CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761345Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: July 19, 2023

1. Application/Product Information

BLA number	761345
Submission Type	Original
Regulatory Pathway	351 (a), Fast track, Breakthrough, Accelerated
Associated IND/BLA	IND 133940
Review Designation	Priority
Applicant	Pfizer Inc.
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD 38 monoclonal antibody.
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name** Elrexfio
	Non-proprietary Name/Code Name Elranatamab-bcmm/PF-06863135
	OBP Naming BSMAB: MAB HUMANIZED (IGG2) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [PF06863135]
Drug Product Description	The drug product is supplied as a clear to slightly opalescent, and colorless to pale brownish liquid solution. Each mL contains 40 mg elranatamab-bcmm, edetate disodium (0.045 mg), histidine (1.12 mg), L-histidine hydrochloride monohydrate (2.67 mg), polysorbate 80 (0.2 mg), sucrose (85 mg) and Water for injection. The pH is 5.8.

	Elranatamab is a heterodimeric humanized full-length bispecific antibody (BsAb) consisting of a BCMA binding arm and a CD3 binding arm, as well as a modified human IgG2ΔA Fc region		
Dosage Form	Injection		
Strength	44 mg per 1.1 mL and 76 mg per 1.9 mL (40 mg/mL)		
Route of Administration	Subcutaneous		
Primary Container Closure System	5 mL glass vial sealed with a stopper and an aluminum seal with flip-off plastic cap		
Device Information	N/A (vial product only)		
Co-packaged Product Information	N/A		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	You (Joy) Zhuo	Anjali Shukla
	Drug product	You (Joy) Zhuo	Anjali Shukla
	Immunogenicity Assay	You (Joy) Zhuo	Anjali Shukla
	Facilities	Hamet Touré (Drug substance (DS)) Maria Gutierrez-Hoffmann (Drug product (DP))	Michael Shanks
	Microbiology	Hamet Touré (DS) Maria Gutierrez-Hoffmann (DP)	Madushini Dharmasena

	RBPM	Anika Lalmansingh
	ATL	Anjali Shukla
OPQ Issued Consults	None	

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

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761345 for Elrexfio manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Elrexfio is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Wyeth BioPharma
  Division of Wyeth Pharmaceuticals LLC
  1 Burtt Road
  Andover, Massachusetts (MA) 01810
  United States
- **Drug Product:** Pharmacia & Upjohn Company LLC
  7000 Portage Road
  Kalamazoo, Michigan (MI) 49001,
  United States

b. Fill size and dosage form: 44 mg/1.1 mL and 76 mg/1.9 mL; injection

c. Dating Period:

- **Drug Product:** 18 months when stored at 5 ± 3°C
- **Drug Substance:** (b) (4) months when stored at (b) (4) °C [1]
- **Intermediate Substance, if applicable:** Not applicable
- **For packaged products:** Not packaged
- **Stability Option:**
  - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration

[1] The response to information request received July 19, 2023 corrected the discrepancy between Sections 2.3.S.7.1 and 3.2.S.7.1 regarding the proposed drug substance shelf life. The shelf life of the drug substance is (b) (4) months when stored at (b) (4) °C.

dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Elrexfio is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments:

Conduct a Low Endotoxin Recovery (LER) study at process relevant temperature and duration to ensure that the bacterial endotoxins analytical method for release can reliably detect endotoxin in elranatamab drug product. (b) (4) In case the study shows endotoxin recoveries below 50% at process relevant conditions, develop an alternative endotoxin method to mitigate LER.

4. Basis for Recommendation

a. Summary:

Elranatamab is a heterodimeric BsAb consisting of a BCMA binding arm and a CD3 binding arm, as well as a modified human IgG2ΔA Fc region for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD 38 monoclonal antibody (mAb). The mechanism of action of elranatamab is to simultaneously bind the BCMA cell surface receptor on multiple myeloma cells and the CD3 epsilon (CD3ε) T-cell co-receptor on the surface of cytotoxic T-cells, to enable targeted T-cell mediated lysis of BCMA presenting tumor cells. This mechanism of action allows T cells to recognize specific antigenic peptides in the context of MHC class I through direct co-engagement of CD3ε expressed on the T cell and BCMA expressed on the myeloma tumor cell surface. This expands the repertoire of T cells that can recognize and respond against BCMA-expressing cells.

A cell-based bioassay is used to control the potency of elranatamab. This assay measures the ability of elranatamab to enable T-cell mediated BCMA tumor cell apoptosis. Potency results are reported as percentage relative to a qualified reference standard.

(b) (4)

(b) (4) Current data suggests a possible LER effect in the drug product. A post-marketing commitment (PMC) has been agreed upon to conduct a LER study to ensure reliability of the endotoxin method to detect endotoxin in the DP, and to develop an alternate endotoxin method if this study showed unacceptable endotoxin recovery. This is not an approvability issue because data from two DP lots provides reasonable assurance of endotoxin detectability by the current endotoxin method. Additionally, the endotoxin acceptance criteria in the DP specifications provides a safety margin of (b) (4) should LER occur. The manufacturing processes and overall control strategies for Elrexfio are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Wyeth BioPharma (FEI 1222181) and Pharmacia & Upjohn Company LLC (FEI 1810189), proposed for elranatamab-bcmm DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Elrexfio (i.e., there is no specific test method described in regulation for Elrexfio that establishes an official standard of potency). We next considered whether potency is a factor for Elrexfio within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Elrexfio for purposes of § 610.61(r) because lot variability is not a concern for Elrexfio as Elrexfio's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

- (b) (4)
- Post-Approval Drug Substance Stability Protocol and Stability Commitment
- Extension of Drug Substance Shelf-life

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

- Extension of Drug Product Shelf-life
- Post-Approval Drug Product Stability Protocol and Stability Commitment
- Comparability Protocol for the Introduction of New Products to Pfizer, Andover, MA

ii. Residual risk: Refer to Sections 3e and 4 of this memo regarding discussion of low endotoxin recovery and associated PMC.
iii. Future inspection points to consider: None

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

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 7/19/2023 02:24:32PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

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/

ANIKA A LALMANSINGH
07/20/2023 09:22:38 AM

ANJALI A SHUKLA
07/20/2023 10:06:25 AM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 28, 2023
Assessor:	Liming Lu, PharmD, RPh. Labeling Assessor Office of Biotechnology Products (OBP)
Through:	You Zhuo, PhD. Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761345
Applicant:	Pfizer Inc
Submission Date:	December 19, 2022
Product:	Elrexfio (elranatamab-bcmm)
Dosage form(s):	Injection
Strength and Container-Closure:	44 mg/1.1 mL (40 mg/mL) single-dose vial 76 mg/1.9 mL (40 mg/mL) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the approval of bispecific BCMA/CD3 antibody ELREXFIO (elranatamab-bcmm) injection for subcutaneous use by the healthcare provider only for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
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).

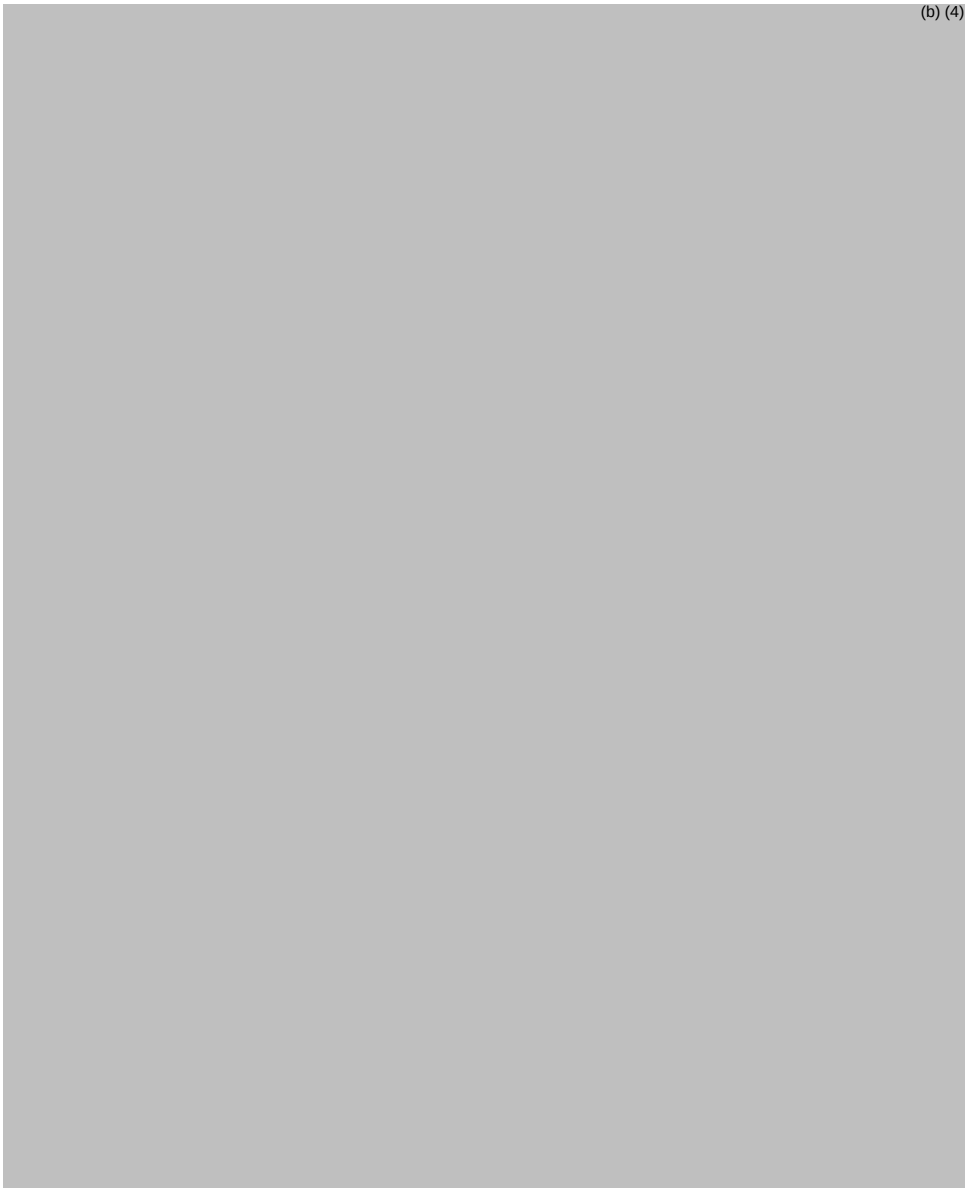
CONCLUSION

The prescribing information (submitted on July 27, 2023), medication guide (submitted on July 27, 2023), container labels (submitted on July 3, 2023), and carton labeling (submitted on July 3, 2023) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

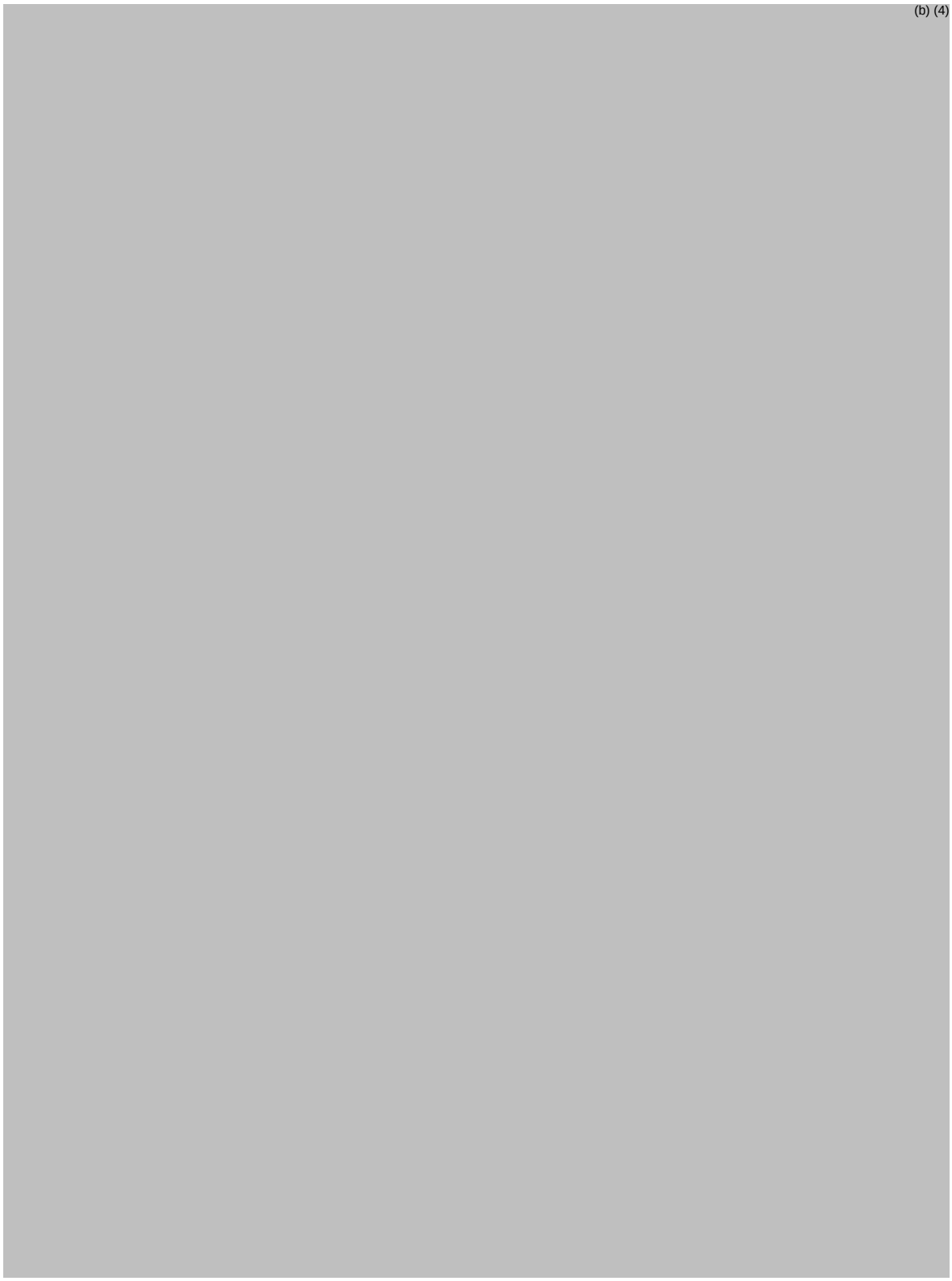
Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on December 19, 2022)
  \\CDSESUB1\EVSPROD\bla761345\0002\m1\us\elranatamab-uspi-fpi-lab-1518-0-1-mg-1551-0-1-clean.docx
- Container Labels (submitted on December 19, 2022)
  44 mg/1.1 mL (40 mg/mL) single-dose vial
  \\CDSESUB1\EVSPROD\bla761345\0002\m1\us\draft-vial-44mg.pdf



- Carton Labeling (submitted on December 19, 2022)
  44 mg/1.1 mL (40 mg/mL) single-dose vial
  \\CDSESUB1\EVSPROD\bla761345\0002\m1\us\draft-carton-44mg.pdf

(b) (4)



76 mg/1.9 mL (40 mg/mL) single-dose vial
\\CDSESUB1\EVSPROD\bla761345\0002\m1\us\draft-carton-76mg.pdf

(b) (4)

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

[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.

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: For biological products, the Applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Refer to 21 CFR 600.3(t) for the definition of "manufacturer". We note that there is a discrepancy in the way you have listed the manufacturer address "Groton, CT 06340 in the form FDA 356h and address "NY, NY 10017" in the proposed labeling. Ensure that the manufacturer address appear exactly as the applicant listed on the submitted Form FDA 356h and revise accordingly across all labels and labeling. If necessary, correct this on your form FDA 356h.

The applicant has submitted an updated Form FDA 356h to align with the manufactured by address "NY, NY 10001" in the revised labeling.

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

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17, 21 CFR 211.137	✓ Yes ☐ No ☐ N/A

[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."

Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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

Comment/Recommendation: this is a single-dose vial.

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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

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

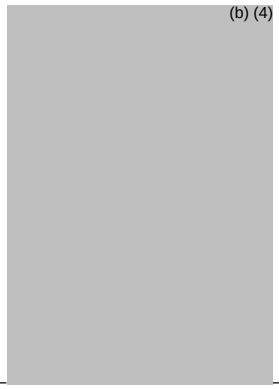
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

The applicant has confirmed 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 has confirmed that the vial circumference is 65.19 mm and the label length is 63.5 mm, leaving a 1.69 mm label gap along the full length of the vial to allow visual inspection.



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

Comment/Recommendation: Relocate the route of administration statement to appear below the strength statement.

The applicant has revised as requested.

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

No 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) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure the linear bar code is surrounded by enough white space to facilitate proper scanning.

The applicant confirmed that for both vial labels, the vertical orientation of the bar code ensures there is sufficient white space above and below the code for scanning. The applicant also confirmed the bar code orientation is horizontal in the carton labeling with adequate white space on either side of the code for scanning.

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: OBP labeling agrees with DMEPA's comment that the statement "One Single-dose vial" was sufficient for the net quantity especially the volume is already part of the strength.

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

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: vial small enough to be considered as partial label, see carton labeling comments.

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

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

Comment/Recommendation: For biological products, the applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Refer to 21 CFR 600.3(t) for the definition of "manufacturer". We note that there is a discrepancy in the way you have listed the manufacturer address "Groton, CT 06340 in the form FDA 356h and address "NY, NY 10017" in the proposed labeling. Ensure that the manufacturer address appear exactly as the applicant listed on the submitted Form FDA 356h and revise accordingly across all labels and labeling. If necessary, correct this on your form FDA 356h.

The applicant has submitted an updated Form FDA 356h to align with the manufactured by address "NY, NY 10001" in the revised labeling.

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

[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

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 ☐ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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

Comment/Recommendation: Relocate the route of administration statement to appear after the strength statement.

The applicant has revised as requested.

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: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names and amounts for inactive ingredients in your products have been revised according to the USP/NF monographs titles and per the monograph definition. Revise the inactive ingredient information to the compendial names and definitions. Inactive ingredient amounts were calculated per the USP monograph definition for edetate disodium. Edetate disodium was listed as (b) (4) (b) (4) Please confirm the calculated amount of edetate disodium (b) (4) per the monograph definition. Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the

table that includes the calculation between mg of edetate disodium (b) (4) The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 to the name and quantity presented in the USPI, container label, and carton labeling. Revise the inactive ingredient content as follows:

"Each mL of solution contains 40 mg elranatamab-bcmm, edetate disodium (0.045mg), histidine (1.12 mg), L-histidine hydrochloride monohydrate (2.67 mg), polysorbate 80 (0.2 mg), sucrose (85 mg) and Water for injection"

The applicant has 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: Remove the statement (b) (4) from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable.

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 elranatamab products (i.e., there is no specific test method described in regulation for elranatamab 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 ELREXFIO (elranatamab-xxxx) 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 (b) (4) is not required to appear on the carton labeling.

The applicant has revised as requested.

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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 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

No 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: OBP labeling agrees with DMEPA's comment that the statement "One Single-dose vial" was sufficient for the net quantity especially the volume is already part of the strength.

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

Comment/Recommendation: Revise the Statement of Dosage to both 76 mg/1.9 mL and 44 mg/1.1 mL cartons to read "Recommended Dosage: See prescribing information." to be in alignment with PLR labeling format.

The Applicant has revised as requested.

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

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 and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A

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 required verbatim statement for parenterals per 21 CFR 201.57(c)(3)(iv).

The Applicant has accepted the revision as requested.

We revised to read "… for one-time use in a single patient" to indicate how the vial is supposed to be used and not to be confused with the package type term for the product "single-dose".

The Applicant has accepted the revision as requested.

Clarify how long the vial should be held out of the refrigerator to bring it to ambient temperature.

The Applicant responded that no requirement to equilibrate to room temperature. It will be at HCP's discretion whether the injection can be comfortably administered to the patient. Providing a requirement for equilibrating to ambient temperature may lead to reporting of dosing errors unnecessary. ICH stability data at room temperature (3.2.P.8) supports storage of the vial at ambient conditions for foreseeable reasonable preparation periods and allows for flexibility in healthcare practice. OBPL considered this response is acceptable.

We revised and relocated the discard statement to the end of the preparation section.

The Applicant has accepted the revision as requested.

We added "Protect from light" statement to be consistent with the Storage and Handling information in section 16.

The Applicant responded that the "Protect from light" statement is not needed in the section. OBPL has confirmed with PQ assessor that it is acceptable as the submitted data supported the prepared dosing syringes at 30c under ambient light for 24 hours showed no impact on product quality.

Revised to include needle and syringe information "…syringe with stainless steel injection needles (b) (4) 30G) and polypropylene or polycarbonate syringe material"

The Applicant has accepted the recommendation and revised to include "30G or wider" so that the needle width is not limited beyond 30G for the healthcare professional, which is confirmed by CMC team and is acceptable from an OBP labeling perspective.

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 this statement since the dosage form is "injection".

The Applicant has accepted the revision 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 moved up this paragraph as this is still talking about drug substance.

We added the proper name to the second paragraph of section 11 for drug product.

We revised to read "ELREXFIO™ (elranatamab-bcmm) injection is a …" as the dosage form of drug product is "injection".

The Applicant has accepted the above recommendations and revised as requested.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). The established names and amounts for inactive ingredients in your products have been revised according to the USP/NF monographs titles and per the monograph definition. Edetate disodium was listed (b) (4) .

Confirm the recalculation for edetate disodium. Re-submit an updated Description and Composition Table to section 3.2.P.1 adding a footnote to the table (b) (4) The foot note should serve as a link between the names and quantities presented in section 3.2.P.1 to the name and quantities presented in the Prescribing Information and carton labeling. Ensure that all inactive ingredients with a USP monograph are provided as such. Also, inactive ingredients names have been revised to appear in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients. We've also revised the presentation of the inactive ingredients to have the quantitative amounts of the active ingredients appear in front of the name and the quantitative amounts of the inactive ingredients appear in after the name in parenthesis to differentiate the actives from inactives. *The Applicant has accepted the revision as requested to align with the inactive ingredients list from the acceptable carton labeling.*

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

Comment/Recommendation: For biological products, the applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. We note that there is a discrepancy in the way you have listed the manufacturer address "Groton, CT 06340 in the form FDA 356h and address "NY, NY 10017" in the proposed labeling. Ensure that the manufacturer address appear exactly as the applicant listed on the submitted Form FDA 356h and revise accordingly across all labels and labeling. If necessary, correct this on your form FDA 356h.

The applicant has submitted an updated Form FDA 356h to align with the manufactured by address "NY, NY 10001" in the revised labeling.

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: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names for inactive ingredients in your products are revised according to the USP/NF monographs titles: "edetate disodium,

histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and Water for Injection"
Also, inactive ingredients names have been revised to appear in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients.

The Applicant has accepted and 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

Comment/Recommendation: For biological products, the applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Refer to 21 CFR 600.3(t) for the definition of "manufacturer". We note that there is a discrepancy in the way you have listed the manufacturer address "Groton, CT 06340" in the form FDA 356h and address "NY, NY 10017" in the proposed labeling. Ensure that the manufacturer address appear exactly as the applicant listed on the submitted Form FDA 356h and revise accordingly across all labels and labeling. If necessary, correct this on your form FDA 356h.

The applicant has submitted an updated Form FDA 356h to align with the manufactured by address "NY, NY 10001" in the revised labeling.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on July 27, 2023)
  \\CDSESUB1\EVSPROD\bla761345\0068\m1\us\lab-1518-0-7-pkg-insert-uspi-clean.docx
- Medication Guide (submitted on July 27, 2023)
  \\CDSESUB1\EVSPROD\bla761345\0068\m1\us\lab-1551-0-3-pkg-insert-mg-clean.docx
- Container Labels (submitted on July 3, 2023)
  44 mg/1.1 mL (40 mg/mL) single-dose vial
  \\CDSESUB1\EVSPROD\bla761345\0054\m1\us\vial-label-44mg.pdf

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Liming Lu

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GUID: 633d82d0001fb9cd8535e78c71271f3d

You Zhuo

Digitally signed by You Zhuo
Date: 7/28/2023 10:20:50AM
GUID: 60c39a3f0023a03a304eca615370b5c7

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

Application ID	BLA-761345
Submission Type	Original BLA
Drug Product Name	ELREXFIO (elranatamab)
Strengths	76 mg/1.9 mL and 44 mg/1.1 mL (40 mg/mL)
Dosage Form	Solution for injection in a single-dose vial
Administration Route	Subcutaneous injection
Indication	For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Applicant Name	Pfizer Inc.
Application Type	351(a)
Primary Reviewer	Maria G. Gutierrez-Hoffmann, Ph.D.
Secondary Reviewer	Madushini Dharmasena, Ph.D.
Facilities Secondary Reviewer	Michael Shanks, Ph.D.
Goal Date	08/19/2023

Recommendation for Approvability:

- This BLA was reviewed from a sterility assurance perspective and is recommended for Approval with the following Post Marketing Commitment:

    - Conduct a Low Endotoxin Recovery (LER) study at process relevant temperature and duration to ensure that the bacterial endotoxins analytical method for release can reliably detect endotoxin in elranatamab drug product. (b) (4) In case the study shows endotoxin recoveries below 50% at process relevant conditions, develop an alternative endotoxin method to mitigate LER.
      Implementation Date: **29 March 2024**

- 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):

(b) (4)

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Maria Gutierrez-Hoffmann

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Madushini Dharmasena

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BLA STN 761345

Elranatamab-bcmm

Pfizer Inc.

OBP CMC Assessment Data Sheet

1. BLA#: STN 761345

2. Assessment Date: July 5, 2023

3. Primary Assessment Team:

Medical Officer		Rachel Ershler / Bindu Kanapuru
Clinical Pharmacology		Yue Xiang / Xiling Jiang
Pharm/Tox		Daniela Torres / Brenda Gehrke
Statistics		Jing Zhang / Qing Xu
DMEPA		Christina Topper / Hina Mehta
Product Quality Team	OBP Drug Substance, Drug Product, and Immunogenicity	You (Joy) Zhuo
	Drug Substance Microbiology/Facility	Hamet Touré
	Drug Product Microbiology/Facility	Maria Gutierrez-Hoffmann
	Facility secondary	Michael Shanks
	Micro Secondary	Madushini Dharmasena
	OBP Labeling	Liming Lu
	RBPM	Anika Lalmansingh
	Application Technical Lead	Anjali Shukla

4. Major GRMP Deadlines:

   a. Filing Meeting (Internal): February 01, 2023
   b. Mid-cycle meeting (Internal): March 21, 2023
   c. Mid-cycle meeting (Sponsor): April 12, 2023
   d. Late-Cycle meeting (Internal): June 23, 2023
   e. Primary assessment due: July 05, 2023
   f. Secondary assessment due: July 19, 2023
   g. Late-Cycle meeting (Sponsor): July 13, 2023
   h. Project Orbis Partners (POP) CMC teleconference: July 20, 2023
   i. Wrap-up meeting: July 24, 2023
   j. PDUFA action date: August 19, 2023

5. Communications with Sponsor and OND:

Communication/Document:	**Date:**
CMC Pre-BLA Meeting	March 9, 2022
Application Orientation Meeting	January 20, 2023

Mid-Cycle Meeting	April 12, 2023
Late-Cycle Meeting	July 13, 2023

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (yes or no):
Original BLA Submission (SDN 1)	November 3, 2022	Yes
Response to IR#1 (SDN 16/eCTD 0017)	March 9, 2023	Yes
Response to IR#2 (SDN 26/eCTD 0027)	April 4, 2023	Yes
Response to IR#3 (SDN 30/eCTD 0031)	April 14, 2023	Yes
Response to IR#4 (SDN 38/eCTD 0039)	May 25, 2023	Yes
Response to IR#5 (SDN 41/eCTD 0042)	June 9, 2023	Yes
Response to IR#6 (SDN 46/eCTD 0047)	June 16, 2023	Yes
Response to IR#7 (SDN 49/eCTD 0050)	June 23, 2023	Yes
Response to IR#8 (SDN 52/eCTD 0053)	June 29, 2023	Yes

7. Drug Product Name/Code/Type:

a. Proprietary Name: Elrexfio
b. Trade Name: Elrexfio
c. Non-Proprietary Name/USAN: Elranatamab-bcmm

d. CAS Name: 2408850-14-4

e. Common Name: *Not Applicable*

f. INN Name: Elranatamab

g. Compendial Name: *Not Applicable*

h. OBP systematic name: BSMAB: MAB HUMANIZED (IGG2) ANTI Q02223 (TNR17_HUMAN) & ANTI P07766 (CD3E_HUMAN) [PF06863135]

i. Other names: PF-06863135

8. Pharmacological Category: Bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager

9. Dosage Form: Injection

10. Strength/Potency:

(i) The concentration/strength of the Drug Product: 44 mg elranatamab per 1.1 mL (40 mg/mL) and 76 mg elranatamab per 1.9 mL (40 mg/mL)

(ii) Type of potency assay: A cell-based bioassay to measure the biological activity of T-cell activation upon BCMA binding is used for elranatamab drug substance and drug product release and stability testing. The bioassay uses an effector Jurkat cell line co-incubated with a BCMA-presenting cell line (MM.1S). The effector cell line expresses endogenous TCR/CD3 and has been genetically engineered to express a luciferase reporter driven by an NFAT-response element (NFAT-RE). Elranatamab simultaneously binds to BCMA on the target cells and CD3 on the effector cells, leading to a dose-dependent increase in T-cell activation that generates an NFAT-RE mediated luminescence that is proportional to the concentration of elranatamab.

11. Route of Administration: Subcutaneous injection

12. Referenced Drug Master Files (DMF):

Table 1. DMF information

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

13. Inspectional Activities: Pre-license inspections of the elranatamab drug substance and drug product manufacturing facilities are waived. Refer to Site Inspection Determination finalized in Panorama on March 16, 2023.

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

A Cause-and-Effect matrix was used to evaluate the relationship of process parameters/material attributes (MA) to product quality attributes (QA) and process performance attributes. The criticality of drug substance and drug product QA was assessed based on the impact of the QA on potency, safety, immunogenicity, and pharmacokinetics (PK) of elranatamab.

(b) (4)

16. Precedents: None

17. Administrative:

Signature Block	
Name and Title	**Signature and Date**
You Zhuo, Ph.D. Primary Reviewer, CDER/OPQ/OBP/DBRR II	See electronic signature and date
Anjali Shukla, Ph.D. Application Technical Lead, CDER/OPQ/OBP/DBRR II	See electronic signature and date

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V. Assessment of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

The Pfizer Inc. requests a categorical exclusion from the preparation of an environmental assessment on the basis of 21 CFR 25.31(c) for the production of elranatamab (PF-06863135). To Pfizer Inc.'s knowledge, no extraordinary circumstances exist.

Assessor's comment: *Elranatamab is composed of proteins that are expected to be rapidly degraded to amino acids and mineralized to carbon dioxide by microbial activity. The Applicant's assessment and claim of categorical exclusion from preparation of an environmental assessment are acceptable.*

VI. Primary Container Labeling Assessment

The OBP assessment of the primary container labeling was performed by Liming Lu with concurrence from You Zhuo. The OBP labeling assessment will be uploaded as a separate file in Panorama.

VII. Assessment of Common Technical Document- Quality Module 3.2

Table 3. Critical Quality Attributes

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
Identity					
Identity by peptide mapping	Both	Potency, safety, efficacy	Intrinsic to molecule	(b) (4)	Primary structure is confirmed by peptide mapping, unique to elranatamab. (refer to 3.2.S.3.1)
Higher order structure	Both	Potency, safety, efficacy	Intrinsic to molecule		(b) (4)
Biological Activities					
Potency by cell-based bioassay	Both	Potency, safety, efficacy	Intrinsic to molecule, in-process, storage and handling	(b) (4)	The cell-based bioassay reflects the presumed primary mechanism of action and is adequately validated.
Antigen binding	Both	Potency, safety, efficacy	Intrinsic to molecule, in-process, storage and handling		(b) (4)

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
FcRn binding	Both	PK, efficacy	Intrinsic to molecule, in-process, storage and handling	(b) (4)	
General Properties					
Appearance-Color	Both	Safety and efficacy	Formulation, contamination, and storage	(b) (4)	n/a
Appearance-Clarity	Both	Safety and efficacy	Formulation, contamination, in-process and storage		n/a
Appearance-Visible particles	DP	Safety, immunogenicity, efficacy	In-process, CCS, storage and handling		(b) (4)
Subvisible particles	DP	Safety, immunogenicity, efficacy	In-process, CCS, storage and handling		
pH	Both	Safety and efficacy	Formulation		n/a
Osmolality	DP	Safety and efficacy	Formulation		n/a
Protein concentration	Both	Safety and efficacy	In-process, Formulation		n/a

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
Container Content for Injection	DP	Safety and efficacy	In-process	(b) (4)	n/a
Gross Content per vial	DP	Safety and efficacy	In-process		(b) (4)
Polysorbate 80 Content	DP	Safety and efficacy	Formulation and storage		
Product Variants					
Glycan profile	DS	Potency, immunogenicity, PK, safety, and efficacy	Cell bank and Fermentation		(b) (4)
Charge variants by iCE	Both	Potency, immunogenicity, PK, safety, and efficacy	Fermentation, in-process and storage.		

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
Monomer and Aggregates by SE-HPLC	Both	Potency, immunogenicity, safety, PK and efficacy.	Fermentation, In-process and storage.	(b) (4)	
HC+LC and Fragments by reducing CGE (rCGE)	Both	Potency, immunogenicity, safety, PK and efficacy.	Fermentation, In-process and storage.		
Intact IgG and Fragments by non-reducing CGE (nrCGE)	Both	Potency, immunogenicity, safety, PK and efficacy.	Fermentation, In-process and storage.		
Anti-BCMA mAb	Both	Potency and efficacy	In-process and storage.		
Anti-CD3 mAb	Both	Potency, safety and efficacy	In-process and storage.		
Anti-BCMA/Anti-CD3 mAb bispecific clip	Both	Potency, safety, and efficacy	Fermentation, In-process and storage.		
Process-related Impurities					
Host cell protein (HCP)	DS	Potency, safety, immunogenicity, PK and efficacy	Fermentation and In-process	(b) (4)	n/a
Host cell DNA (HCDNA)	DS	Safety	Fermentation and in-		(b) (4)

Critical Quality Attributes	Derived from DS, DP, or Both	Risk	Origin	Control Strategy	Other
			process	(b) (4)	
(b) (4)	DS	Potency, safety, immunogenicity, PK and efficacy	In-process ((b) (4))		
Leachables	Both	Safety	Product-contact materials and CCS		
Contaminants					
Mycoplasma	DS	Safety	Raw materials and in-process	(b) (4)	
Viral agents	DS	Safety	Raw materials and in-process		

VIII. Assessment of Immunogenicity Assays- Module 5.3.1.4

The assessment of immunogenicity assays is provided in this memorandum of review.

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You Zhuo

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Anjali Shukla

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

Application ID	BLA 761345
Submission Type	Original BLA
Drug Product Name	elranatamab
Strengths	76 mg/1.9 mL and 44 mg/1.1 mL (40 mg/mL)
Dosage Form	Solution for injection in a single-dose vial
Administration Route	Subcutaneous
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least (b) (4) prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Applicant Name	Pfizer Inc.
US License Number	2001
Application Type	351 (a)
Primary Reviewer	Hamet Touré, PharmD MPH
Secondary Reviewer	Madushini Dharmasena, Ph.D.
Goal Date	19 August 2023

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective for Drug Substance 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):

(b) (4)

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Hamet Touré

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Madushini Dharmasena

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