CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761197Orig1s000

PRODUCT QUALITY REVIEW(S)

Priority Review (Tropical Disease Priority Review Voucher)

Recommendation: Approval

EXECUTIVE SUMMARY

BLA 761197
Review Number: First round
Review Date: September 27, 2021

Drug Name/Dosage Form	Susvimo (ranibizumab) injection
Strength/Potency	10 mg/0.1 mL solution in a single-dose vial
Route of Administration	Intravitreal use via Susvimo ocular implant
Rx/OTC dispensed	Rx
Indication	Neovascular (Wet) Age-Related macular Degeneration (AMD) who have (b) (4)
Applicant/Sponsor	Genentech

Product Overview

Susvimo is a drug-device combination product. The drug constituent (ranibizumab) is a recombinant humanized IgG1κ isotype monoclonal antibody F(ab') fragment. Ranibizumab binds to the receptor binding site of all human alternatively spliced Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including VEGF-A 121, VEGF-A 165, and the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells resulting in the reduction of endothelial cell proliferation, vascular leakage and new blood vessel formation. Ranibizumab drug product (DP) is a preservative-free, sterile, clear to slightly opalescent, colorless to pale brown solution supplied in a single-dose vial designed to deliver 10 mg of ranibizumab, histidine HCl (0.1 mg), polysorbate 20 (0.01 mg), sucrose (8.2 mg), and Water for Injection, in 0.1 mL of solution with a pH of 5.5. The device constituent [i.e., port delivery system (PDS)] includes a surgically implantable, refillable ocular delivery device (implant), and four ancillary devices used for implant, fill, refill and explant. After placement of the implant in the pars plana of the eye, the PDS is filled with 0.02 mL of ranibizumab DP, specifically formulated for use in the PDS. The mechanism of DP release from the implant is passive, concentration gradient-driven diffusion via a porous release control element. Susvimo (ranibizumab) shares the same (b) (4) as that of approved Lucentis (ranibizumab) for intravitreal use, and the same (b) (4) . The (b) (4) results in different formulation (b) (4) (b) (4) between Susvimo and Lucentis.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance/Drug Product/Immunogenicity	Amy Hsu	OBP/DBRR1
OBP Labeling	Koung Lee	OBP/IO
Drug Substance Microbiology/Facilities	Amy Devlin	OPMA/DBM
Drug Product Microbiology/Facilities	Jeanne Fringer	OPMA/DBM
Facilities Assessment Lead	Zhong Li	OPMA/DBM
Microbiology Quality Assessment Lead	Maxwell Van Tassell	OPMA/DBM
CMC RBPM	Anh-Thy Ly	OPRO/DRBPM1
Application Technical Lead	Kristen Nickens	OBP/DBRR1
OBP Review Chief	Qing Zhou	OBP/DBRR1
Device facility (port delivery system)	Alan Gion/Charles Chang	CDRH/OHT1
Device facility (initial and refill needle)	David Wolloscheck/Rumi Young	CDRH/OHT3

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Lois Almoza/Diana Willard	ORO/DROSM
Signatory Authority	Wiley Chambers	OSM/DO
Cross-disciplinary Team Lead	William Boyd	OSM/DO
Clinical Reviewer	Wiley Chambers	OSM/DO
Nonclinical	Maria Rivera	ORDPURM/DPTRDPURM
Clinical Pharmacology	Amit Somani	OCP/DIIP
Biostatistics	Elena Rantou	OB/DBIV
OSE/DMEPA	Valerie Vaughan/Nasim Roosta	OMEPRM/DMEPAI
OSE/DPV	Rachna Kapoor/Ronald Wassel	OSE/OPE/DPVII
OSE/DEPI	Natasha Pratt/Mingfeng Zhang	OSE/OPE/DEPII

1. Names:
    a. Proprietary name: Susvimo
    b. Trade name: Susvimo
    c. Non-proprietary name: ranibizumab
    d. CAS registry number: 347396-82-1
    e. Common name: RO4893594, rhuFab V2
    f. INN Name: ranibizumab
    g. USAN Name: ranibizumab
    h. OBP systematic name: MABFRAG HUMANIZED (IGG1) ANTI P15692 (VEGFA_HUMAN) [GENENTECH]
2. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody Fab fragment.

Submissions Reviewed:

Communication	Date Received:
STN 761197/0002 (Clinical: immunogenicity assays)	March 1, 2021
/0003 (Module 3)	April 23, 2021 (start of BLA)
/0005 (response to IR #1)	May 18, 2021
/0007 (response to IR #2)	May 26, 2021
/0008 (response to IR #3)	June 8, 2021
/0012 (response to IR #4)	July 12, 2021
/0017 (response to IR #5)	July 28, 2021
/0020 (response to IR #6)	August 20, 2021

/0021 (response to IR #7)	August 23, 2021
/0023 (response to IR #8)	August 27, 2021
/0028 (response to IR #9)	September 16, 2021
/0029 (response to IR #10)	September 17, 2021
/0031 (interim response to IR #9)	September 21, 2021
/0032 (response to IR #11)	September 24, 2021
/0033 (final response to IR #9)	September 28, 2021
/0034 (response to IR #12)	September 28, 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]	Date review completed	Comments (status)
(b) (4)	III		(b) (4)	3	N/A	N/A	None
	III			3	N/A	N/A	None
	V			3	N/A	N/A	None

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 are 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.
   IND 113552 (Susvimo), BLA 125156 (Lucentis)

3. Consults: Two Intercenter consult requests (ICCRs; 0084990 and 0085003) were requested by the Office of Pharmaceutical Quality (OPQ) for device facility review. Additional ICCRs were requested by OND to review the manufacturing information pertaining to the PDS device components including the implant, initial fill needle, refill needle, insertion tool, and explant tool. See DARRTS and the ICCR database for the ICCRs and associated Center for Device Evaluation and Radiological Health (CDRH) memos.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761197 for Susvimo (ranibizumab) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Susvimo is well-controlled and leads to a product that is pure and potent. OPQ recommends that this product be approved for human use under conditions specified in the package insert. The OPQ recommendation takes into account the outcomes of the Office of Regulatory Affairs (ORA)-led CDRH-recommended device facility inspections.

B. Approval Action Letter Language:

- Manufacturing location
  - Drug Substance: Roche Singapore Technical Operations (RSTO) Pte. Ltd., 10 Tuas Bay Link, Singapore, Singapore (FEI: 3007164129)
  - Drug Product: (b) (4)
  - Co-packaging of Drug Product vial and Initial Fill Needle: Genentech, Inc., 4625 NE Brookwood Parkway, Hillsboro Technical Operations, OR 97124
  - Device Manufacture: Philips-Medisize, LLC, 409 Technology Drive East, Menomonie, Wisconsin, 54751 (FEI : 3002919960)
  - Device Design Controls: Genentech, Inc., 1 DNA Way, South San Francisco, CA, 94080 (FEI: 2917293)
- Fill size and dosage form: 0.1 mL of (b) (4) mg/ mL solution in a single-dose vial
- Dating Period:
  - Drug Product: 24 months at 2-8°C, do not freeze, protected from light, do not shake
  - Drug Substance: (b) (4) months at (b) (4) °C
  - For packaged products: Susvimo (ranibizumab) vial and initial fill needle kit; the expiration date for the co-package containing the initial fill needle and a ranibizumab vial shall be based on the earlier expiration date of the two components within. The co-packaged carton is labeled as follows: Refrigerate at 2°C to 8°C. Prior to use, the unopened vial may be kept at 9°C to 30°C for up to 24 hours. Do not freeze. Protect from light. Do not shake.
    - Susvimo Drug Product vial: 24 months: 2-8°C

  - Susvimo Initial Fill Needle: (b) (4) months (b) (4) °C
- For stability protocols:
  - We have approved 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
  Note: Susvimo is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Susvimo (ranibizumab) is intended for use in patients with chronic retinal disease, specifically neovascular (wet) Age-Related Macular Degeneration (AMD). The PDS enables ranibizumab to be continuously released into the eye over time, with the intent to maintain the vitreous concentration of ranibizumab at therapeutic levels until refill in needed. The implant is refilled every 24 weeks through the refill-exchange procedure in which the contents of the implant are exchanged with fresh ranibizumab. The approach of continuous delivery of ranibizumab via the PDS implant over a 24-week period is intended to result in less frequent treatment regimens for impacted patients and a reduced patient monitoring schedule. The resulting decrease in treatment frequency is expected to decrease the need for patients to visit the point of care unit, increase adherence to the treatment schedule, and reduce the burden of the treatment regimen to patients, caregivers, and healthcare systems, with no impact on efficacy.

The overall control strategy for Susvimo manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency, and DS and DP that have appropriate quality and are free of adventitious agents.

Inspection waivers for the ranibizumab (10 mg/0.1 mL) DS manufacturing facility (RSTO, Singapore) and DP manufacturing facility ((b) (4)) were recommended by Office of Pharmaceutical Manufacturing Assessment (OPMA) based on previous inspectional history and experience manufacturing Lucentis, as part of DS facility inspection risk assessment. Pre-licensing inspections were requested by the CDRH device reviewer for the device manufacturing site (Philips-Medisize, LLC, USA) and the device design control site (Genentech, South San Francisco). On-site inspections of both device-related inspections were performed by ORA. The outcomes were to recommend approval.

D. Environmental Assessment or Claim of Categorical Exclusion:

A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.15(d) was provided. The citation states that specifically, under 21 CFR Section 25.31(c), any action on an NDA, abbreviated application, application for marketing approval or a biologic product, or a supplement to such applications, or action on an OTC monograph, is categorically excluded and ordinarily does not require the preparation of an EA or statement for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the

environment. Genentech states that to their knowledge, no extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action. Therefore, a categorical exclusion from the requirement of an EA under 21 CFR 25.31(c) is applicable to Susvimo.

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

1. Perform real-time Susvimo drug product commercial container closure system leachable studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, and non-VOC, and elemental impurities at regular intervals through the end of shelf-life. The leachables results will be updated annually in the BLA Annual Report. The final results of this study and the toxicological risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

III. Summary of Quality Assessments:

B. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other notes
VEGF-A 165 binding (potency)	Efficacy	Intrinsic to the molecule Minimal change is expected under recommended storage conditions through expiry	(b) (4)	N/A
HUVEC anti-proliferation (potency)	Efficacy	Intrinsic to the molecule Minimal change is expected under recommended storage conditions through expiry		N/A

Identity	Safety and Efficacy	Intrinsic to the molecule	(b) (4)	N/A
High Molecular Weight (HMW) species/ Aggregates (product-related impurities)	Efficacy and Safety/ Immunogenicity	Manufacturing process and exposure to high pH, heat stress, light stress and oxidation Minimal change is expected during storage under recommended conditions through expiry		N/A
Low Molecular Weight Species (Fragments) (product-related impurities)	Efficacy	Manufacturing process and high pH stress, heat stress, light stress and oxidation Minimal change in fragments is expected during storage under recommended conditions		N/A
(b) (4)	Efficacy	Exposure to light stress and oxidative stress Minimal change is expected during storage under recommended conditions		(b) (4)

			(b) (4)	(b) (4) The labeled DP has a protect from light statement.
(b) (4)	Efficacy	Exposure to thermal stress Minimal change is expected during storage under recommended conditions		(b) (4) has no impact on biological activity. Low levels of (b) (4) were detected in the clinical materials.
Protein Content (mg/mL)	Efficacy	Manufacturing process		N/A
Osmolality	Efficacy	Formulation process		N/A
Appearance (color and clarity)	Efficacy and Safety	Formulation, contamination, or degradation		N/A
pH	Efficacy and Safety	Formulation process		N/A
(b) (4)	Efficacy and Safety	Intrinsic to DS and DP formulation		N/A

Drug Substance [ranibizumab] Quality Summary

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

Category (type)	Risk	Origin	Control Strategy	Other notes
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line (e. coli)	(b) (4)	(b) (4) (b) (4)
Host Cell DNA (process-related impurity)	Safety	Production cell line (e. coli)		N/A
(b) (4) (process-related impurity)	Safety and Immunogenicity	Process-related impurity (b) (4)		Scale-down spiking studies were performed to evaluate (b) (4) Susvimo-specific manufacturing run was used in the study.

(b) (4) (process-related impurity)	Safety, immunogenicity	Process-related impurity (b) (4)	(b) (4)	
Leachables (process-related impurity)	Safety	Manufacturing components and the DS container closure system		N/A
Microbial Enumeration (Bioburden)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process		N/A
Endotoxin (Contaminant)	Safety, Purity, Raw Materials manufacturing process	Raw Materials and manufacturing process		N/A

- **Description (ranibizumab):**

  Ranibizumab is a recombinant humanized IgG1 kappa monoclonal antibody fragment manufactured in *E. coli*. Ranibizumab is composed of one light chain (214 amino acid residues) linked by a C-terminal disulfide bond to one heavy chain (231 amino acid residue). The total molecular weight of ranibizumab is 48 kilodaltons. The CDRs

recognize the receptor binding sites of all human alternatively spliced VEGF-A isoforms. Ranibizumab harbors no glycosylation site. Ranibizumab contains norleucine and methylnorleucine misincorporation at methionine positions. The levels found in Susvimo are consistent with those observed in approved Lucentis.

- **Mechanism of Action (MoA):**
The clinical efficacy of Susvimo for its indication is mediated by binding to VEGF-A which neutralizes its interaction with VEGFR-1 and VEGFR-2 and subsequently reduces endothelial cell proliferation, neovascularization, and vascular leakage associated with Neovascular (Wet) Age-Related macular Degeneration (AMD).

- **Potency Assay:**
VEGF HUVEC Assay**:** The Susvimo potency assay is the same assay as approved for Lucentis. The assay measures the ability of ranibizumab to inhibit VEGF-induced HUVEC proliferation. Varying concentrations of ranibizumab standard, control, and samples are mixed with VEGF, incubated and then added to a 96-well plate, followed by the addition of the HUVECs. Following incubation, the number of viable cells is quantitated indirectly using the alamarBlue redox dye. The results are expressed in relative fluorescent units (RFU) and plotted against the tested sample concentrations. Parallel-line analysis is used to estimate the inhibitory activity of the tested samples relative to the reference standard. Results are reported in U/mg relative to the reference standard, by converting relative potency to U/mg through multiplying the relative potency (percent of RS) and the specific activity of the reference standard expressed as U/mg.

- **Reference Materials:**
(b) (4)

- **Critical starting materials or intermediates:**
(b) (4)

- **Manufacturing process summary:**
(b) (4)

(b) (4)

- **Container closure:**

(b) (4)

- **Dating period and storage conditions**:
  The dating period for the Susvimo DS is (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Susvimo] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

The following table provides a summary of the identification, risk, and lifecycle knowledge management for the drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

CQA (type)	Risk	Origin	Control Strategy	Other
Particulate matter (visible and subvisible) (Product or process	Safety/immunogenicity	Manufacturing process and container closure system	(b) (4)	N/A

related impurities)			(b) (4)	
Extractable Volume (general)	Efficacy/dosing	Manufacturing process		N/A
Leachables (process related impurities)	Safety	Manufacturing equipment and container closure		Long-term leachable study results for the DP container closure system were only available during the review cycle through 6 months under long-term and accelerated conditions. A post-marketing commitment will be issued for providing updated study results annually in the BLA Annual Report and to submit the final study report, including the toxicological risk evaluation, to the BLA.
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process		N/A
Endotoxin (Contaminant)	Safety, Purity, Raw materials, manufacturing process	Controlled by the bioburden control and sterility-assurance strategies.		N/A
Container closure integrity	Safety (sterility assurance)	Container closure breaches during storage. May be impacted by storage conditions.		N/A

- **Potency and Strength:**
  Susvimo is supplied at a strength of 10 mg/0.1 mL. Potency is reported in U/mg relative to the current ranibizumab WRS determined using VEGF HUVEC assay, the same method as described for DS.

- **Summary of Product Design:**
  Susvimo is supplied in a single-dose vial as a preservative-free, sterile, clear to slightly opalescent, colorless to slightly brownish solution for intravitreal use with the PDS. The single-dose vial contains 0.1 mL of ranibizumab ([(b) (4)] [(b) (4)]) to ensure a minimum fill volume of [(b) (4)] mL of 10 mg ranibizumab, 0.1 mg histidine HCl, 8.2 mg sucrose, 0.01 mg polysorbate 20 at pH 5.5.

- **List of Excipients:**
  Histidine HCl, sucrose, and polysorbate 20 are all compendial excipients.

- **Reference Materials:**
  The same reference material is used for DS and DP.

- **Manufacturing process summary:**
  [(b) (4)]

(b) (4)

- **Container closure:**
  The DP container closure system is comprised of a 2 mL Type (b) (4) glass vial, 13 mm (b) (4), latex free rubber stopper, and 13 mm aluminum seal with a plastic flip-off cap.

- **Dating period and storage conditions:**
  The dating period for Susvimo is (b) (4) months when stored at 2-8°C, protected from light.

- **List of co-packaged components, if applicable:** Susvimo DP vial, initial fill needle.

D. **Novel Approaches/Precedents:** Susvimo is a novel approach for administration of ranibizumab.

E. **Any Special Product Quality Labeling Recommendations:** Do not freeze, protect from light, do not shake

F. Establishment Information:

Overall recommendation: APPROVAL					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, (b) (4)	Roche Singapore Technical Operations Pte. Ltd.	3007164129/ 937189173	PLI waiver; site has prior experience manufacturing ranibizumab drug substance	NA	Approve
Manufacture and primary storage of MCB and WCB	Genentech, Inc. (South San Francisco)	2917293/ 080129000	Approve-Based on previous history	NA	Approve
Secondary storage of MCB and WCB	Genentech, Inc. (Vacaville)	3002902534/ 004074162	Approve-Based on previous history	NA	Approve
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation

DP manufacture, QC release testing, In-process testing, Stability testing, Bulk DP storage	(b) (4)		Approve-Based on previous history	PLI waived	Approve
Stability testing			Approve-Based on previous history	NA	Approve
Stability Testing			Approve-Based on previous history	NA	Approve
Stability Testing			Approve-Based on previous history	NA	Approve
Secondary Packaging	Genentech, Inc. 4625 NE Brookwood Pkwy Hillsboro, OR 97124 USA	3007232634	Approve-Based on previous history	NA	Approve
DEVICE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Contract Manufacturer	Phillips-Medisize LLC	3002919960	PAI inspection required	NAI	Approve

Sponsor, Design Controls	Genentech SSF	2917293	PAI inspection required	NAI	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Roche Singapore Technical Operations (FEI 3007164129) and (b) (4), proposed for ranibizumab DS and DP manufacture, respectively, and the PDS device at Philips-Medisize, LLC (FEI 3002919960) and Genentech South San Francisco (FEI 2917293) are acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- (b) (4)
- MCB and WCB stability protocol
- Future WCB qualification protocol
- Post-approval annual stability protocol
- (b) (4)

ii. Outstanding review issues/residual risk: N/A

iii. Future inspection points to consider: N/A

b. Drug Product

i. Protocols approved:
- Post-approval annual stability protocol
- Future reference standard qualification protocol

ii. Outstanding review issues/residual risk: N/A

iii. Future inspection points to consider: N/A

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/

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