategy

			(manufacturing experience)
Process-related impurities	Host Cell DNA	Safety	(b) (4)
	Host Cell Proteins (HCP)	Safety	
	Leached Protein A	PK, Immunogenicity, Safety	
	Raw Materials (subset), Leachables	Immunogenicity, Safety	Raw materials, manufacturing process
Adventitious Agents	Viral Safety	Safety	Raw materials and manufacturing process
	Leptospira and mycoplasma	Safety	Raw materials and manufacturing process
Bacterial Endotoxins	Bacterial Endotoxins	Safety, Purity	Raw materials and manufacturing process
Bioburden	Bioburden	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process
Composition and Strength	Protein Content	Bioactivity	Manufacturing process (DS (b) (4) DP (b) (4)
	Osmolality	Bioactivity	Formulation (L-Arg content).
	pH	Bioactivity	Formulation. QbD studies show impact by (b) (4) process.
	Appearance (physical state, color, clarity/opalescence)	Bioactivity, Safety	Product, formulation
	L-His, L-Arg, L-Asp Content	Bioactivity	Formulation component. QbD studies show impact by (b) (4) process.
	Poloxamer188 Content	Bioactivity, Safety	Formulation component

DS - drug substance, DP - drug product
[1]The potential impact of the attribute was assessed as described in Table 1.

- **Description:** Emicizumab-kxwh is a humanized modified IgG4 monoclonal antibody with a bispecific antibody structure of which one Fab arm binds to FIXa and FIX, and the

other Fab arm binds to FX and FXa. Emicizumab was designed by humanization and further amino acid substitutions to optimize mimetic cofactor activity (functional properties of FVIII) and other properties (isoelectric point of each chain, stability, solubility, immunogenicity). Emicizumab molecule contains two different heavy chains and two identical light chains. The Fc regions of the heavy chains were engineered to preferentially heterodimerize by electrostatic steering mutations. Emicizumab-kxwh has an approximate molecular weight of 145.6 kDa and is produced in CHO (b) (4) cells.

- **Mechanism of Action (MoA):** Emicizumab Fab arms bind FIXa and FX mimicking FVIIIa activity, and this bridging promotes the activation of FX by FIXa and downstream hemostasis at the site of bleeding in patients with hemophilia A.
- **Potency Assay:** Chromogenic Assay - method based on Ph. Eur. 2.7.4 *Assay of Human Coagulation Factor VIII (Chromogenic Assay)*. The chromogenic assay is a functional assay that mimics the response mechanism *in vitro*.
- **Reference Materials (RM):** Two-tiered approach is applied to the commercial RM; primary RM (b) (4) (b) (4) vials; manufactured in (b) (4) and secondary RM (b) (4) (b) (4) vials; manufactured in (b) (4)). Both RMs were derived from the same clinical drug substance Batch (b) (4) which was produced using the manufacturing process and formulation representative of the commercial (b) (4) process. The primary and secondary RMs are stored at (b) (4) °C. The protocols for stability of the RMs and for qualification of future RMs are acceptable.
- **Critical starting materials or intermediates:** The Master Cell Bank (MCB, (b) (4)) is derived from CHO (b) (4) cells, which were transfected with emicizumab expression plasmids and cloned. The Working Cell Bank (WCB, (b) (4) was prepared by expansion of the MCB. (b) (4) materials were used in the manufacture of the WCB. Both the MCB and WCB were adequately tested to ensure product safety from adventitious agents. Viability of both the MCB and WCB is monitored as part of a stability program.
- **Manufacturing process summary:** The drug substance manufacturing consists of (b) (4)

(b) (4)

The emicizumab drug substance was developed using a Quality by Design (QbD) approach with risk assessment tools to define critical quality attribute acceptance criteria

(CQA-ACs), critical process parameters (CPPs), and the control strategy. No design space is claimed for the manufacturing process.

- **Container closure:** Emicizumab drug substance is stored in [redacted], manufactured by [redacted].
- **Dating period and storage conditions:** A shelf-life of [redacted] months when stored at [redacted]°C.

C. Drug Product, Hemlibra, Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product specific CQAs that derive from the drug product manufacturing process and general drug product attributes. Active pharmaceutical ingredient and drug substance CQAs apply to drug product (see Tables 1 and 2).

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

CQA type	CQA	Risk	Origin	Control Strategy
Particles	Subvisible Particles	Safety, Immunogenicity	DP manufacturing process, CCS and product	[redacted]
	Visible Particles	Safety, Immunogenicity	DP manufacturing process, CCS and product	
Vial Content	Extractable Volume	Bioactivity	DP manufacturing process (fill)	
Sterility (contaminant)	Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process	
Container closure integrity (maintenance of sterility during shelf-life)	Container closure integrity	Safety	Container closure breaches during storage	
Endotoxin (contaminant)	Endotoxin	Safety, Purity and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process	
Composition and Strength	Protein Content	Bioactivity	Manufacturing process ([redacted])	
	Appearance (physical state, color, clarity/opalescence)	Bioactivity, Safety	Product, formulation	

- **Potency and Strength:** 60 mg/0.4 mL, 105 mg/0.7 mL, 150 mg/1.0 mL (150 mg/mL concentration); 30 mg/1.0 mL (30 mg/mL concentration)
- **Summary of Product Design:** A sterile, colorless to slightly yellow solution for subcutaneous injection and contains no preservatives. Presented in single-dose vials.
- **List of Excipients:** L arginine, L histidine, and poloxamer 188, adjusted to pH 6.0 with L aspartic acid.
- **Reference Materials:** Same as the emicizumab drug substance RMs.
- **Manufacturing process summary:** The Hemlibra drug product manufacturing includes the following steps: (b) (4) Labeling and secondary packaging are performed in the separate facility. (b) (4)
  The drug product was developed using a QbD approach with risk assessment tools to define CQA-ACs, CPPs, and the control strategy.
  All drug product-contact equipment and components are sterilized (b) (4) using validated processes. The drug product is sterilized (b) (4) Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.
- **Container closure:** 3 mL type I glass vial ((b) (4), colorless) with a (b) (4) (b) (4) rubber stopper crimped with an aluminum cap fitted with a color plastic flip-off disk (30 mg - sky blue, 60 mg - purple, 105 mg - turquoise, 150 mg - brown).
- **Dating period and storage conditions:** 24 months when stored at 2-8 °C, protected from light.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Single-Dose Vial.
- Discard Unused Portion.
- Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If the unopened vial is stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)
- ATTENTION: Dispense the enclosed Medication Guide to each patient.

F. Establishment Information:

Overall Recommendation:				
DRUG SUBSTANCE				
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Final Recommendation**

DS manufacture (b) (4)	Chugai Pharma Manufacturing Co., Ltd. (CPMC), 5-1, Ukima 5-Chome, Kita-ku, Tokyo, 115-8543, Japan	3004109596 (3002926698)	Voluntary action indicated (VAI) *	Approve
(b) (4)			n/a	Approve based on facility profile
			Withhold*	Approve
			n/a	Approve based on facility profile
			n/a	Approve based on facility profile
			n/a	Approve based on facility profile
			n/a	Approve based on facility profile

DRUG PRODUCT				
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Final Recommendation**
DP manufacture DP storage DP QC testing IPC testing of DP	Chugai Pharma Manufacturing Co., Ltd. (CPMC) 16-3, Kiyohara Kogyodanchi Utsunomiya City, Tochigi, Japan	3006942691	Withhold*	Approve
DP packaging and labeling DP QC testing DP storage	F. Hoffmann-La Roche Ltd. Wurmisweg 4303 Kaiseraugst, Switzerland	3003973536	n/a	Approve based on facility profile
DP QC testing	Chugai Pharma Manufacturing Co., Ltd. (CPMC), 5-1, Ukima 5-Chome, Kita-ku, Tokyo, 115-8543, Japan	3004109596 (3002926698)	Voluntary action indicated (VAI) *	Approve

DS - drug substance, DP - drug product, QC – quality control, IPC – in-process control, MCB - Master Cell Bank, WCB - Working Cell Bank, PHCCF - preharvest cell culture fluid
* See section G. Facilities.

G. Facilities:

A pre-license inspection of emicizumab drug substance manufacturing facility at Chugai Pharma Manufacturing Co., Ltd. (Ukima, Tokyo, Japan) was conducted on September 19 - 27, 2017 by OPQ/OFP/DMA and OPQ/OBP in support of this BLA. This is a multiproduct facility manufacturing multiple licensed as well as investigational drugs, however Building (b) (4) is a dedicated facility for emicizumab. The inspection covered drug substance manufacturing, the testing laboratories and the warehouse. A FDA 483 form with following observations (in brief) was issued to the firm:

1. Multiple deviations are not resolved in a timely manner in accordance with established procedures.
2. Raw materials are approved by the Quality Assurance group for use in manufacturing prior to the completion of required testing.
3. Standard Operation Procedures (SOPs) are deficient in providing adequate instructions.
4. Emicizumab equipment cleaning verification and validation are inadequate.
5. Procedural controls for preventing the use of defective materials are deficient.
6. Procedural controls for maintaining a clean environment in Building (b) (4), where emicizumab drug substance is manufactured, are inadequate.
7. Preventative maintenance of equipment is inadequate.
8. The master batch record for emicizumab manufacturing does not provide sufficient details for consistent manufacturing.

The initial recommendation for this inspection is VAI. The final facility recommendation is for approval.

A pre-license inspection of emicizumab drug product manufacturing facility at Chugai Pharma Manufacturing Co., Ltd. (Utsunomiya, Japan) was conducted on August 24 - September 1, 2017 by OPQ/OFP/DIA and OPQ/OFP/DMA in support of this BLA. This is a multiproduct facility manufacturing multiple licensed as well as investigational biotechnology and small molecule products. A FDA 483 form with following observations (in brief) was issued to the firm:

1. (b) (4).
2. Quality oversight is inadequate.
3. Deviations are not fully investigated or initiated within the established time frame.
4. The validated Batch Record (implemented in January 2017) showed no release test is necessary and the lot is approved by QC, when in fact release testing has not been performed and the lot has not been approved. An error (b) (4) was detected on August 4, 2017.
5. Pest control procedures are not followed.

The initial recommendation for this inspection is withhold. The sponsor responded to the 483 observations and submitted a new (b) (4) performed in Building (b) (4) The final facility recommendation is for approval.

The compliance recommendations for the other facilities described in the tables (section F), which are not inspected within scope of this BLA, are for approval.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. **Protocols approved** (section):

1. Stability of the MCB and WCB (3.2.S.2.3.3)
2. Production and Qualification of Future WCB (3.2.S.2.3.3)
3. Cycle Lifetime Verification (b) (4) (3.2.R)
4. (b) (4) Validation (3.2.R)
5. (b) (4) Validation (3.2.S.2.5.6)
6. Stability Studies for the Primary and Secondary Reference Materials (3.2.S.5)
7. Qualification of Future Reference Materials (3.2.S.5)

8. Ongoing Primary Stability Study (3.2.S.7.2)
9. Post-Approval Annual Stability Protocols (3.2.S.7.2, at recommended storage condition of (b) (4) °C and accelerated condition of (b) °C)

ii. Outstanding review issues/residual risk:
See Post Marketing Commitments in section I D.

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved (section)**:**
1. Ongoing Stability Studies of Primary Batches (3.2.P.8.2 [150/105/60 mg per vial] [30 mg per vial])
2. Post-Approval Annual Stability Protocols (3.2.P.8.2 [150/105/60 mg per vial] [30 mg per vial])
3. Ongoing Leachables Studies (3.2.P.2.4 [150/105/60 mg per vial] [30 mg per vial])

ii. Outstanding review issues/residual risk: None

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			(b) (4)	
2.	Naturally Derived Product				
3.	Botanical				
4.	Human Cell Substrate/source material				
5.	Non-Human Primate Cell Substrate/Source Material				
6.	Non-Primate Mammalian Cell Substrate/source material		X		
7.	Non-Mammalian Cell Substrate/Source Material			(b) (4)	
8.	Transgenic Animal source				
9.	Transgenic Plant source				
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [bispecific monoclonal antibody]		X		
	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-BLA Agreements		X		
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [orphan and breakthrough designation, priority review]		X		
	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}				

Review documents related to this Executive Summary (links to document in Panorama)**:**

- Drug substance quality review by Leslie A. Rivera Rosado, PhD (OPQ/OBP/DBRRIV) link
- Drug product quality review by Nina Brahme, PhD, MPH (OPQ/OBP/DBRRIV) link

- Drug substance microbiology review by Maxwell Van Tassell, PhD (OPQ/OPF/DMA IV) link
- Drug product microbiology review by Aimee Cunningham, PhD (OPQ/OPF/DMA IV) link
- Facility review by Marion Michaelis, CSO (OPQ/OPF/DIA) link
- Immunogenicity assay review by Haoheng Yan, MD, PhD (OPQ/OBP/DBRRIV) link
- OBP Labeling review by Vicky Borders-Hemphill, PharmD (OPQ/OBP) link

Bazarragchaa Damdinsuren

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Reyes Candau-Chacon

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Zhihao Peter Qiu

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Joel Welch

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761083**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, DMA Branch IV
Subject: New 351(a) Biologics License Application (BLA)
US License: 1048
Applicant: Genentech, Inc.
Product: Hemlibra (emicizumab)
Indication: Treatment of patients with hemophilia A with factor VIII inhibitors
Dosage: (b) (4) vial, liquid for SC injection; 150 mg/mL (1.0, 0.7, 0.4 mL), 30 mg/1.0 mL
Facilities: Chugai Pharma Manufacturing Co., Ltd., Kita-ku, Tokyo, Japan (FEI: 3004109596)
Receipt Date: 05/31/2017
Action Date: 11/15/2017

Recommendation for Approvability: The drug substance part of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

Review Addendum

In Section 1.11.1 *CMC Response to Request for Information Dated 2017-08-18*, dated 08-28-2017 (eCTD 0007), the applicant indicated in response to Question 12 that they would implement additional (b) (4) sampling for the (b) (4) . The applicant specified that method suitability studies would be performed for all three pools, to be completed in October 2017, and would submit updated Module 3 sections by November 2017. The interim review of the drug substance product quality microbiology recommended approvability, noting that the additional method suitability data would be reviewed upon submission.

The additional method suitability data have not been provided as of the submission of this addendum and will be reviewed on the next surveillance inspection of the DS manufacturing facility. This does not negatively impact approvability of the application, as post-conditioning samples are comprised of matrices similar to those of pre-conditioning samples that have already been included in satisfactory method suitability tests. Furthermore, microbial control of the (b) (4) continues to be monitored prior to hold.

SATISFACTORY

Conclusion

I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. Method suitability data for the (b) (4) samples will be reviewed on the next surveillance inspection at Chugai Pharma Manufacturing Co., Ltd. (FEI: 3004109596).

Maxwell Van Tassell

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Reyes Candau-Chacon

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51,10903 New Hampshire Ave.
Silver Spring, MD 20993

To: Administrative File, STN 761083/0
From: Marion Michaelis, CSO, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA – Final Review Memo
US License: 1048
Applicant: Genentech, Inc.
Mfg Facility: **Drug Substance**: Chugai Pharma Manufacturing Co., Ltd., Ukima, Japan
FEI: 3004109596
Drug Product: Chugai Pharma Manufacturing Co., Ltd., Utsunomiya, Japan
FEI: 3006942691
Product: Established/Proper Name: emicizumab
Dosage: Liquid (b) (4) Vial, 150mg/mL (1.0, 0.7, 0.4 mL); 30mg/1.0 mL, subcutaneous injection
Indication: Treatment of patients with hemophilia A (congenital Factor VIII deficiency) with factor VIII inhibitors

Due Date: 2/23/2018

RECOMMENDATION:

Approval is recommended from a facility perspective.

SUMMARY

Genentech, Inc (Genentech) submitted this new Biologics License Application (BLA) dated May 17, 2017 for emicizumab, also referred to as ACE910, RO5534262. The proposed indication for use of emicizumab is the treatment of patients with hemophilia A with factor VIII inhibitors. As part of this BLA there were two pre-license (PLI) inspections conducted which were the following:

- Chugai Pharma Manufacturing Co., Ltd. (CPMC), Ukima, Japan, FEI: 3004109596 (Submitted on 356h) FEI: 3002926698 supersedes the aforementioned FEI in Firm Management – Drug Substance (DS) Manufacturing Inspection Conducted 9/19-22 & 25-27/ 2017 – CMS Work# 180616

- Chugai Pharma Manufacturing Co., Ltd. (CPMC), Utsunomiya, Japan, FEI: 3006942691 – Drug Product (DP) Manufacturing Conducted 8/24-25, 28-31 & 9/1/2017 – CMS Work##185827

The scope of this review is for equipment and facilities. Items documented as "reviewed on inspection" in this memo are discussed in the Establishment Inspection Report (EIR) associated with the individual PLI for this application.

Marion Michaelis
Consumer Safety Officer
CDER/OPQ/OPF/DIA/B1
Date: 10/12/2017 – Updated Final Memo11/9/2017

Zhihao Peter Qiu, Ph.D.
Branch Chief
CDER/OPQ/OPF/DIA/B1
Date Reviewed: 10/12/2017 – Reviewed Updated Final Memo 11/9/2017

Marion Michaelis

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Zhihao Peter Qiu

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	November 1, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Bazarragchaa Damdinsuren, PhD, Product Quality TL OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761083
Product:	Hemlibra (emicizumab-kxwh)
Applicant:	Genentech, Inc.
Submission Date(s):	May 31, 2017, June 23, 2017, October 12, 2017, October 20, 2017, October 26, 2017, October 31, 2017

I) RECOMMENDATION

The container labels (submitted on October 20, 2017) and carton labeling (submitted on October 31, 2017), prescribing information (submitted October 12, 2017), Medication Guide (submitted October 26, 2017), and Instructions for Use (submitted October 26, 2017) for Hemlibra (emicizumab-kxwh) injection, 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, or 150 mg/mL single-dose vial for subcutaneous administration are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted rolling BLA 761083 Hemlibra (emicizumab-kxwh) on May 31, 2017 and June 23, 2017.

Table 1: Proposed Product Characteristics of Hemlibra (emicizumab-kxwh).

Dosage Form:	Injection
Strength and Container-Closure:	30 mg/mL, 60 mg/0.4 mL (150 mg/mL), 105 mg/0.7 mL (150 mg/mL), or 150 mg/1 mL (150 mg/mL) single-dose vial (3 mL vial size)
Route of Administration:	subcutaneous
Storage and Handling:	refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake. Unopened vials of HEMLIBRA can be removed from and returned to the

	refrigerator, if necessary. If removed from the refrigerator, the cumulative time out of refrigeration should not exceed 7 days at a temperature that does not exceed 30°C (86°F).
Indication:	routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
Dose and Frequency:	3 mg/kg once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly

III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (N/A)
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

We evaluated proposed labels for compliance with the applicable requirements in the Code of Federal Regulations, United States Pharmacopeia (USP) standards, and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

The prescribing information, Medication Guide, instructions for use, container labels, and carton labeling for Hemlibra (emicizumab-kxwh) injection, 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, or 150 mg/mL single-dose vial for subcutaneous administration were reviewed and found to comply with pertinent regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), USP standards, and CDER Labeling Best Practices.

The container labels (submitted on October 20, 2017) and carton labeling (submitted on October 31, 2017), prescribing information (submitted October 12, 2017), Medication Guide (submitted October 26, 2017), and Instructions for Use (submitted October 26, 2017) are acceptable (see Appendix D) from a quality perspective.

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

Appendix B: Other (N/A)

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label* **Comment/Recommendation:** (b) (4)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *for container of a product capable of bearing a full label* **Comment/Recommendation:** (b) (4) To comply with 21 CFR 610.60(a)(2) add the license number to the bottom panel of the (b) (4) container label after the manufacturer name and address to appear as: Manufactured by: Genentech, Inc A Member of the Roche Group South San Francisco, CA 94080-4990 US License No. xxxx *The applicant revised as requested.*	☒ No ☐ Yes ☐ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) *for container of a product capable of bearing a full label* **Comment/Recommendation:** (b) (4).	☐ No ☒ Yes ☐ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17) *for container of a product capable of bearing a full label* **Comment/Recommendation:** (b) (4).	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60 **Comment/Recommendation:** single-dose vials	☐ No ☐ Yes ☒ N/A

[1] Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 **Comment/Recommendation:** appears on carton labeling	☐ No ☒ Yes ☐ N/A
No Package for container 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Partial label 21 CFR 610.60 21 CFR 201.10 **Comment/Recommendation:** Although vial size is 3 mL, (b) (4)	☐ No ☐ Yes ☒ N/A
No container label 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Ferrule and cap overseal **Comment/Recommendation:** FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals. *The Applicant confirmed*	☒ No ☐ Yes ☐ N/A
Visual inspection 21 CFR 610.60 **Comment/Recommendation:** FOR VIALS: Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e). *The applicant responded: The label is placed around the circumference of the vial (Figures 1-4). A sufficient area of the container remains uncovered for the label's full length or circumference to permit full inspection of the vial contents (see appendix D).* *We find the response acceptable.*	☒ No ☐ Yes ☐ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A

Route of administration 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A

Comment/Recommendation: To allow for important storage information to appear on the middle panel, relocate the statement "Discard Any Unused Portion" to appear on the surface panel underneath the package type term to read as follows:
"**Single-Dose Vial.**
Discard Unused Portion.
For Subcutaneous Use."

The applicant revised as requested.

Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Strength 21 CFR 201.10 21CFR 201.100	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:

Per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL", (b) (4) Revise the strength presentation (b) (4) to read "30 mg/mL"; (b) (4) "60 mg/0.4 mL"; (b) (4) " 105 mg/0.7 mL"; and (b) (4) (b) (4) "150 mg/mL".

The applicant revised as requested.

Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A

Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Inactive ingredients 21 CFR 201.100 **Comment/Recommendation:** *Container label lacks space, this information must appear on the carton, PI, and IFU (if applicable).*	☐ No ☒ Yes ☐ N/A
Storage requirements	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
For consistency with the prescribing information and to provide complete storage information to the end user, revise the storage statement from (b) (4) (b) (4) to read "**Storage:** Refrigerate at 2˚C to 8˚C (36˚F to 46˚F) in the original carton to protect from light.
Do Not Freeze. Do Not Shake. If stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)".

The applicant revised as requested.

Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label[5] Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: You may include the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11. However, consider revising the country of origin labeling statement to appear as "Product of Japan". *The applicant revised as requested.*	
Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

Preservative
21 CFR 610.61

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Bear the name of preservative used and its concentration. If no preservative, ensure "No preservative" appears on the carton labeling per 21 CFR 610.61 (e).

The applicant revised as requested.

Number of containers
21 CFR 610.61

☐ No
☒ Yes
☐ N/A

Strength/volume
21 CFR 610.61
21 CFR 201.10
21 CFR 201.100

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL (b) (4) Revise the strength presentation (b) (4) to read "30 mg/mL"; (b) (4) "60 mg/0.4 mL"; (b) (4) " 105 mg/0.7 mL"; and (b) (4) "150 mg/mL".

The applicant revised as requested.

Storage temperature
21 CFR 610.61

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
For consistency with the prescribing information and to provide complete storage information to the end user, and space for documentation of date removed from the refrigeration, revise the storage statement from (b) (4) o read "**Storage:** Refrigerate at 2˚C to 8˚C (36˚F to 46˚F) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)". Write the date removed from the refrigerator ___/___/___."

The Sponsor agrees to the change and will incorporate the statement "**Storage:** Refrigerate at 2˚C to 8˚C (36˚F to 46˚F) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)."

The Sponsor proposes not to include the statement "Write the date removed from the refrigerator ___/___/___." The statement "If stored out of and returned to refrigeration, the total combined time of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)" indicates that the drug can be taken out of the refrigerator multiple times. This may be confusing to the patient as the date written would only cover one removal from refrigeration. We acknowledge the Applicant's concern. To clarify that this statement is referring to an unopened vial, we recommend that the statement read "Storage: Refrigerate at 2˚C to 8˚C (36˚F to 46˚F) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If the unopened vial is stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)." *The applicant revised as requested.*	
Handling: "Shake Well", "Do not Freeze" or equivalent (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Source of the product 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Minimum potency of product 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Rx only 21CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A

Divided manufacturing 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
Distributor 21 CFR 610.64	☐ No ☐ Yes ☒ N/A
Bar code 21 CFR 610.67 21 CFR 201.25	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A

Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 **Comment/Recommendation:** Ensure the Medication Guide statement ("ATTENTION: Dispense the enclosed Medication Guide to each patient") appears on the carton labeling per 21 CFR 208.24(d). *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A
Other	☐ No ☐ Yes ☒ N/A

Prescribing Information, Instructions for Use, and Medication Guide Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8) **Comment/Recommendation:** Per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL", (b) (4) Revise throughout PI. *The applicant revised as requested* Revise the package type term to the appropriate term "single-dose" per Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry. Revise throughout PI. *The applicant revised as requested* Added dosage form per 21 CFR 201.57(a)(8) *The applicant revised as requested* Route of administration is not required information here per 21 CFR 201.57(a)(8) *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3) **Comment/Recommendation:** *Internal comment: applicant provides recommended syringes in section 2.2. PQ reviewer determined that the Applicant provided data supporting emicizumab DP compatibility with 1 mL syringes with polypropylene (PP) or polycarbonate (PC) contact surface materials, 18G transfer stainless steel (s.steel) needles, and 26G (b) (4) injection s.steel needles for (b) (4) (b) (4) There were no other details provided (about specific brands) in this DP compatibility section. We defer to clinical to determine if these listed materials are standard/widely used or were the same as those used in clinical studies.*	☐ No ☒ Yes ☐ N/A

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Add identifying characteristics per 21 CFR 201.57(c)(4)

The applicant revised as requested

Revise the package type term to the appropriate term "single-dose" per Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry. Revise throughout PI.
The applicant revised as requested

Per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL" (b) (4)
(b) (4)
Revise throughout PI.

The applicant revised as requested

6.2 IMMUNOGENICITY
Draft Guidance for Industry: Labeling for Biosimilar Products

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Revised and relocated the standard statement to appear at the beginning of the Immunogenicity subsection preceding the immunogenicity data.

The applicant revised as requested

11 DESCRIPTION
(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Removed the proprietary name from the first paragraph since the paragraph describes the drug substance.
The applicant revised as requested

We added the identity of the microorganism/cell line used in manufacture per 21 CFR 610.61 (q).
The applicant revised as requested

We added the dosage form per 21 CFR 201.57(c)(12).

The applicant revised as requested

Revise the package type term to the appropriate term "single-dose" per Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry. Revise throughout PI.
Per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL" (b) (4)
(b) (4)

Revise throughout PI.

The applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING
21 CFR 201.57(c)(17)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
We added the dosage form and identifying characteristics per 21 CFR 201.57(c)(17)

The applicant revised as requested

Revise the second bulleted sentence to read: "Prior to administration, if needed, unopened vials of Hemlibra may be stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 7 days or temperatures above 30°C (86°F)."
We find the applicant's revision acceptable.

Deleted (b) (4) to avoid inclusion of statements that are not applicable to special handling and storage conditions for the health care provider.

The applicant revised as requested

MANUFACTURER INFORMATION
21 CFR 610.61, 21 CFR 610.64

☐ No
☒ Yes
☐ N/A

MEDICATION GUIDE and INSTRUCTIONS FOR USE

TITLE (NAMES AND DOSAGE FORM)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Added the correct dosage form per USP nomenclature and route of administration to be consistent with the prescribing information. This was also included as part of DMPP recommendations
The applicant revised as requested

We had recommended the following to the Applicant: For the medication Guide, per USP General Chapters <7> Labeling: Strength per single mL should be expressed as "mg/mL (b) (4)
(b) (4)

(b) (4) *However, this strength information was removed from the medication guide as part of DMPP recommendations; we agree.*	
STORAGE AND HANDLING **Comment/Recommendation:** See section 16 for the PI regarding room temperature storage. *The applicant's revision is acceptable*	☒ No ☐ Yes ☐ N/A
INGREDIENTS	☐ No ☒ Yes ☐ N/A
MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64 **Comment/Recommendation:** to the bottom of the medication guide, add the licensed manufacturer name, address, and license number per 21 CFR 610.61(b) *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A

APPENDIX D. Acceptable Labels and Labeling

Prescribing Information (Submitted October 12, 2017
\\cdsesub1\evsprod\bla761083\0024\m1\us\draft-labeling-text.pdf)

Medication Guide (submitted October 26, 2017
\\cdsesub1\evsprod\bla761083\0030\m1\us\draft-med-guide.pdf)

Instructions for Use (Submitted October 26, 2017
\\cdsesub1\evsprod\bla761083\0030\m1\us\draft-ifu.pdf)

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BLA STN 761083

Emicizumab

Manufacturer: Genentech, Inc.

Drug Substance Quality Reviewer: Leslie A. Rivera Rosado, Ph.D.
Drug Product Quality Reviewer: Nina Brahme, Ph.D., M.P.H.
ATL Reviewer: Bazarragchaa Damdinsuren, M.D., Ph.D.
Review Chief: Joel Welch, Ph.D.

Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. BLA#: STN 761083
Orphan Drug Designation: 13-4169 granted on January 10, 2014
Breakthrough Therapy Designation: granted on September 2, 2015

2. REVIEW DATE: October 20, 2017

3. PRIMARY REVIEW TEAM:
Medical Officer: Lori Ehrlich
Pharm/Tox: Shwu-Luan Lee
Product Quality Team:
Drug substance quality reviewer: Leslie Rivera-Rosado (OPQ/OBP)
Drug product quality reviewer: Nina Brahme (OPQ/OBP)
Immunogenicity assay reviewer: Haoheng Yan (OPQ/OBP)
Drug substance microbiology reviewer: Maxwell Van Tassell (OPQ/OPF/DMA)
Drug product microbiology reviewer: Aimee Cunningham (OPQ/OPF/DMA)
Microbiology QAL: Reyes Candau-Chacon (OPQ/OPF/DMA)
Facility reviewer: Marion Michaelis (OPQ/OPF/DIA)
Facility lead: Zhihao Peter Qiu (OPQ/OPF/DIA)
OBP Labeling reviewer: Vicky Borders Hemphill (OPQ/OBP)
OPQ RPM: Andrew Shiber (OPQ/OPRO)
CMC Application Team Lead (ATL): Bazarragchaa Damdinsuren (OPQ/OBP)
Clinical Pharmacology: Yuhong Chen
Statistics: Xin Gao
RPM (clinical): Laura Wall

4. MAJOR GRMP DEADLINES

Filing Meeting	July 24, 2017
Filing Date	August 22, 2017
Applicant Mid-Cycle Communication T-con	September 28, 2017
Primary Reviews Complete (target)	October 16, 2017
Secondary Reviews Complete (target)	October 19, 2017
Applicant Late-Cycle Communication T-con	October 24, 2017
Complete CDTL Memo (target)	November 1, 2017
Action Goal Date (target)	November 15, 2017
PDUFA Goal Date (Priority)	February 23, 2018

5. COMMUNICATIONS WITH APPLICANT:

Communication/Document	Date
CMC Pre-BLA Meeting	4/25/2017
Information Request #1	8/18/2017
Information Request #2	8/25/2017
Information Request #3	9/19/2017
Information Request #4	9/22/2017

Information Request #5	10/6/2017
Information Request #6	10/10/2017

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (responsible group)
STN 761083/1	5/31/2017	Yes (OBP/DMA/DIA)
STN 761083/2	6/23/2017	Yes (OBP/DMA)
STN 761083 /7 (response to IR #1) STN 761083 /9 (response to IR #1)	8/28/2017 9/6/2017	Yes (OBP, DMA)
STN 761083 /8 (response to IR #2)	9/1/2017	Yes (DMA)
STN 761083 /16 (response to IR #3) STN 761083 /17 (response to IR #3)	9/28/2017 10/4/2017	Yes (OBP)
STN 761083 /19 (response to IR #4)	10/6/2017	Yes (DMA)
STN 761083 /22 (response to IR #5)	10/11/2017	Yes (OBP)
STN 761083 /23 (response to IR #6)	10/12/2017	Yes (DMA)
STN 761083 /28 (response to IR #3)	10/16/2017	Yes (OBP)

7. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: Hemlibra (pending)
b. Non-Proprietary/USAN/ INN: Emicizumab-kxwh
c. CAS Registry number: 1610943-06-0
d. Company/Laboratory code: RO5534262
e. OBP systematic name[1]: MAB HUMANIZED BISPECIFIC (IGG4) ANTI P00740 (FA9_HUMAN) & ANTI P00742 (FA10_HUMAN) [RO5534262]
f. Other Names: ACE-910, CH5534262, hBS910

8. PHARMACOLOGICAL CATEGORY: bispecific antibody bridging factor IXa and factor X *(under review)*

9. DOSAGE FORM: Injection, for subcutaneous use (liquid in single-dose vial)

10. STRENGTH/POTENCY:

(i) Hemlibra Drug Product: 60 mg/0.4 mL, 105 mg/0.7 mL, 150 mg/1.0 mL (150 mg/mL concentration); 30 mg/1.0 mL (30 mg/mL concentration)
(ii) Type of potency assay: Chromogenic Assay - method based on Ph. Eur. 2.7.4 *Assay of Human Coagulation Factor VIII (Chromogenic Assay)*. The chromogenic assay is a functional assay that mimics the response mechanism *in vitro*.

11. ROUTE OF ADMINISTRATION: Subcutaneous (s.c.)

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	Not reviewed. Sufficient information related to compatibility with the product is in the BLA.
			Yes	Not reviewed. Sufficient information related to compatibility with the product is in the BLA.

13. INSPECTIONAL ACTIVITIES

Drug Substance Manufacturing Facility Inspection: September 19 - 27, 2017

Chugai Pharma Manufacturing Co., Ltd. (CPMC)
5-1, Ukima 5-Chome, Kita-ku, Tokyo, 115-8543, Japan

FDA Inspectors: Bo Chi, Maxwell Van Tassell (both from OPQ/OPF/DMA), Leslie Rivera Rosado, Nina Brahme (both from OPQ/OBP)

The preliminary recommendation of the inspection is voluntary action indicated (VAI).

483 Observations *(in brief)*	**Resolution**
1. Multiple deviations are not resolved in a timely manner in accordance with established procedures.	*pending*
2. Raw materials are approved by the Quality Assurance group for use in manufacturing prior to the completion of required testing.	*pending*
3. Standard Operation Procedures (SOPs) are deficient in providing adequate instructions.	*pending*
4. Emicizumab equipment cleaning verification and validation are inadequate.	*pending*
5. Procedural controls for preventing the use of defective materials are deficient.	*pending*
6. Procedural controls for maintaining a clean environment in Building (b) (4) where emicizumab drug substance is manufactured, are inadequate.	*pending*
7. Preventative maintenance of equipment is inadequate.	*pending*
8. The master batch record for emicizumab manufacturing does not provide sufficient details for consistent manufacturing.	*pending*

Drug Product Manufacturing Facility Inspection: August 24 - September 1, 2017

Chugai Pharma Manufacturing Co., Ltd. (CPMC)
16-3 Kiyohara, Kogyodanchi, Utsunomiya City, Japan

FDA Inspectors: Marion Michaelis (OPQ/OPF/DIA), Aimee Cunningham (OPQ/OPF/DMA)

The preliminary recommendation of the inspection is withhold.

483 Observations *(in brief)*	**Resolution**

[redacted] (b) (4)	*pending*
2. Quality oversight is inadequate.	*pending*
3. Deviations are not fully investigated or initiated within the established time frame.	*pending*
4. Validation of the electronic Manufacturing Execution System (MES) HITPHAMS and preparation of the Master Batch Record (MBR) took place December 2014 through December 2016. The validation included internal testing, but there was no testing performed when the MBR was implemented in production January 2017. An error [redacted] (b) (4) was detected on August 4, 2017. This error shows that no release test is necessary and that the lot is approved by QC, when in fact release testing has not been performed and the lot has not been approved.	*pending*
5. Pest control procedures are not followed.	*pending*

14. CONSULTS REQUESTED BY OBP

None.

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment / Risk Management
x	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Summary of QbD Elements

1) Critical quality attributes (CQAs) of emicizumab include product variants, product and process related impurities, obligatory CQAs, and raw materials CQAs. These were identified using a CQA risk ranking and filtering (RRF) approach.

2) The process parameters (PPs) that potentially impact CQAs were selected by RRF risk assessments and evaluated in the process characterization/process validation (PC/PV) studies using scale-down models. Linkage studies were performed for the CQAs impacted by multiple unit operations in order to confirm the CQAs are within the target ranges under the worst-case conditions.

3) The PC/PV studies were used to identify the critical process parameters (CPP) and to define the multivariate acceptable ranges (MARs) for commercial manufacture. Movement within the MARs is not considered a change and will not be reported to FDA.

4) An attribute testing strategy (ATS) RRF assessment was used to determine what testing would be required for each CQA. The ATS uses the CQA impact score along with process and stability impact scores. The PC/PV studies were used to determine process impact scores while available stability data were used to assign stability impact scores.

5) A post-approval lifecycle management (PALM) plan is proposed as an agreement between the applicant and the Agency with regard to the assurance of the product quality throughout the product lifecycle. The PALM plan describes how the applicant will monitor the process and product, manage changes within the MARs, and update the control system.

16. PRECEDENTS

None.

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Joel Welch, Ph.D. Review Chief (Acting) Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
Bazarragchaa Damdinsuren, M.D, Ph.D. Team Leader DBRR IV, OBP, OPQ	See attached
LCDR Leslie Ann Rivera Rosado, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached
Nina Brahme, Ph.D., M.P.H. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient	Date
Laura Wall Clinical Division BLA RPM	
OBP/DBRR IV File/BLA STN 761083	

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Leslie Rivera-Rosado

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Bazarragchaa Damdinsuren

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Joel Welch

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Nina Brahme

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

BLA STN 761083

Emicizumab

Drug Product Review

Manufacturer: Genentech, Inc.

Drug Product Quality Reviewer: Nina Brahme, Ph.D., M.P.H.
ATL Reviewer: Bazarragchaa Damdinsuren, M.D., Ph.D.
Review Chief: Joel Welch, Ph.D.

Division of Biotechnology Review and Research IV

STN:	BLA761083 EDR link
Subject:	**Drug Product Review**
Submission Date:	June 23, 2017
Review/Revision Date:	October 17, 2017
Primary Reviewer:	Nina Brahme, PhD, MPH (Drug Product Quality) Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Bazarragchaa Damdinsuren, MD, PhD Team Leader, OPQ/OBP/DBRR IV
Tertiary Reviewer:	Joel Welch, PhD Acting Review Chief, OPQ/OBP/DBRR IV
Applicant:	Genentech, Inc.
Product:	Emicizumab
Indications:	Treatment of patients with hemophilia A (congenital Factor VIII deficiency) with factor VIII inhibitors
Action Due Date:	November 15, 2017

Product Quality Team:

Drug substance quality reviewer: Leslie Rivera-Rosado (OPQ/OBP)
Drug product quality reviewer: Nina Brahme (OPQ/OBP)
Immunogenicity assay reviewer: Haoheng Yan (OPQ/OBP)
Drug substance microbiology reviewer: Max Van Tassell (OPQ/OPF/DMA)
Drug product microbiology reviewer: Aimee Cunningham (OPQ/OPF/DMA)
Microbiology QAL: Reyes Candau-Chacon (OPQ/OPF/DMA)
Facility reviewer: Marion Michaelis (OPQ/OPF/DIA)
Facility lead: Zhihao Peter Qiu (OPQ/OPF/DIA)
OBP Labeling reviewer: Vicky Borders Hemphill (OPQ/OBP)
OPQ RPM: Andrew Shiber (OPQ/OPRO)
CMC Application Team Lead (ATL): Bazarragchaa Damdinsuren (OPQ/OBP)

Contents

The BLA summary information, OBP CMC Review Data Sheet and Summary of Quality Assessments, sections 3.2.A Appendices and 3.2.R Regional Information (USA) are in the Drug Substance (DS) Review by Dr. Leslie Rivera Rosado. Several DS sections and DS assessments are referenced throughout my review. The DS Review can be found in Panorama.

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Emicizumab drug product (DP) is provided as a sterile, colorless to slightly yellow solution for subcutaneous injection and contains no preservatives in Type I glass vial with a rubber stopper crimped with an aluminum cap fitted with a plastic flip-off disk. The DP is formulated as 30 mg/mL (30 mg/vial) or 150 mg/mL (150, 105 and 60 mg/vial) emicizumab, with the composition stated in the reviewer-generated tables that summarize the sponsor information. Verified with FPL

	Nominal Amount per Vial						
Ingredients	**Emicizumab 150 mg/1.0 mL DP**	**Emicizumab 105 mg/0.7 mL DP**	**Emicizumab 60 mg/0.4 mL DP**	**Emicizumab 30 mg/1.0 mL DP**	Concentration	function	specification
Emicizumab	150 mg	105 mg	60 mg	30 mg	150 mg/mL	Active ingredient	Section S.4.1 *Specification*
L-Histidine	3.1 mg	2.2 mg	1.2 mg	3.1 mg	(b) (4)	(b) (4)	USP-NF/Ph.Eur./JP
L-Aspartic Acid	QS	QS	QS	QS	QS to pH of 6.0	pH adjusting agent	USP-NF/Ph.Eur./JP
L-Arginine	26.1 mg	18.3 mg	10.5 mg	26.1 mg	(b) (4)	(b) (4)	USP-NF/Ph.Eur./JP
Poloxamer 188[b]	0.5 mg	0.4 mg	0.2 mg	0.5 mg			USP-NF/Ph.Eur./JP
(b) (4)						(b) (4)	USP-NF/Ph.Eur./JP

Abbreviations: NA=not applicable; QS = quantity sufficient

[a] Buffer concentration to obtain a pH of 6.0

[b] Poloxamer 188 = (b) (4)

3.2.P.2 Pharmaceutical Development

(b) (4)

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Joel Welch

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Nina Brahme

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761083**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, DMA Branch IV
Subject: New 351(a) Biologics License Application (BLA)
US License: 1048
Applicant: Genentech, Inc.
Product: Hemlibra (emicizumab)
Indication: Treatment of patients with hemophilia A with factor VIII inhibitors
Dosage: (b) (4) vial, liquid for SC injection; 150 mg/mL (1.0, 0.7, 0.4 mL), 30 mg/1.0 mL
Facilities: Chugai Pharma Manufacturing Co., Ltd.
5-1, Ukima 5-Chome, Kita-ku, Tokyo, Japan
(FEI: 3004109596)
Receipt Date: 05/31/2017
Action Date: 11/15/2017

Recommendation for Approvability: The drug substance part of this BLA is recommended for approval from a product quality microbiology perspective (b) (4) and reviewed in an addendum to this review memo.

Review Summary

Genentech, Inc. has submitted 351(k) BLA 761083 to obtain approval of emicizumab. Emicizumab is a recombinant, bispecific monoclonal IgG4 that mimics the function of FVIII in promoting the activation of FX by FIXa in hemostasis at the site of bleeding in patients with hemophilia A who have low or no circulating levels of FVIII.

BLA 761083 was submitted in eCTD on May 31, 2017. This review contains the assessment of the microbial quality attributes of the emicizumab drug substance from a microbiological quality perspective. For microbiology review of Drug Product (DP) aspects of the application, please see review by Aimee Cunningham, PhD.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0001	05/31/2017	Original 351(a) BLA submission
eCTD 0007	08/28/2017	Response to Information Request
eCTD 0009	09/06/2017	Response to Information Request
eCTD 0017	10/04/2017	Response to Information Request
eCTD 0019	10/06/2017	Response to Information Request

Review Assessment

3.2.S DRUG SUBSTANCE

3.2.S.1 GENERAL INFORMATION

Emicizumab is a recombinant humanized monoclonal modified IgG4 produced in a genetically engineered Chinese Hamster Ovary (CHO) cell line. Emicizumab contains one anti-FIXa heavy chain (Q chain; 448 amino acids), one anti-FX heavy chain (J chain; 444 amino acids), and two light chains (214 amino acids each). Both heavy chains have a single conserved glycosylation site and their Fc regions were engineered to heterodimerize.

SATISFACTORY

3.2.S.2 MANUFACTURE

(b) (4)

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(b) (4)

3.2.S.7 STABILITY

3.2.S.7.1 Stability Summary and Conclusions

The proposed shelf life for DS is (b) (4) months at ≤ (b) (4) °C in (b) (4) bags. Three PPQ batches (AA16AA, AA16BA, AA16CB) were placed on stability in addition to seven clinical batches and one technical batch. (b) (4) bags and/or (b) (4) bags are used for DS stability studies of long-term storage at ≤ (b) (4) °C. (b) (4) bags are used for accelerated stability study at (b) (4) °C. Endotoxin and bioburden testing were not incorporated into stability studies.

Reviewer's Comments:
Endotoxin and bioburden testing are not required for stability testing of drug substance.

SATISFACTORY

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval. Additional information (b) (4) will be reviewed in an addendum to this review memo.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.

III. A pre-license inspection was conducted at Chugai Pharma Manufacturing Co., Ltd., Tokyo, Japan, from September 19th-22nd and September 25th-27th 2017 by OPF/DMA (Bo Chi and Maxwell Van Tassell) and OBP (Leslie Rivera Rosado and Nina Brahme). An eight-item Form FDA 483 was issued. Refer to Panorama for compliance status of the facilities.

Maxwell Van Tassell

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Reyes Candau-Chacon

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