CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761263Orig1s000

PRODUCT QUALITY REVIEW(S)

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

Application ID	BLA 761263
Submission Type	Original BLA
Drug Product Name	mosunetuzumab
Strengths	1 mg/1 mL, 30 mg/30 mL (1 mg/mL)
Dosage Form	Liquid single-use vial
Administration Route	Intravenous infusion
Indication	The treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies
Applicant Name	Genentech, Inc.
US License Number	1048
Application Type	351 (a)
Primary Reviewer	Lindsey Brown, Ph.D.
Secondary Reviewer	Maxwell VanTassell, Ph.D.
Secondary Reviewer	Zhong Li, Ph.D.
Goal Date	12/29/2022

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and is recommended for Approval with the following post-marketing commitment(s):

(b) (4)

- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized using a validated (b) (4) process and (b) (4) is integrity tested after use. (b) (4) (b) (4) (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.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other

Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
0001	8/9/2021
0041	8/26/2022
0066	10/25/2022
0068	11/02/2022
0076	11/17/2022
Email correspondence	12/05/2022
0085	12/05/2022
0089	12/07/2022

List of DMFs Assessed (Table):

DMF #	Item Referenced	Date Reviewed	Finding	Document Reference
(b) (4)		4/26/2021	Adequate	(b) (4)
		11/17/2021	Adequate	

Application Submission Background

Reviewer's Comment: For Information

MODULE 1
1.14 LABELING

(b) (4)

Reviewer's Comment: For Information

MODULE 3.2.P

Module 3.2.P Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

P.1 Description and Composition of the Drug Product

Mosunetuzumab drug product (DP) is a sterile solution for infusion with two presentations: 1mg/vial and 30 mg vial. The composition of each vial is diagrammed in Table P.1-1 (table not shown). The formulation includes (b) (4) excipients (sucrose) as well as excipients (b) (4).

Reviewer's Comment: For Information

P.2 Pharmaceutical Development

(b) (4)

Reviewer's Evaluation: The data from the microbial challenge study supports the proposed storage condition of (b) (4) 2-8°C (b) (4).

Assessment: **SATISFACTORY**

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(b) (4)

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FACILITY ASSESSMENT

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Genentech, Inc. 1 DNA Way , South San Francisco, CA, USA, 94080	2917293	Drug Substance: Manufacture, In-Process Control Testing, including adventitious agent testing, Quality Control Testing, Stability Testing, Storage of Drug Substance, Preparation and Storage of MCB and WCB Drug Product: Manufacture: In-Process Control Testing, Quality Control Testing, Stability Testing, Storage of Drug Product || 356h Status: Pending SVS	Approve - Based on Inspection
(b) (4)		Drug Substance In-Process Control Testing for Adventitious Agents, excluding Mycoplasma testing || 356h Status: Pending LBI	Approve - Based on Previous History

Genentech, Inc. 1000 New Horizons Way , Vacaville, CA, USA, 95688	3002902534	Additional Storage Site for MCB and WCB || 356h Status: Pending LBI	Approve - Based on Previous History
(b) (4)		Drug Subtstance Stability Testing, Drug Product Quality Control Testing, Drug Product Stability Testing || 356h Status: Pending LBI	Approve - Based on Previous History
F. Hoffmann-La Roche AG Wurmisweg , Kaiseraugst , N/A, Switzerland, 4303	3003973536	Labelling and Secondary Packaging, Storage of Drug Product, Release of Finished Drug Product || 356h Status: Pending LBI	Approve - Based on Previous History

Facility Level Evaluation of Manufacturer: Pre-License Inspection Conducted

Facility name/FEI	Genentech Inc./FEI: 2917293
Proposed Manufacturing Area(s) (b) (4)	(b) (4)
Facility Background Assessment	
1. Does the proposed Facility have biologics inspection history via FDA/MRA ?	Yes The most recent CDER-led FDA biologics inspection was a PLI conducted in 2014 (b) (4) (b) (4) during 04/21/2014-05/02/2014, Final Classification was NAI with Approval recommendation.
2. Do the proposed process areas (b) (4) have biologics inspection history via FDA/MRA?	Yes- (b) (4) (b) (4) .
3. Is there a gap in recent inspection history?	Yes,
4. Are there unresolved potential GMP concerns in areas related to the processes in the BLA or systematic problems, such as QC/QA oversight?	1. Mosunetuzumab is a bi-specific antibody (b) (4) (b) (4) (b) (4) . It is the first bi-specific antibody manufactured at the facility and the PPQ campaign experienced failures. 2. Quality defect signals were identified from 6 BPDRs reported to the agency in early 2022 related to site-wide data integrity breaches by contract personnel responsible for cleaning of commercial and clinical DS and DP manufacturing areas. Batch release of biologics DS and DP at the site has been paused pending investigation and impact assessment. A 704(a)(4) records review was conducted by ORA, completed on 03/25/2021, had identified follow-up inspection items in deviation investigation and OOS invalidation.
5. Is the Site experienced with similar equipment and processes?	Yes, the site is experienced (b) (4) .
6. Are there any concerns with application (unique process/molecule?)	Yes Mosunetuzumab is a bi-specific antibody (b) (4) It is the first bi-specific

	antibody manufactured at the Genentech SSF facility. During PPQ campaigns, 3 out of the 6 PPQ batches were rejected (b) (4) (b) (4) (PPQ 1 and PPQ3) or operator error (PPQ5).
Final OPQ Inspection Recommendation:	**On-Site Pre-License Inspection**
CMS Work Activities:	459358

Reviewer's Evaluation:

A pre-license inspection (PLI) of Genentech, Inc located in South San Francisco, CA (FEI: 2917293) was conducted from 05/17/2022-05/26/2022 in support of DS and DP manufacture of BLA 761263 mosunetuzumab, Applicant Genentech Inc.. Profile Classes covered were CBI and SVS. A 2-item Form FDA 483 was issued to the firm on 05/26/2022 for the following deficiencies:

1) Laboratory controls do not include established scientifically sound and appropriate standards designed to ensure that components and in-process materials conform to appropriate standards of identity, strength, quality, and purity.
2) Reliability of supplier's test analyses of critical components are not established and validated at appropriate intervals.

Based on the firm's adequate response to objectionable conditions uncovered during the PLI, CDER/OPQ/OPMA/DBM-B1 concurs with the VAI recommendation and recommends Approval of BLA 761263/0.

Facility Status Assessment: Approve - Based on Inspection

Maxwell Van Tassell

Digitally signed by Maxwell Van Tassell
Date: 12/13/2022 01:55:59PM
GUID: 588f9a18000bb6ac3ec7300751755758

Lindsey Brown

Digitally signed by Lindsey Brown
Date: 12/13/2022 01:01:26PM
GUID: 57d6b6e00198444ec5ee4152ac22a902

Zhong Li

Digitally signed by Zhong Li
Date: 12/13/2022 01:10:33PM
GUID: 5452326f000475beaec6af628762212a

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 12, 2022
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Andrea George, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761263
Applicant:	Genentech, Inc.
Submission Date:	August 9, 2021
Product:	Lunsumio (mosunetuzumab-axgb)
Dosage form(s):	Injection
Strength and Container-Closure:	1 mg/mL in single-dose vial 30 mg/30 mL (1 mg/mL) in single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of mosunetuzumab-axgb for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least two prior systemic therapies.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are **acceptable** from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (See Appendix B)

CONCLUSION

The prescribing information and medication guide submitted on December 12, 2022, container labels submitted on September 21, 2022, and carton labeling submitted on November 10, 2022, and December 5, 202,2 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on December 28, 2021) \\CDSESUB1\evsprod\bla761263\0006\m1\us\draft-labeling-text.docx

- Container Labels (submitted on December 28, 2021)

(b) (4)

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Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: If space permits, consider adding the U.S. License Number next to the manufacturer name. *The applicant revised as requested.*	

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ 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.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

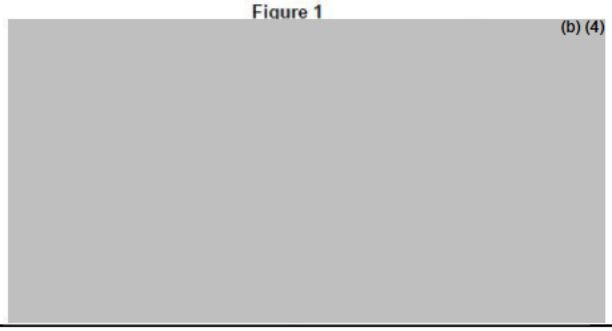
No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The applicant confirms that there is no text on the ferrule and cap overseal of the vials.*	

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located. *The applicant confirms that a sufficient area of the container remains uncovered for the label's full length or circumference to permit full inspection of the vial contents. The viewing window between the ends of the vial labels are approximately 0.5 cm (0.20 in) for the 1 mg vial and 0.4 cm (0.16 in) for the 30 mg vial.*	

Figure 1



Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: 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 (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No

[6] 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.

	☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	✓ Yes ☐ No ☐ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Revise the inactive ingredient names to their compendial names to ensure compliance with the Federal Food Drug, and Cosmetic Act (FD&C Act) section 502(e) as follows: "Each single-dose vial contains x mL of solution of mosunetuzumab-xxxx (xx mg), acetic acid (x mg), histidine (x mg), methionine (x mg), polysorbate 20 (x mg), sucrose (x mg), and Water for Injection, USP."

Applicant's response October 14, 2022*: The Sponsor agrees to revise the ingredient names to "histidine" and "methionine." However, the component in the vial is acetic acid, and the* (b) (4) *pH 5.8. Therefore, the Sponsor proposes to change the ingredients list as follows:*

(b) (4)

We note that you acknowledged to revise the inactive ingredient names on carton labeling and confirm that the component in the vial is acetic acid. We recommend retaining the original format to include the quantity of the acetic acid as follows:

- 1 mg carton: "Each single-dose vial contains 1 mL of solution of mosunetuzumab-axgb (1 mg), acetic acid (0.4 mg), histidine (1.6 mg), methionine (1.5 mg), polysorbate 20 (0.6 mg), sucrose (82.1 mg), and Water for Injection, USP. The pH is 5.8."

- 30 mg carton: "Each single-dose vial contains 30 mL of solution of mosunetuzumab-axgb (30 mg), acetic acid (12.8 mg), histidine (46.6 mg), methionine (44.8 mg), polysorbate 20 (18 mg), sucrose (2462.4 mg), and Water for Injection, USP. The pH is 5.8."

The applicant revised as requested.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for mosunetuzumab products (i.e., there is no specific test method described in regulation for mosunetuzumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Lunsumio because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.* (b) (4) our view is that 21 CFR 610.61(r) is not applicable. (b) (4)	

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable	✓ Yes ☐ No ☐ N/A

Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	☐ Yes ☐ No ☒ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Add the net quantity statement "1 mL" and "30 mL" as a distinct item on the carton labeling in accordance with 21 CFR 201.51(a). To accommodate this change, consider revising "1 vial" on the PDP to the appropriate net quantity statement as follows: "One 1 mL vial" and "One 30 mL vial"

Applicant's response September 21, 2022: *The Sponsor prefers to leave the phrase "1 vial" instead of switching to "One 1 mL vial" and "One 30 mL vial". The reasons include but are not limited to:*

- *The net quantity of contents within each carton is 1 vial. Therefore, the use of "1 vial" is compliant with 21 CFR 201.51(a).*
- *Prevent confusion between size of the vial and volume of product contained within the vial. For example, the 30 mg/30 mL configuration has a vial size of 50 mL, which could lead to a misunderstanding.*
- *Consistency in labeling with other FDA-approved products within Genentech's portfolio.*
- *The volume of product is captured in the horizontal strength color bar, which makes it recognizable*

The net quantity is included in the content statement, applicant's response to retain "1 vial" is acceptable from OBP labeling perspective.

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: 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 (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to the appropriate dosage form "Injection". *The applicant revised as requested.*	

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter*	✓ Yes ☐ No ☐ N/A

and discoloration prior to administration, whenever solution and container permit."	
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv). *The applicant revised as requested.* We revised the diluent name to comply with USP nomenclature. *The applicant revised as requested.*	

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: 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 (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to a format consistent with other product labeling. *The applicant revised as requested.*	

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 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)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	

We deleted [redacted] (b) (4) from the first paragraph which discusses the drug substance.
The applicant revised as requested.

We added additional information about the drug substance per 21 CFR 201.57(c)(12).
The applicant revised as requested.

We added additional information about the drug product per 21 CFR 201.57(c)(12).
The applicant revised as requested.

We removed trailing zero.
The applicant revised as requested.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, [redacted] (b) (4) acetic acid, histidine, methionine, polysorbate 20, and sucrose.

Applicant's response October 18, 2022*: The Applicant responded to the Agency's artworks information request dated 5-Oct-2022 and submitted to on 14 October 2022 (Serial No. 0057). The Applicant agrees to revise the ingredient names to "histidine" and "methionine." However, the component in the vial is acetic acid, and the* [redacted] (b) (4) [redacted] (b) (4) *pH 5.8. Therefore, the Applicant has revised the text accordingly.*

We note that you acknowledged to revise the inactive ingredient names on carton labeling and confirm that the component in the vial is acetic acid. We recommend retaining the original format to include the quantity of the acetic acid.
The applicant revised as requested.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised inactive ingredient names to their compendial names to ensure compliance with the Federal Food Drug, and Cosmetic Act (FD&C Act) section 502(e). *The applicant revised as requested.*

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information and Medication Guide (submitted on December 12, 2022) \\CDSESUB1\EVSPROD\bla761263\0090\m1\us\draft-labeling-text.pdf

- Container Labels (submitted on September 21, 2022)

(b) (4)

[redacted]

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Jennifer Kim

Digitally signed by Jennifer Kim
Date: 12/12/2022 10:51:54AM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Andrea George

Digitally signed by Andrea George
Date: 12/12/2022 10:59:39AM
GUID: 59b99181005cc7b0a3e954078ede1be9

BLA STN 761263
Lunsumio (mosunetuzumab-axgb)
Genentech, Inc.

OBP Technical Report
Analytical Method Validation/Immunogenicity Assay Validation

OBP Product Quality Assessment Data Sheet

1. **BLA#: STN 761263**
2. **Assessment Date:** December 08, 2022
3. **Primary Assessment Team:**

Clinical Reviewer:	Pamela Seam
Non-clinical Reviewer:	Simon Williams
Product Quality Team (OBP):	Andreas Siegel (DS), Andrea George (DP), Jens Fricke, (Analytical Method Validation)/ Immunogenicity), Willie Wilson (Application Technical Lead), Joanna (Qing) Zhou (Review Chief)
Product Quality Team (OPMA):	Yun Wu (DS Microbiology/Facilities), Lindsey Brown (DP Microbiology/Facilities), Zhong Li (Facilities Lead), Maxwell Van Tassell (Microbiology Lead)
OQS:	Kathleen Culver
Clinical Pharmacology:	Miao Zhao
Risk Management Reviewer:	Laura Zendel and Brian Caruth
DRISK Team Lead:	Naomi Boston
Epidemiology Reviewer:	Steven Bird
Marketing and Advertising Reviewer:	Jennifer Chen
MA Professional Secondary Reviewer:	Jina Kwak
Medication Error Reviewer:	Nicole Iverson and Hina Mehta
Statistics:	
Pharmacovigilance Reviewer:	Graca Dores, Afrouz Nayernama and Lauren McBride
Associate Director for Safety:	Shan Pradhan
OBP Labeling:	Jennifer Kim
OSE RPM:	Frances Fahnbulleh
OPRO RBPM:	Anh-Thy Ly
OND RPM:	Kimberly Scott

4. Major GRMP Deadlines:

Filing Meeting: June 21, 2022
Mid-Cycle Meeting: August 31, 2022
Late-Cycle Meeting: November 07, 2022
Wrap-up Meeting: November 14, 2022
Primary Review Date: September 15, 2022
Secondary Review Date: September 29, 2022
PDUFA Action Date: December 29, 2022

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #03 (Q12)	11/04/2022
Information Request #06 (Q12)	02/03/2022
Information Request #10	04/25/2022
Information Request #11	05/31/2022

Information Request #15	10/03/2022
Information Request #16	10/12/2022
Information Request #19 (Q12)	10/28/2022
Information Request #20	11/04/2022
Information Request #21 (Q12)	11/14/2022
Information Request #23 (Q12)	11/22/2022
Information Request #24	11/22/2022

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed:
761263/1 (Original Submission)	08/09/2021	Yes
761263/05 Response to OBP Information Request #03 (Q12)	11/10/2021	Yes
761263/11 Response to OBP Information Request #06 (Q12)	02/11/2022	Yes
761263/21 Response to OBP Information Request #10	05/02/2022	Yes
761263/23 Response to OBP Information Request #11	06/08/2022	Yes
761263/52 Response to OBP Information Request #15	10/07/2022	Yes
761263/62 Response to OBP Information Request #16	10/24/2022	Yes
761263/71 Response to OBP Information Request #19 (Q12)	11/04/2022	Yes
761263/72 Response to OBP Information Request #20	11/10/2022	Yes
761263/77 Response to OBP Information Request #21 (Q12)	11/18/2022	Yes
761263/82 Response to OBP Information Request #23 (Q12)	12/01/2022	Yes
761263/80 Response to OBP Information Request #24	11/23/2022	Yes

7. Drug Product Name/Code/Type:

a. Proprietary name: Lunsumio
b. Trade Name: Lunsumio
c. Non-proprietary name: mosunetuzumab-axgb
d. CAS registry number: 1905409-39-3
e. Company or Laboratory Code: RO7030816
f. Other Names: BTCT4465A
g. OBP name: MAB HUMANIZED (IGG1) ANTI (b) (4) (CD20_HUMAN) & ANTI (b) (4) (CD3E_HUMAN) [BTCT4465A]

8. Pharmacological Category:
Humanized IgG1 bispecific monoclonal antibody against human CD20 and human CD3

9. Dosage Form: Liquid in vial

10. Strength/Potency:

i. Concentration/strength: 1.0 mg/1.0 mL and 30 mg/30 mL (1 mg/mL)
ii. Type of potency assay: VEGF binding ELISA; cell-based VEGF neutralization assay
iii. Drug product dating period: (b) (4)

11. Route of Administration: (b) (4) injection

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Yes	Type III
			Yes	Type III
			Yes	Type V

13. Inspectional Activities:

A pre-approval inspection of the drug substance and drug product manufacturing facility was conducted at Genentech, Inc. in South San Francisco, CA (FEI: 2917293) from May 17, 2022, to May 26, 2022. Thuy Nguyen (OPMA), Jeanne Fringer (OPMA), Riley Myers (OBP) and Andrea George (OBP) performed the inspection. Refer to the Establishment Inspection Reports for details regarding the two item 483 observations and recommendations. The classification of the inspection is VAI.

14. Consults Requested by OBP: None

15. Quality by Design Elements:

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

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

16. Precedents: This is the first original BLA submission that contains a proposal for product lifecycle management per ICH Q12.

17. Administrative: Provided a letter of authorization to cross-reference the parent IND 120651 initially submitted March 18, 2015.

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the analytical methods used in in-process, lot release, and stability testing of mosunetuzumab are validated or verified to be suitable for their intended use at the intended commercial testing sites to ensure a pure and potent product. The data also support the immunogenicity assays used to screen and confirm the presence of anti-drug antibodies to mosunetuzumab in post-exposure patient serum. From the perspective of manufacturing process and product control through analytical testing, it is recommended that mosunetuzumab be approved for human use under conditions specified in the package insert.

II. List of Deficiencies to be Communicated: None

III. List of Post-Marketing Commitments/Requirements: None

IV. Assessment of Common Technical Document- Quality Module 1
Environmental Assessment of Claim of Categorical Exclusion:
The sponsor requested a categorical exclusion from the environmental assessment for BLA 761263 under 21 CFR 24.31(c). This is acceptable.

V. Primary Container Labeling Assessment
The CMC labeling review was performed by Jennifer Kim.

VI. Assessment of Common Technical Document- Quality Module 3.2
This document contains an assessment of the information provided for analytical procedures and validation of analytical procedures for DS (Section 3.2.S.4.2 and 3.2.S.4.3) and DP (Section 3.2.P.5.2 and 3.2.S.5.3) and product lifecycle management document element for analytical procedures.

VII. Assessment of Immunogenicity Assays- Module 5.3.1.4
The review of the immunogenicity assays is provided in Module 5.3.1.4 below.

Table of Contents

Description of Drug Substance and Drug Product

***Note**: The memo below includes the product quality assessment of analytical procedures for mosunetuzumab (b) (4) drug substance (DS) and drug product (DP) testing and their validation, as well as the assessment of immunogenicity assay validation. Several rounds of information requests (IR) were communicated to (b) (4) regarding analytical procedure and their validation, as well as the immunogenicity assays validation. Updates were made to the BLA accordingly. The memo reflects product quality assessment of the final data and information provided through the IR exchanges.*

In addition, this BLA also includes designated Established Conditions (ECs) defined for the manufacture and testing of mosunetuzumab DS and DP at Genentech, Inc. in South San Francisco, California, which was submitted as part of the FDA ICH Q12 Pilot Program. ECs, reporting categories, and Product Lifecycle Management (PLCM) documents were introduced with the aim to update the mosunetuzumab manufacturing control and testing strategy to align with the ICH Q12 guidance. All information/documents were submitted in Module 3.2.R. This memo focuses on ECs related to analytical tests. The review of ECs related to DS and DP manufacture is documented in two separate memos.

Assessor Comments are in italicized test. Unless otherwise noted, tables and figures are copied from the submission. Assessment of information and data pertaining to the bioburden and endotoxin controls as well as the facilities is deferred to the OPMA assessor.

S. Drug Substance

(b) (4)

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Overall assessor comment: *The totality of assay validation data supports assay performance of the ELISA method used to evaluate clinical immunogenicity samples* (b) (4).

Jens Fricke

Digitally signed by Jens Fricke
Date: 12/08/2022 04:27:57PM
GUID: 57d6a75701b1361db26ba4f78c02a5a9

Willie Wilson

Digitally signed by Willie Wilson
Date: 12/09/2022 02:30:57PM
GUID: 542e18bc000444f367cd79bb56beba7a

Breakthrough Designation

Recommendation: Approval

EXECUTIVE SUMMARY

BLA 761263
Review Number: First round
Review Date: December 9, 2022

Drug Name/Dosage Form	Lunsumio (mosunetuzumab-axgb) injection, for intravenous use
Strength/Potency	1 mg/mL and 30 mg/30 mL (1 mg/mL)
Route of Administration	Intravenous injection
Rx/OTC dispensed	Rx
Indication	Adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy
Applicant/Sponsor	Genentech, Inc.

Product Overview

Lunsumio (mosunetuzumab-axgb, BTCT4465A) is a recombinant humanized T-cell-engaging bispecific IgG1 antibody comprised of one half-antibody directed against CD20-expressing B-cells and one half-antibody directed against CD3-expressing T-cells. Mosunetuzumab binds simultaneously to CD20 on the surface of B-cells and CD3 on the surface of T-cells. The resulting immune synapse leads to T-cell activation, subsequent release of cytolytic granules, and killing of CD20-expressing B-cells. Lunsumio is manufactured as a sterile, preservative-free, colorless solution for intravenous injection supplied in single-dose glass vials containing mosunetuzumab-axgb at 1 mg/1 mL and 30 mg/30 mL strengths. Lunsumio is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance	Andrea Siegel	OBP/DBRR1
Drug Product	Andrea George	OBP/DBRR1
Analytical Methods/Immunogenicity Assay	Jens Fricke	OBP/DBRR1
OBP Labeling	Jennifer Kim	OBP/IO
Drug Substance Microbiology/Facilities	Yun Wu	OPMA/DBM
Drug Product Microbiology/Facilities	Lindsey Brown	OPMA/DBM
Facilities Assessment Lead	Zhong Li	OPMA/DBM
Microbiology Quality Assessment Lead	Maxwell Van Tassell	OPMA/DBM
Facilities Assessment (Established Conditions)	Kathleen Culver	OQS/DQII
CMC RBPM	Anh-Thy Ly	OPRO/DRBPM1
Application Technical Lead	Willie Wilson	OBP/DBRR1
OBP Review Chief/Q12AIT	Qing Zhou	OBP/DBRR1
Established Conditions Coordinating Committee	Joel Welch	OBP/IO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Kimberly Scott	ORO/DROOD
Signatory Authority	Marc Theoret	OCE
Cross-disciplinary Team Lead	Nicholas Richardson	OOD/DHMII
Clinical Reviewer	Pamela Seam	OOD/DHMII
Nonclinical	Simon Williams	OOD/DHMII
Clinical Pharmacology	Miao Zhao	OCP/DCPI
Biostatistics	Xin Wang, Jay Zhao	OB/DBIX
Pharmacometrics	Yuzhuo Pan, Ying-Hong Wang	OCP/DPM
OOD Safety	Shan Pradhan	OOD/DOIII
AOD Labeling	Elizabeth Everhart	OOD
OSI Consult	Anthony Orencia	OSI/DCCE/GCPAB
OSE Consult	Steven Bird, Nicole Iverson, Naomi Boston	OSE/OPE/DEPII

1. Names:
    a. Proprietary name: Lunsumio
    b. Trade name: Lunsumio
    c. Non-proprietary name: mosunetuzumab-axgb
    d. CAS registry number: 1905409-39-3
    e. Common name: BTCT4465A, RO7030816
    f. INN Name: mosunetuzumab
    g. USAN Name: mosunetuzumab
    h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI (b) (4) (CD20_HUMAN) & ANTI (b) (4) (CD3E_HUMAN) [BTCT4465A]
2. Pharmacologic category: T-cell engaging bispecific antibody

Submissions Reviewed:

Communication	Date
761263/1 (Rolling Submission, Part 1 of 4)	8/9/2021
761263/2 Response to OPMA Information Request #2, Inspection Schedule	9/24/2021
761263/3 Response to OBP Information Request #1,	9/27/2021
761263/4 (Rolling Submission, Part 2 of 4)	9/30/2021
761263/5 Response to OQS Information Request #3, Established Conditions	11/10/2021
761263/6 (Rolling Submission, Part 3 of 4)	12/28/2021
761263/8 Response to OPMA Information Request #4, Inspection Schedule	1/12/2022
761263/9 Response to OPMA Information Request #5	2/1/2022
761263/11 Response to OBP Information Request #6, Established Conditions	2/11/2022
761263/16 Response to OBP Information Request #7	3/31/2022
761263/17 Partial Response to OBP Information Request #8	4/11/2022
761263/18 Partial Response to OBP Information Request #8	4/18/2022
761263/19 Response to OPMA Information Request #9	4/22/2022
761263/20 (Rolling Submission, Part 4 of 4)	4/29/2022
761263/21 Response to OBP Information Request #10	5/2/2022

761263/23 Response to OBP Information Request #11	6/8/2022
761263/28 Response to OPMA Information Request	7/13/2022
761263/30 Update to Stainless Steel Vessel Comparability Protocol	7/22/2022
761263/35 Partial Response to OBP Information Request #12	8/16/2022
761263/36 Response to OBP Information Request #13	8/18/2022
761263/38 Partial Response to OBP Information Request #12	8/19/2022
761263/41 Response to OPMA Information Request #14	8/26/2022
761263/52 Response to OBP Information Request #15	10/7/2022
761263/63 Response to OBP Information Request #16	10/24/2022
761263/65 Response to OPMA Information Request #17	10/25/2022
761263/68 Response to OBP Information Request #18	11/2/2022
761263/71 Response to OBP Information Request #19, Established Conditions	11/4/2022
761263/72 Response to OBP Information Request #20	11/10/2022
761263/77 Response to OBP Information Request #21 Established Conditions	11/18/2022
761263/76 Response to OPMA Information Request #22	11/17/2022
761623/82 Response to OBP Information Request #23, Established Conditions	12/1/2022
761263/80 Response to OBP Information Request #24	11/23/2022
761263/87 Partial Response to OPMA Information Request #25, Established Conditions	12/5/2022
761263/89 Partial Response to OPMA Information Request #25,	12/7/2022

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			2	Adequate	04/06/2021 11/17/2021	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.
None

3. Consults: None

4. Environmental Assessment or Claim of Categorical Exclusion:

A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.31(c) was provided and is acceptable.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761263 for Lunsumio (mosunetuzumab-axgb) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Lunsumio (mosunetuzumab-axgb) 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. Summary of Complete Response Issues:

N/A

C. Approval Action Letter Language:

- Manufacturing location
  - Drug Substance and Drug Product: Genentech, Inc., South San Francisco, CA (FEI: 2917293)
- Fill size and dosage form: 1 mg/1 mL and 30 mg/30 mL single-dose vial
- Dating Period:
  - Drug Product: 24 months at 2 – 8°C, protected from light
  - Drug Substance: (b) (4) months at (b) (4)
  - For packaged products: Not packaged
- For stability protocols:
  - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug product and drug substance under 21 CFR 601.12.
- Exempt from lot release: Yes
  Note: Lunsumio is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations:

The proposed indication for Lunsumio (mosunetuzumab-axgb) is for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Existing treatment options for FL include anti-CD20 monoclonal antibodies, cytotoxic chemotherapy, and CAR-T therapy. However, the utility and effectiveness of these therapies are limited due to increasing refractoriness and decreasing duration of response upon repeat dosing. CAR-T therapy also has limited accessibility to patients due to the requirement of ex vivo T-cell manipulation. Patients with relapsed or refractory FL after ≥ 2 lines of prior therapies are a particularly poor prognostic group. Therefore, there remains to be an unmet medical need for novel therapies that can significantly extend the disease-free survival and overall survival, while providing acceptable safety and tolerability. Genentech was granted breakthrough designation and orphan designation for Lunsumio with an agreed upon rolling submission review.

The overall control strategy for Lunsumio 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 drug substance and drug product that have appropriate quality and are free of adventitious agents. Drug substance and drug product facilities operate in compliance with cGMP and are acceptable for manufacturing.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: None

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)	Risk	Origin	Control Strategy	Other notes
CD3+ T cell activation in the presence of CD20+ B cells (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.	(b) (4)	N/A

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

(b) (4) (product-related impurities)	Efficacy	Manufacturing process and exposure to basic and heat stress	(b) (4)	
Deamidation (b) (4) (b) (4) (product-related impurities)	Efficacy and PK	Manufacturing process and exposure to basic and heat stress		
Oxidation (b) (4) (b) (4) (product-related impurities)	Efficacy	Manufacturing process and exposure to oxidative and light stress		
Glycation (b) (4) (b) (4) (product-related impurities)	Efficacy	Exposure to glucose in culture medium	(b) (4)	N/A
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	(b) (4)	N/A
pH	Efficacy and Safety	Formulation process		N/A
(b) (4)	Efficacy and Safety	Intrinsic to DS and DP formulation		N/A
(b) (4)	Efficacy and Safety	Intrinsic to DS and DP formulation		N/A

B. Drug Substance [mosunetuzumab-axgb] 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	(b) (4)	
Host Cell DNA (process-related impurity)	Safety	Production cell line		
(b) (4) (process-related impurity)	Safety and Immunogenicity	Process-related impurity (b) (4) (b) (4)		
(b) (4) (process-related impurity)	Safety, immunogenicity	Cell bank cryopreservation medium or culture medium		

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

- Description (mosunetuzumab-axgb):

  Mosunetuzumab-axgb (BTCT4465A) is a recombinant humanized T-cell-engaging bispecific IgG1 antibody manufactured in CHO cells and is comprised of one half-antibody directed against CD20-expressing B-cells (b) (4) and one half-antibody directed against CD3-expressing T-cells (b) (4). (b) (4) half-antibody is composed of one heavy chain (452 amino acid residues) and one light chain (213 amino acid residues). (b) (4) half-antibody is composed of one heavy chain (449 amino acid residues) and one light chain (219 amino acid residues). (b) (4) (b) (4) (b) (4). The intact molecular mass of mosunetuzumab is 146,045 daltons. Mosunetuzumab harbors a (b) (4) amino acid substitution in both heavy chains (b) (4)

(b) (4)

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

  The biological activity of mosunetuzumab-axgb (BTCT4465A) against the indication of relapsed or refractory follicular lymphoma is facilitated by the simultaneously binding to CD20 on the surface of B-cells and CD3 on the surface of T-cells. The resulting immune synapse leads to T-cell activation, subsequent release of cytolytic granules, and killing of CD20-expressing B-cells.

- **Potency Assay:**

  Mosunetuzumab potency is assessed using a quantitative cell-based assay (96-well plate format) that measures the ability of mosunetuzumab to induce the activation of (b) (4) T cells in the presence of (b) (4) B cells. (b) (4) (b) (4) (b) (4) cell banks are appropriately qualified and are used directly in assay runs without additional passages. The potency assay evaluates serial dilutions of mosunetuzumab test articles, reference standard, and positive product control in the presence of a (b) (4) (b) (4) co-culture. The simultaneous binding of mosunetuzumab to (b) (4) cells induces dose-dependent luciferase expression. Luciferase expression is measured by luminescence on a plate reader upon incubation with a luciferase substrate. Data are fit using a 4-parameter logistic model. Relative potency of test articles is reported relative to the reference standard.

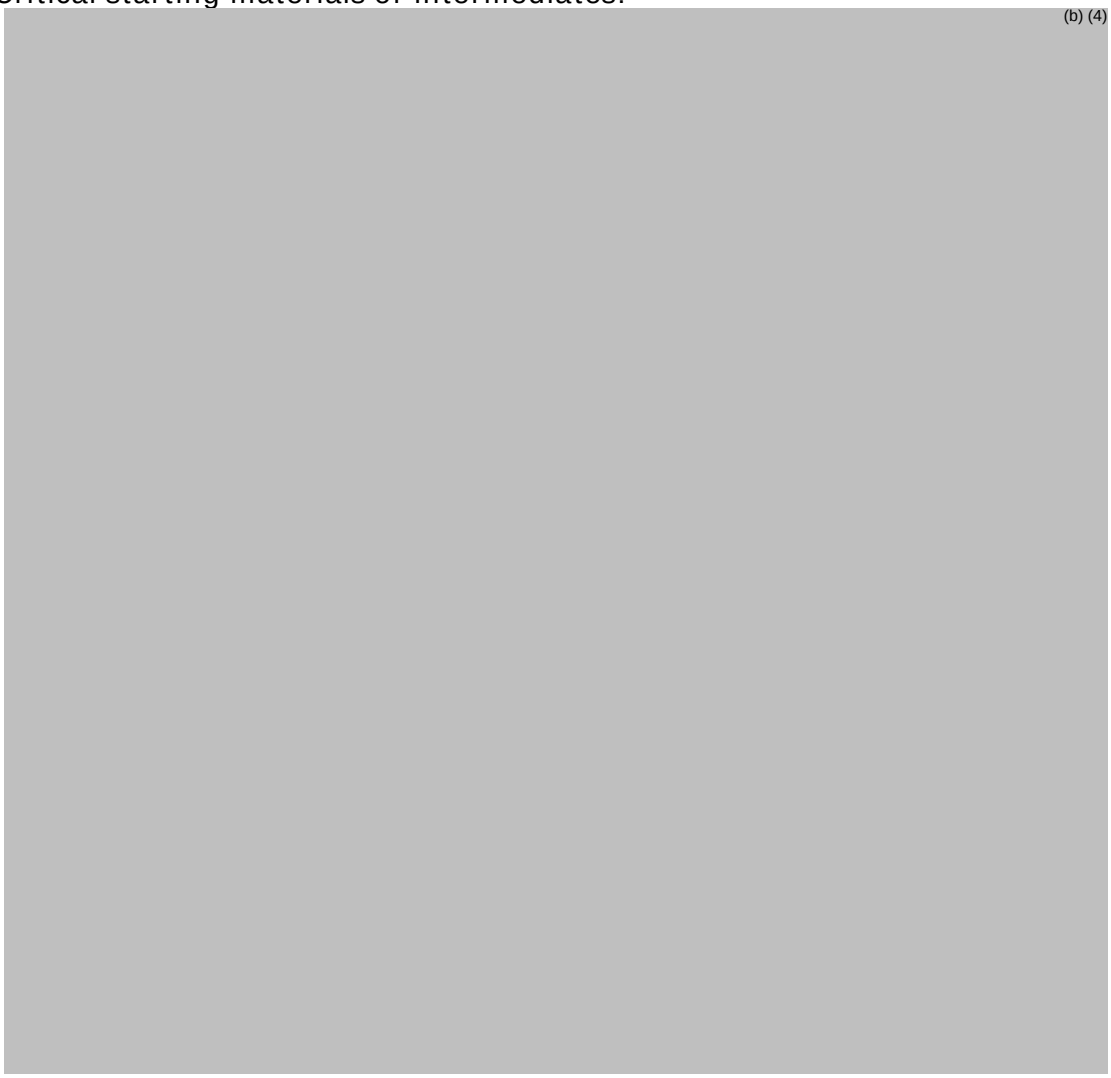
- **Reference Materials:**

(b) (4)

(b) (4)

- Critical starting materials or intermediates:

(b) (4)



- Manufacturing process summary:

Mosunetuzumab DS is manufactured at Genentech, Inc. South San Francisco.

(b) (4)

(b) (4)

Microbial control during DS manufacturing is achieved by bioburden-reduction (b) (4) (b) (4) and control of raw materials. Bioburden and endotoxin are monitored in-process (b) (4) (b) (4)

- **Container closure:**

  The DS container closure system is (b) (4) (b) (4)

- **Dating period and storage conditions**:

  The dating period for mosunetuzumab DS is (b) (4) months when stored at ≤ (b) (4)

C. Drug Product [Lunsumio] 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 related impurities)	Safety/immunogenicity	Manufacturing process and container closure system	(b) (4)	N/A

Extractable Volume (general)	Efficacy/dosing	Manufacturing process	(b) (4)	N/A
Leachables (process related impurities)	Safety	Manufacturing equipment and container closure		Acceptable long-term leachable study results for the DP container closure system were available during the review cycle through the currently proposed 24-month expiry at 2 - 8°C.
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:
  Lunsumio is supplied at 1 mg/1 mL and 30 mg/30 mL strength. Potency is defined as the percent of T cell activity (i.e., luciferase activity) relative to the current mosunetuzmab-axgb reference standard when (b) (4) T cells and (b) (4) B cells are co-cultured in the presence of mosunetuzumab. The potency assay is

the same as described for DS.

- **Summary of Product Design:**
  Lunsumio is a sterile, preservative-free, colorless solution for intravenous infusion. The 1 mg/1 mL strength is supplied in a single-dose 2 mL vial containing 1 mg mosunentuzumab-axgb, 1.6 mg (b) (4) Histidine, 0.4 mg (b) (4) acetic acid, 1.5 mg (b) (4) methionine, 82.1 mg sucrose, 0.6 mg polysorbate 20 at pH 5.8. The 30 mg/30 mL strength is supplied in a single-dose 50 mL vial containing 30 mg mosunentuzumab-axgb, 46.6 mg (b) (4) Histidine, 12.8 mg (b) (4) acetic acid, 44.8 mg (b) (4) methionine, 2462.4 mg sucrose, 18 mg polysorbate 20 at pH 5.8.

- **List of Excipients:**
  (b) (4) Histidine, (b) (4) Methionine, (b) (4) Acetic Acid, Sucrose, Polysorbate 20 and Water for Injection are all compendial.

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

- **Manufacturing process summary:**
  Lunsumio DP (1 mg/mL and 30 mg/30 mL) is manufactured at Genentech, Inc. South San Francisco. (b) (4)
  (b) (4)
  (b) (4) Bioburden and endotoxin are tested during DP manufacture, and sterility and endotoxin are tested at release. Container closure integrity is tested using a validated dye immersion or helium leak test method and is included in the stability program along with sterility.

- **Container closure:**

The 1 mg/1 mL DP container closure system is comprised of a 2 mL [(b) (4)] [(b) (4)] glass vial, 13 mm [(b) (4)] rubber stopper (latex-free), and 13 mm aluminum seal with [(b) (4)] flip-off cap.

The 30 mg/30 mL DP container closure system is comprised of a 50 mL [(b) (4)] [(b) (4)] glass vial, 20 mm [(b) (4)] rubber stopper (latex-free), and 20 mm aluminum seal with [(b) (4)] flip-off cap.

- **Dating period and storage conditions:**
  The dating period for Lunsumio is 24 months when stored at 2 - 8°C, protected from light.

- **List of co-packaged components, if applicable:** N/A

D. **Novel Approaches/Precedents:** First original BLA with proposed Established Conditions and Post-approval Lifecyle Management based on ICH Q12 principles.

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall recommendation: *APPROVED*					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, IPC testing, QC and stability testing, DS Storage, Cell Bank Storage	Genentech, Inc., South San Francisco, CA	2917293/ 080129000	PLI is required	VAI 1) Inadequate laboratory controls to assure samples conform to appropriate standards of identity, strength, quality, and purity 2) Failure to establish and validate the reliability of component suppliers' test analyses	Approved based on PLI

IPC testing	Genentech, Inc., Oceanside, CA	3006129086/ 146373191	Approve- Based on Previous History	N/A	Approve
IPC testing	(b) (4)		Approved Based on Previous History	N/A	Approve
QC and stability testing			Approved Based on Previous History	N/A	Approve
Cell Bank Storage	Genentech, Inc., Vacaville, CA	3002902534/ 004074162	No evaluation Necessary (NEN)	N/A	N/A
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture, IPC testing, QC and stability testing, DP storage	Genentech, Inc., South San Francisco, CA	2917293/ 080129000	PLI is required	VAI (Refer to DS facilities above for inspectional observations)	Approved based on PLI
QC testing (excluding endotoxin), Stability testing	(b) (4)		Approved Based on Previous History	N/A	Approve

(b) (4) Labeling and Secondary packaging, (b) (4) (b) (4)	F. Hoffmann-La Roche AG, Kaiseraugst, Switzerland	3003973536/ 485244961	No evaluation Necessary (NEN)	N/A	N/A

G. Facilities:

Genentech, Inc., South San Francisco (FEI: 2917293) is responsible for the manufacture and testing of commercial mosunetuzumab DS and DP. An onsite pre-license inspection (PLI) was conducted by the Agency from May 17 – 26, 2022. A 2-item Form FDA 483 related to laboratory controls and failure to validate the reliability of supplier's test analyses was issued to the firm upon completion of the PLI. The observations were adequately addressed by the firm. The final outcome of the inspection was Voluntary Action Indicated (VAI). All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- Master cell bank and working cell bank stability protocol
- Primary and secondary reference standard re-qualification protocol
- Future secondary reference standard qualification protocol
- Post-approval annual stability protocol
- Multi-use drug substance facility expanded protocol for Genentech, Inc. South San Francisco, Building 3 (FEI: 2917293)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
- Post-approval annual stability protocol
- (b) (4) comparability protocol
- (b) (4) protocol – manufacturing-scale bioburden reduction (b) (4)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

c. Established Conditions based on ICH Q12 principles: Yes

Comments: See details in PLCM document and PLCM Addendum under Seq#0089

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/s/

WILLIE N WILSON
12/09/2022 03:36:25 PM

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

Application ID	BLA 761263
Submission Type	Original BLA
Drug Product Name	LUNSUMIO® (mosunetuzumab-axgb)
Strengths	1 mg/1 mL, 30 mg/30 mL (1 mg/mL)
Dosage Form	Liquid single-use vial
Administration Route	Intravenous infusion
Indication	Treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior systemic therapies
Applicant Name	Genentech, Inc.
US License Number	1048
Application Type	351 (a)
Primary Reviewer	Yun Wu, Ph.D., Staff Fellow, OPQ/OPMA/DBM-1
Secondary Reviewer	Microbiology: Maxwell Van Tassell, Ph.D., Senior Pharmaceutical Quality Assessor (SPQA), OPQ/OPMA/DBM-1 Facilities: Zhong Li, Ph.D., SPQA, OPQ/OPMA/DBM-1
Goal Date	12/29/2022

Recommendation for Approvability:

- The drug substance portion of BLA 761263, as amended, was reviewed from a product quality microbiology perspective and is recommended for Approval.
- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) (b) (4). Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at DS release. Microbial control (b) (4) (b) (4) was demonstrated by including microbial monitoring in their lifetime studies. Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Genentech Inc, South San Francisco, CA (FEI 2917293), proposed for mosunetuzumab DS manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	N/A
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process		N/A

List Submissions being assessed (Table):

Document (SD #)	Description	Date Received
Sequence 0001 (SDN 1)	Rolling Submission, Part 1 of 2	08/09/2021
Sequence 0002 (SDN 2)	Production Schedule	09/24/2021
Sequence 0008 (SDN 8)	Updated Production Schedule	01/12/2022
Sequence 0009 (SDN 9)	Response to IR 01/18/2022	02/01/2022
Sequence 0011 (SDN 11)	Updated ICH 12 documents	02/11/2022
Sequence 0019 (SDN 19)	IR Response	04/22/2022
Sequence 0023 (SDN 23)	IR Response (OBP)	06/08/2022
Sequence 0029 (SDN 28)	IR Response	07/13/2022

Application Submission Background

Reviewer's Comment: For Information

Genentech Inc. has submitted BLA 761263 for the market approval of mosunetzumab, a humanized T-cell dependent bi-specific antibody. Mosunetuzumab drug substance (DS) (b) (4) and drug product (DP) are manufactured at Genentech Inc., South San Francisco, CA (FEI: 2917293).

BLA 761263 was submitted in eCTD format, with the rolling submission completed in sequence 0020, dated 04/29/2022. This review contains an assessment of the DS manufacturing process for mosunetuzumab DS from a microbial control and product quality microbiology perspective. For microbiology review of the DP manufacturing process, refer to review memo by Dr. Lindsey Brown.

MODULE 3.2.S

Module 3.2.S Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

S.1 General Information

Mosunetzumab is a recombinant humanized bi-specific IgG1 antibody composing of two half-antibodies that target B-cell antigen CD20 and T-cell antigen CD3ε, respectively. Simultaneous binding of mosunetuzumab to CD20 and CD3 leads to immune synapse formation, T-cell activation, and subsequent release of cytolytic granules from the T-cell, which kills the CD20-expressing B-cells in patients with non-Hodgkin Lymphoma. (b) (4)

(b) (4)

Reviewer's Comment: For Information

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are proposed for mosunetuzumab DS manufacturing and/or testing.

Facility	FEI	Location	Proposed operations
Genentech, Inc (SSF)	2917293	South San Francisco, CA	DS manufacturing, in-process control, release, and stability testing of DS, DS storage, Adventitious agent testing (including mycoplasma and MMV by qPCR), MCB/WCB preparation and storage
(b) (4)			Stability testing
Genentech, Inc	3006129086	Oceanside, CA	Adventitious agent testing (including mycoplasma and MMV by qPCR)
(b) (4)			Adventitious agent testing (mycoplasma by qPCR only, general viral screening, MMV by qPCR)
Genentech, Inc	3002902534	Vacaville, CA	MCB/WCB storage

Reviewer's Evaluation: Refer to Table S.2.1-1 for analytical tests performed at each facility (updated in sequence 0023). Refer to Facility Assessment at the end of this review memo for CGMP compliance status of the facilities.
Assessment: **SATISFACTORY**

S.2.2 Description of the Manufacturing Process and Process Controls

(b) (4)

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Zhong Li

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Yun Wu

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Date: 7/27/2022 10:53:01AM
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Maxwell Van Tassell

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