

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761212Orig1s000

PRODUCT QUALITY REVIEW(S)



**U.S. FOOD & DRUG
ADMINISTRATION**

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	November 25, 2025
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Prabuddha Sengupta, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761212
Applicant:	Lupin Limited (Biotech Division)
Submission Date:	May 30, 2025
Product:	Armlupeg (pegfilgrastim-unne)
Dosage form(s):	Injection
Strength and Container-Closure:	6 mg/0.6 mL in single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Armlupeg (pegfilgrastim-unne) for patients with cancer receiving myelosuppressive chemotherapy and patients with hematopoietic subsyndrome of acute radiation syndrome to decrease incidence of infection and increase survival as a biosimilar to the reference product Neulasta (pegfilgrastim) BLA 125031.
Recommendations:	The prescribing information, patient labeling, instructions for use, container labels, and carton labeling are acceptable from an OPQA III 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 carton labeling submitted on November 25, 2025 and the patient labeling, instructions for use, and container labels submitted on November 17, 2025, were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on May 30, 2025)
<\\CDSESUB1\EVSPROD\bla761212\0054\m1\us\bla-761212-uspi-clean.docx>
- Patient Information (submitted on May 30, 2025)
<\\CDSESUB1\EVSPROD\bla761212\0054\m1\us\bla-761212-ppi-clean.doc>
- Instructions for Use (submitted on May 30, 2025)
<\\CDSESUB1\EVSPROD\bla761212\0054\m1\us\bla-761212-ifu-0046.docx>
- Container Labels (submitted on May 30, 2025)

(b) (4)

- Carton Labeling (submitted on May 30, 2025)
Blister



Carton



Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ 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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.</i>	

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

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."

	☐ N/A

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

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

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ 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
<i>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)</i>	☒ 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
Comment/Recommendation: <i>The container is enclosed in a package.</i>	

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The product contains a container label.</i>	

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☐ Yes ☐ No ☒ N/A

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. <i>The applicant confirms that transparent area of 43 x 9 mm is provided as part of the proposed container label which allows visual inspection when the label is affixed to the container.</i>	

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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

<u>NDC numbers (container label)</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

<u>Preparation instructions (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☐ Yes ☐ No ☒ N/A

<u>Package type term (container label)</u>	<u>Acceptable</u>
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

<u>No misleading statements (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

<u>Prominence of required label statements (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

<u>Spanish-language (Drugs) (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The label does not display text in Spanish.</i>	

<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.20	☐ Yes ☐ No

	☒ N/A
Comment/Recommendation: <i>The drug product does not contain FD&C Yellow No. 5 or 6.</i>	

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011)</i> <i>Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ 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
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>The label is small and would be considered a partial label. Thus, a net quantity statement is not required per 21 CFR 610.60(a)(7).</i>	

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: <i>The label is small and could be considered a partial label. Thus, a dosage statement is not required per 21 CFR 610.60(a)(7).</i>	

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes

	☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required per 21 CFR 610.60(a)(7).</i>	

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: <i>The label is small and could be considered a partial label. Thus, an storage requirement statement is not required per 21 CFR 610.60(a)(7).</i>	

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

Package⁶ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ 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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

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.

Comment/Recommendation: *Note the applicant does not have a U.S. License number so the labeling contains a placeholder. The U.S. License number will be issued at the time of the licensure of the BLA.*

Relocate the placeholder for U.S. license number to appear directly underneath the manufacturer information as follows:

Manufactured by:
 Lupin Limited (Biotech Division)
 Gat No. 1156, 1157, 1158, 1159 and 1160,
 Village-Ghotawade, Taluka0Mulshi,
 Pune – 412115, Maharashtra, India
 U.S. License No.

The applicant revised as requested.

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
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ 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
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ 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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ 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, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comments/Recommendations: The Applicant revised the quantity for sodium acetate to (b) (4) mg. The correct quantity for sodium acetate anhydrous should be 0.066 mg. Please revise the quantity back to 0.066 mg. Refer to 3.2.P.1 Description and Composition of the Drug Product submitted on 11/08/25: (b) (4) Inactive ingredients should be listed using established names for drugs to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) Section 502(e). The established name is sodium acetate. Thus, sodium acetate should appear as "sodium acetate (0.066 mg)". <i>The Applicant revised as recommended.</i>	

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: <i>Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for pegfilgrastim-unne products (i.e., there is no specific test method described in regulation for pegfilgrastim-unne 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 Armlupep 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.</i>	

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ 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 <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (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
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Package type term (package labeling)	Acceptable
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ 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
Comment/Recommendation: <i>The label does not display text in Spanish.</i>	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The drug product does not contain FD&C Yellow No. 5 or 6.</i>	

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

	☒ N/A
Comment/Recommendation: <i>The drug product does not contain phenylalanine.</i>	

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: <i>The drug product does not contain sulfites.</i>	

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

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

Other (package labeling)	Acceptable
	☐ 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
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv) <i>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</i>	☒ Yes ☐ No ☐ N/A

<i>and discoloration prior to administration, whenever solution and container permit.”</i>	
<i>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</i> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
<u>3 DOSAGE FORMS AND STRENGTHS</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
<u>11 DESCRIPTION</u>	<u>Acceptable</u>
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), FD&C Act Section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We relocated the drug product description to the second paragraph. The Applicant revised the quantity for sodium acetate to (b) (4) mg. The correct quantity for sodium acetate (b) (4) should be 0.066 mg. Please revise the quantity back to 0.066 mg. Refer to 3.2.P.1 Description and Composition of the Drug Product submitted on 11/08/25: (b) (4) (b) (4) Inactive ingredients should be listed using established names for drugs to ensure that all FDA approved labeling fulfills the Federal	

Food, Drug, and Cosmetic Act (FD&C Act) Section 502(e). The established name is sodium acetate. Thus, sodium acetate should appear as "sodium acetate (0.066 mg)" in the Prescribing Information.

The applicant revised as requested.

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

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

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes
	☐ No
	☐ N/A
<i>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)</i>	☒ Yes
	☐ No
	☐ N/A

Medication Guide Evaluation: NA

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	Acceptable
<i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018)). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	Acceptable
<i>Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☒ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
<i>Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022)). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	
<i>Recommended labeling practices for IFU: Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	Acceptable ☒ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	Acceptable ☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	
21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
<i>Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). 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)</i>	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on November 25, 2025)
<\\CDSESUB1\EVSPROD\bla761212\0061\m1\us\bla-761212-uspi-clean.docx>
- Patient Information (submitted on November 17, 2025)
<\\CDSESUB1\EVSPROD\bla761212\0059\m1\us\bla-761212-ppi-clean.doc>
- Instructions for Use (submitted on November 17, 2025)
<\\CDSESUB1\EVSPROD\bla761212\0059\m1\us\bla-761212-ifu-0046.docx>
- Container Labels (submitted on November 17, 2025)

(b) (4)

- Carton Labeling (submitted on November 25, 2025)

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as
b4 (CCI/TS) immediately following this page



Diana
Pei

Digitally signed by Diana Pei

Date: 11/26/2025 10:18:10AM

GUID: 6352da2c009ad0777a2c3b47ec094b9a

Comments: Approved on behalf of Jennifer Kim



Prabuddha
Sengupta

Digitally signed by Prabuddha Sengupta

Date: 11/26/2025 10:40:02AM

GUID: 626b341b016e86a817c5193a7d0ac483

BLA Executive Summary

Assessment Date: 11/10/2025

1. Application/Product Information

BLA number	761212
Submission Type	2 nd Resubmission
Regulatory Pathway	351 (k)
Associated IND/BLA	IND 131463
Review Designation	Class 2 resubmission
Applicant	Lupin Limited (Biotech Division)
Indication	Armlupeg is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Armlupeg Non-proprietary Name/Code Name Pegfilgrastim-unne/LUBT 004 OBP Naming CONJ: RPROT P09919 (CSF3_HUMAN); PEG [LUBT 004]
Drug Product Description	Armlupeg drug product (DP) is a sterile, clear, colorless, and preservative-free solution. Armlupeg is supplied in a single-dose prefilled syringe (PFS) with a 27G½ inch needle and rigid needle shield with UltraSafe Plus Passive Needle Guard. Each PFS contains 6 mg/0.6 mL of pegfilgrastim-unne at 10 mg/mL concentration at pH

	4.0. Each DP injection of 0.6 mL dose contains 6 mg pegfilgrastim-unne, 0.77 mg glacial acetate acid, 0.02 mg polysorbate 20, 0.066 mg sodium acetate and 30 mg ^{(b) (4)} sorbitol in Water for Injection, USP. Pegfilgrastim-unne is a covalent conjugate of recombinant methionyl human granulocyte colony stimulating factor (G-CSF) and monomethoxypolyethylene glycol. The average molecular weight of pegfilgrastim-unne is approximately 39 kDa.		
Dosage Form	Injection		
Strength	6 mg/0.6 mL		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	The primary packaging components of Armlupeg DP are Type ^{(b) (4)} glass syringe with a 27 G ½ inch fixed injection needle, a rigid needle shield and ^{(b) (4)} ^{(b) (4)} rubber stopper (manufactured by ^{(b) (4)} ^{(b) (4)}).		
Device Information	The final Armlupeg DP is assembled with ^{(b) (4)} Ultrasafe® plus passive needle safety guard. The needle shield contains natural rubber which has been reflected in the final prescribing information.		
Co-packaged Product Information	NA		
	Discipline	Primary	Secondary
	Drug substance	Prabuddha Sengupta	Xiaoshi Wang
	Drug product	Prabuddha Sengupta	Xiaoshi Wang

OPO Review Team at this current resubmission	Immunogenicity Assay	Prabuddha Sengupta	Xiaoshi Wang
	Facility	Ralph Bernstein	Cassandra Abellard
	Microbiology	Ralph Bernstein	Virginia Carroll
	RBPM	Hannah Lee	
	ATL	Xiaoshi Wang	
OPO Issued Consults	NA		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761212 for Armlupeg manufactured by Lupin Limited (Biotech Division). The data submitted in this application are adequate to support the conclusion that the manufacture of Armlupeg is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Armlupeg is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. 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
G-CSF intermediate (unpegylated G-CSF/LUBT 001) and drug substance (pegylated G-CSF/LUBT 004): Lupin Limited (Biotech Division), Gat No. 1156, 1157, 1158, 1159 and 1160, Village- Ghotawade, Taluka-Mulshi, Pune, Maharashtra, India (FEI: 3010977634)
- Drug Product: Lupin Limited (Biotech Division), Gat No. 1156, 1157, 1158, 1159 and 1160, Village- Ghotawade, Taluka-Mulshi, Pune, Maharashtra, India (FEI: 3010977634)

b. Fill size and dosage form: 6 mg/0.6 mL (10 mg/mL) injection in 1 mL PFS

c. Dating Period:

- Drug Product: 36 months when stored at 2°C-8°C
- Drug Substance: (b) (4) months when stored at (b) (4)

- Intermediate Substance: (b) (4) months for G-CSF intermediate when stored at (b) (4)
 - For packaged products: NA
 - Stability Option:
 - Limited stability data
 - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
 - For stability protocols:
 - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- d. Exempt from lot release:
- Yes
 - Rationale, if exempted: Armlupeg is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

Armlupeg is a proposed biosimilar to the US-licensed Neulasta. Pegfilgrastim-unne is a covalent conjugate of recombinant methionyl human G-CSF produced in *Escherichia coli* (*E. coli*) (b) (4) and a 20 kDa polyethylene glycol (PEG). Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. Pegylated G-CSF has the same Mechanism of Action (MoA) as G-CSF.

Armlupeg DP is a sterile, clear, colorless, and preservative-free solution. Each PFS contains 6 mg/0.6 mL of pegfilgrastim-unne at 10 mg/mL concentration at pH 4.0. Each DP injection of 0.6 mL dose contains 6 mg pegfilgrastim-unne, 0.77 mg glacial acetate acid, 0.02 mg polysorbate 20, 0.066 mg sodium acetate and 30 mg (b) (4) sorbitol in Water for Injection, USP.

Refer to OPQ Quality Executive Summary uploaded in DARRTS on January 21, 2022 during the initial review cycle for Armlupeg DS and DP quality summary and evaluation of comparative analytical assessment.

The data submitted in the original BLA 761212, the resubmission submitted on May 14, 2024, and this current 2nd resubmission support the conclusion that the manufacturing process for Armlupeg DS and DP is well-controlled and leads to a product that is pure and potent. The DS and DP are free from endogenous and adventitious infectious agents. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Lupin Limited (Biotech Division) at Pune, Maharashtra, India, (FEI: 3010977634). All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage.

From product quality, microbiology and facility perspectives, it is recommended that Armlupeg be approved for human use under conditions specified in the package insert. The data and information provided in the BLA supports that Armlupeg is highly similar to US-Neulasta, notwithstanding minor differences in clinically inactive components.

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 pegfilgrastim (i.e., there is no specific test method described in regulation for pegfilgrastim that establishes an official standard of potency). We next considered whether potency is a factor for pegfilgrastim 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 Armlupeg for purposes of § 610.61(r) because lot variability is not a concern for Armlupeg as Armlupeg’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: refer to OPQ Quality Executive Summary uploaded in DARRTS on January 21, 2022 during the initial review cycle.
- ii. Residual risk: NA
- iii. Future inspection points to consider: NA

c. Drug Product:

- i. Protocols approved: refer to OPQ Quality Executive Summary uploaded in DARRTS on January 21, 2022 during the initial review cycle.
- ii. Residual risk: NA
- iii. Future inspection points to consider: NA

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.

Appendix. Comparative Analytical Assessment Summary

Refer to OPQ Quality Executive Summary uploaded in DARRTS on January 21, 2022 during the initial review cycle.

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/

XIAOSHI N WANG
11/10/2025 06:13:26 PM

BLA Executive Summary

Assessment Date: 11/7/2024

1. Application/Product Information

BLA number	761212
Submission Type	Resubmission
Regulatory Pathway	351 (k)
Associated IND/BLA	IND 131463
Review Designation	Class 2 resubmission
Applicant	Lupin Limited (Biotech Division)
Indication	LUBT 004 is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Armlupeg (proposed)
	Non-proprietary Name/Code Name Pegfilgrastim-unne (proposed)/LUBT 004
	OBP Naming CONJ: RPROT P09919 (CSF3_HUMAN); PEG [LUBT 004]
Drug Product Description	LUBT 004 drug product (DP) is a sterile, clear, colorless, and preservative-free solution. LUBT 004 is supplied in a single-dose prefilled syringe (PFS) with a 27G½ inch needle and a rigid needle shield with UltraSafe Plus Passive Needle Guard. Each PFS contains 6 mg/0.6 mL of LUBT 004 at 10 mg/mL concentration at pH 4.0. Each

	DP injection of 0.6 mL dose contains 6 mg LUBT 004, 0.77 mg glacial acetate acid, 0.02 mg polysorbate 20, 0.066 mg sodium acetate and 30 mg (b) (4) sorbitol in Water for Injection, USP. LUBT 004 is a covalent conjugate of recombinant methionyl human granulocyte colony stimulating factor (G-CSF) and monomethoxypolyethylene glycol. The average molecular weight of LUBT 004 is approximately 39 kDa.		
Dosage Form	Injection		
Strength	6 mg/0.6 mL (1 mL PFS)		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	The primary packaging components of LUBT 004 DP are Type (b) (4) glass syringe with a 27 G 1/2 inch fixed injection needle, a rigid needle shield and (b) (4) (b) (4) rubber stopper (manufactured by (b) (4) (b) (4))		
Device Information	The final DP is assembled with (b) (4) (4) Ultrasafe® plus passive needle safety guard. The needle shield contains natural rubber which has been reflected in the final prescribing information.		
Co-packaged Product Information	NA		
	Discipline	Primary	Secondary
	Drug substance	Prabuddha Sengupta	Xiaoshi Wang
	Drug product	Prabuddha Sengupta	Xiaoshi Wang

OPQ Review Team	Immunogenicity Assay	Prabuddha Sengupta	Xiaoshi Wang
	Facility	Candace Gomez-Broughton	Virginia Carroll
	Microbiology	Candace Gomez-Broughton	Virginia Carroll
	RBPM	Hannah Lee	
	ATL	Xiaoshi Wang	
OPQ Issued Consults	NA		

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761212 for LUBT 004 manufactured by Lupin Limited (Biotech Division). The data submitted in this application are not sufficient to support a conclusion that the manufacture of LUBT 004 is well-controlled and will lead to a product that is pure and potent. The comparative analytical data support a demonstration that LUBT 004 is highly similar to US-licensed Neulasta. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Lupin Limited (Biotech Division) to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

Following pre-license inspection of Lupin Limited (Biotech Division), Pune, Maharashtra, India (FEI 3010977634) listed in this application, FDA conveyed deficiencies to the representative of the facility. Your complete response should include the date of the facility’s response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

4. Basis for Recommendation

a. Summary:

LUBT 004 is a proposed biosimilar to the US-licensed Neulasta. LUBT 004 is a covalent conjugate of recombinant methionyl human G-CSF produced in *Escherichia coli* (*E. coli*) (b) (4) and a 20 kDa polyethylene glycol (PEG). Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment and functional activation of target cells. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. Pegylated G-CSF has the same Mechanism of Action (MoA) as G-CSF.

LUBT 004 DP is a sterile, clear, colorless, and preservative-free solution. Each PFS contains 6 mg/0.6 mL of LUBT 004 at 10 mg/mL concentration at pH 4.0. Each DP injection of 0.6 mL dose contains 6 mg LUBT 004, 0.77 mg glacial acetate acid, 0.02 mg polysorbate 20, 0.066 mg sodium acetate and 30 mg D-sorbitol in Water for Injection, USP.

Refer to OPQ Quality Executive Summary uploaded in DARRTS on January 21, 2022 during the initial review cycle for LUBT 004 DS and DP quality summary and evaluation of comparative analytical assessment.

The Office of Product Quality Assessment III, OPQ, CDER from a product quality perspective as well as the Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER from a microbiology perspective did not note any deficiencies that would preclude approval of BLA 761212 for LUBT 004 manufactured by Lupin Limited (Biotech Division). The data submitted in the original BLA and this resubmission support the conclusion that the manufacturing process for LUBT 004 is well-controlled and leads to a product that is pure and potent. The DS and DP are free from endogenous and adventitious infectious agents. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs. From product quality and microbiology perspective, it is recommended that LUBT 004 be approved for human use under conditions specified in the package insert. The data and information provided in the BLA supports that LUBT 004 is highly similar to US-Neulasta, notwithstanding minor differences in clinically inactive components.

However, during a recent re-inspection of Lupin Limited (Biotech Division) at Pune, Maharashtra, India, (FEI: 3010977634) for the DS and DP manufacturing and testing facility for this application, our field investigators issued a 5-item FDA Form 483 conveying deficiencies to the representatives of the facility. Based on the facility compliance review of the facility's

response to the FDA Form 483, a withhold is recommended for the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, OPQ is recommending a Complete Response for BLA 761212 during this assessment cycle.

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

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.

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/

XIAOSHI N WANG
11/07/2024 06:06:05 PM

VIRGINIA A CARROLL
11/07/2024 06:08:34 PM

YAN WANG
11/07/2024 06:15:40 PM

BLA Executive Summary - Addendum
Assessment Date: December 20, 2023

1. Application/Product Information

BLA number	761212
Submission Type	Original submission
Regulatory Pathway	Biosimilar 351(k)
Associated IND/BLA	IND 131463
Review Designation	Standard
Applicant	Lupin Limited (Biotech Division)
Indication	LUBT 004 is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Armlupeg (proposed)
	Non-proprietary Name/Code Name: Pegfilgrastim- unne/LUBT 004
	OBP Naming: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [LUPIN]
Drug Product Description	LUBT 004 drug product is a sterile, clear, colorless, and preservative-free solution. Each pre-filled syringe contains 6 mg/0.6 mL of LUBT 004 at 10 mg/mL concentration in pH 4.0. Each drug product injection of 0.6 mL dose for the pre-filled syringe contains 6 mg LUBT 004, 30.0 mg (b) (4) sorbitol, (b) (4) 0.02 mg polysorbate 20 in water-for-injection, USP.

Dosage Form	Solution		
Strength	6 mg/0.6 mL (1 mL pre-filled syringe)		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	1 mL Type (b) (4) glass syringe with a 27 G ½ inch fixed injection needle, a rigid needle shield and (b) (4) rubber stopper		
Device Information	Pre-filled syringe		
Co-packaged Product Information	None		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Arnold Seo, Prabuddha Sengupta and Chih-Jung Hsu	Yan Wang
	Drug product		
	Immunogenicity Assay	Chih-Jung Hsu	
	Facility	Yun Wu, Maria Gema Martin Manso and Candace Gomez-Broughton	Virginia Carroll and Lindsey Brown
	Microbiology		
	Small Molecule (mPEG and pegylation aspects of drug substance)	Zhengfu Wang	Suong Tran
	Inspection	On-site inspection team: Wayne Seifert, Yongmin Liu and Yan Wang Compliance review: Michael Shanks	
Labeling	Jennifer Kim		

	RBPM	Hamet Toure, Melinda Bauerlien and Hannah Lee	
	ATL	Yan Wang	
OPO Issued Consults	CDRH	Dunya Karimi	Alan Stevens

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761212 for LUBT 004 manufactured by Lupin Limited (Biotech Division).

The data submitted in this application are not sufficient to support a conclusion that the manufacture of LUBT 004 is well-controlled and will lead to a product that is pure and potent. The comparative analytical data support a demonstration that LUBT 004 is highly similar to US-licensed Neulasta. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Lupin Limited (Biotech Division) to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments:

Product Quality

The container closure integrity test method has not been adequately validated. The study results do not demonstrate that the limit of detection can be evaluated in the pre-filled syringe as only vials were used as breach controls. Comparability between breached vials and syringes was not demonstrated. In addition, the acceptance criterion for the positive controls in the repeatability experiments is not robust. The established criterion requires the absorbance of a minimum of only (b) (4) of 6 positive controls be greater than that of the spiked LUBT 004 drug product. Repeat the container closure integrity test method validation studies to include the appropriate controls and more robust acceptance criteria.

Facility Inspection

Following pre-license inspection of Lupin Limited (Biotech Division), Pune, Maharashtra, India (FEI 3010977634) listed in this application, FDA conveyed deficiencies to the representative of the facility. Your complete response should include the date of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

Additional Comments

We have the following comments/recommendations that are not approvability issues:



4. Basis for Recommendation

a. Summary:

LUBT 004 is a covalent conjugate of recombinant methionyl human granulocyte-colony stimulating factor (G-CSF, company code: LUBT 001) produced in Escherichia coli (E. coli) (b) (4) and a 20 kDa PEG (polyethylene glycol). LUBT 004 is a proposed biosimilar to the US-licensed Neulasta. Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors and stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is also known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. Pegylated G-CSF has the same Mechanism of Action (MoA) as G-CSF.

The Office of Biotechnology Products (OBP), OPQ, CDER from a product quality perspective as well as the Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER from a microbiology perspective did not note any deficiencies that would preclude approval of BLA 761212 for LUBT 004 manufactured by Lupin Limited (Biotech Division). The analytical similarity data submitted in the application demonstrate that LUBT 004 is highly similar to US-licensed Neulasta. Because the required inspection at Lupin Limited (Biotech Division) could not be conducted due to travel restrictions during the review cycle, the initial recommendation from OPQ for BLA 761212 was pending on the final assessment of facilities compliance, and the OPQ executive summary with detailed assessments including the comparative analytical assessment was uploaded in DARRTS on January 21,

2022. Therefore, the BsUFA date (i.e., April 2, 2022) of BLA 761212 was missed.

An on-site inspection at Lupin Limited (Biotech Division). Pune, India (FEI 3010977634) was conducted from October 3 through October 15, 2022. At the conclusion of the inspection, a seventeen-item FDA Form 483 was issued. Based on the facility compliance review of the firm's response to the FDA Form 483, OPMA recommended a withhold for the facility, and also recommended that the firm's capability, and readiness to manufacture G-CSF intermediate, LUBT 004 drug substance and drug product should be re-evaluated during a re-inspection for BLA 761212. In addition, from microbiology perspective, additional deficiency was identified that the container closure integrity test method has not been adequately validated to ensure sterility assurance of the final drug product. Therefore, OPQ is recommending a Complete Response for BLA 761212 during this assessment cycle due to deficiencies identified related to Lupin Limited (Biotech Division), Pune, India (FEI: 3010977634) facility and microbiology.

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

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.

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/

YAN WANG
12/20/2023 09:17:54 AM

CANDACE GOMEZ-BROUGHTON
12/20/2023 09:57:53 AM

PATRICK J LYNCH
12/20/2023 04:52:37 PM

First Approval for Indication/First Biosimilar/Expedited or Breakthrough Assessment: No

Recommendation: Approval pending outcome of pre-license inspection

BLA Number: 761212
Assessment Number: 1
Assessment Date: January 21, 2022

Drug Name/Dosage Form	LUBT 004 injection (pre-filled syringe for single dose injection)
Strength/Potency	6 mg/0.6 mL
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	LUBT 004 is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Applicant	Lupin Limited (Biotech Division)

Product Overview

LUBT 004 is a covalent conjugate of recombinant methionyl human granulocyte-colony stimulating factor (G-CSF) produced in *Escherichia coli* (*E. coli*) (b) (4) and a 20 kDa PEG (polyethylene glycol). LUBT 004 is a proposed biosimilar to the US-licensed Neulasta. Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. LUBT 004 drug product (DP) is a sterile, clear, colorless, and preservative-free solution. Each pre-filled syringe (PFS) contains 6 mg/0.6 mL of LUBT 004 at 10 mg/mL concentration in pH 4.0. Each DP injection of 0.6 mL dose for the PFS contains 6 mg LUBT 004, 30.0 mg (b) (4) sorbitol, (b) (4) 0.02 mg polysorbate 20 in water-for-injection, USP. The recommended dose for LUBT 004 is same as the dose for US-licensed Neulasta (i.e., 6 mg administered subcutaneously once per chemotherapy cycle).

Quality Assessment Team

Discipline	Assessor	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Arnold Seo and Chih-Jung Hsu	OPQ/OBP/DBRRII
Product Quality (small molecule - mPEG and pegylation aspects of DS)	Zhengfu Wang	OPQ/ONDP/DNDAPI/NDB3
Labeling	Koung Lee Arnold Seo	OPQ/OBP OPQ/OBP/DBRRII
Facility	Yun Wu (DS) Candace Gomez-Broughton (DP)	OPQ/OPMA/DBM/BMB1 OPQ/OPMA/DBM/BMB2
Microbiology	Yun Wu (DS) Candace Gomez-Broughton (DP)	OPQ/OPMA/DBM/BMB1 OPQ/OPMA/DBM/BMB2
Team Lead	Yan Wang (product quality)	OPQ/OBP/DBRRII

	Virginia Carroll (microbiology and facility) Suong Tran (small molecule)	OPQ/OPMA/DBM/BMB2 OPQ/ONDP/DNDAPI/NDB3
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
OBP Biosimilar Policy	Marlene Schultz-DePalo	OPQ/OBP
OBP Associate Director of Biosimilar and Biologic Policy	Joel Welch	OPQ/OBP
RBPM	Hamet Toure and Melinda Bauerlien	OPQ/OPRO

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Carleveva Thompson	OND/ORO/DROCHEN
Cross-disciplinary Team Lead	Ann Farrell	OND/OCHEN/DNH
Medical Officer	Saleh Ayache	OND/OCHEN/DNH
Pharm/Tox	Pedro DelValle; Todd Bourcier	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Xiaomeng Xu and Sudharshan Hariharan	OTS/OC/DCEP
Statistics	Xiaoyu Cai and Yeh-Fong Chen	OTS/OB/DBIX

1. Names:

- a. Proprietary Name: Armlupeg (proposed)
- b. Trade Name: Armlupeg (proposed)
- c. Non-Proprietary Name/USAN: Pegfilgrastim
- d. Chemical Abstract Service (CAS) Registry Number: 208265-92-3
- e. INN Name: Pegfilgrastim
- f. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [LUPIN]
- g. Other name(s): LUBT 004 (laboratory code)

Submissions Assessed:

Submission(s) Assessed	Document Date (disciplines affected)
STN 761212/SN 0001 (Original submission)	April 2, 2021 (OBP and OPMA)
STN 761212/SN 0002 (Information request (IR) response)	May 17, 2021 (OPMA)
STN 761212/SN 0006 (remote interactive inspection request)	July 9, 2021 (OPMA)
STN 761212/SN 0007 (IR response)	July 16, 2021 (OPMA)
STN 761212/SN 0008 (IR response)	August 11, 2021 (CDRH)
STN 761212/SN 0009 (IR response)	August 12, 2021 (OBP-IR1)
STN 761212/SN 0011 (IR response)	August 13, 2021 (OPMA)
STN 761212/SN 0012 (IR response amendment)	August 16, 2021 (OBP)
STN 761212/SN 0013 (IR response)	September 30, 2021 (OBP-IR2)
STN 761212/SN 0015 (IR response)	October 21, 2021 (OPMA, OBP-IR3)
STN 761212/SN 0017 (IR response amendment)	October 29, 2021 (OPMA)
STN 761212/SN 0018 (IR response)	November 2, 2021 (OBP-IR4)
STN 761212/SN 0019 (IR response)	November 8, 2021 (OPMA)
STN 761212/SN 0021 (IR response)	November 30, 2021 (OPMA)
STN 761212/SN 0022 (IR response)	December 2, 2021 (OBP-5)
STN 761212/SN 0023 (IR response amendment)	December 14, 2021 (OPMA)
STN 761212/SN 0026 (IR response amendment)	December 30, 2021 (OBP, OPMA)
STN 761212/SN 0027 (IR response)	January 3, 2022 (OBP-IR6, OPMA)

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

Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	9/20/2021	Assessed by CDER/OPQ/ ONDP
	III			3	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A
	N/A			3	Adequate	N/A	Assessed by CDRH

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

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not 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.

Document	Application Number	Description
IND	131463	Parent IND

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH/OPEQ/OHT3/DHT3C	May 6, 2021	Complete (10/27/2021)	Approvable	Dunya Karimi/Alan Stevens

4. Environmental Assessment:

The Applicant claims a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (a). The Applicant described that the LUBT 004 product will not increase the use of the active moiety per 21 CFR Part 25.31 (a) and no extraordinary circumstances exist per 21 CFR part 25.15 (d). Thus, no environmental assessment needs to be performed.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The recommendation for STN 761212 from the Office of Pharmaceutical Quality (OPQ), CDER, is pending on the final assessment of facilities compliance. An inspection of the facility responsible for G-CSF intermediate (LUBT 001) manufacturing, LUBT 004 DS and DP manufacturing, as well as quality control testing and comparative analytical assessment (Lupin Limited, Pune, India (FEI 3010977634)) is required before the application can be approved. OPQ must assess the ability of the Lupin Limited facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, OPQ may be unable to conduct inspections of these facilities prior to the User Fee Date. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections once safe travel may resume based on public health need and other factors.

The Office of Biotechnology Products (OBP), OPQ, CDER from a product quality perspective as well as the Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER from a microbiology perspective do not note any deficiencies that would preclude approval of STN 761212 for LUBT 004 manufactured by Lupin Limited (Biotech Division) at this time. The analytical similarity data submitted in the application demonstrate that LUBT 004 is highly similar to US-licensed Neulasta. If Lupin Limited (Biotech Division) submits additional manufacturing information during this review cycle, additional assessment may be needed during the current assessment cycle.

B. Approval Action Letter Language:

- Manufacturing location:
 - Drug Substance:
 - G-CSF intermediate (unpegylated G-CSF, LUBT 001): Lupin Limited (Biotech Division), Gat No. 1156, 1157, 1158, 1159 and 1160, Village- Ghotawade, Taluka-Mulshi, Pune, Maharashtra, India (FEI: 3010977634)
 - LUBT 004 drug substance (pegylated G-CSF): Lupin Limited (Biotech Division), Gat No. 1156, 1157, 1158, 1159 and 1160, Village- Ghotawade, Taluka-Mulshi, Pune, Maharashtra, India (FEI: 3010977634)
 - Drug Product:
 - Lupin Limited (Biotech Division), Gat No. 1156, 1157, 1158, 1159 and 1160, Village- Ghotawade, Taluka-Mulshi, Pune, Maharashtra, India (FEI: 3010977634)
- Fill size and dosage form: 6 mg in 0.6 mL (10 mg/mL) solution in a pre-filled syringe
- Dating period:

- Drug Product: 12 months at 5°C ± 3°C (pending on final stability updates committed to be submitted in March 2022)
 - Drug Substance: (b) (4) months at (b) (4)
 - G-CSF intermediate: (b) (4) months at (b) (4)
 - Stability Option:
 - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
 - For stability protocol: We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.
- Exempt from lot release in accordance with 21 CFR 601.2a. LUBT 004 is a specified product.

C. Benefit/Risk Considerations:

LUBT 004 is a proposed biosimilar to US-licensed Neulasta. The Applicant requested the neutropenia indication for which US-licensed Neulasta is approved.

Review of manufacturing has identified that the methodologies used for G-CSF intermediate, LUBT 004 DS and DP manufacturing, and release and stability testing are robust and sufficiently controlled to result in a consistent and safe product.

An inspection of the G-CSF intermediate, LUBT 004 DS and DP facilities as well as the quality control testing and comparative analytical assessment site at Lupin Limited, Pune, India (FEI 3010977634) is required before this application can be approved. OPQ must inspect the facilities to ensure the listed manufacturing operations in compliance with cGMP. However, due to US Government and Agency-wide restrictions on international travel under COVID-19 pandemic, OPQ may be unable to conduct an inspection prior to the User Fee Date.

The data provided in the BLA support that LUBT 004 is highly similar to U.S.-licensed Neulasta.

The OBP product quality and immunogenicity assay, OPMA facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

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

The following post-marketing commitments (PMCs) have been discussed and agreed by the Applicant during the BLA review. These PMCs will be effective once the application is approved.

(b) (4)

II. Evaluation of Comparative Analytical Assessment and Evaluation of the Analytical Component of the Scientific Bridge

A. Summary of Comparative Analytical Assessment

The Applicant provided results of the comparative analytical assessment to support that LUBT 004 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. The Applicant ranked the criticality of the quality attributes based on their potential impact on activity, pharmacokinetic (PK)/ pharmacodynamic (PD), safety and immunogenicity.

For the selected quality attributes with highest criticality (i.e., protein concentration, G-CSF induced M-NFS-60 cell proliferation, G-CSF receptor binding assay by surface plasmon resonance (SPR), aggregates and high molecular weight (HMW) impurities by size exclusion chromatography (SE-HPLC)), both an equivalence testing approach and a quality range (QR) testing approach were applied. For the equivalence testing approach, two-sided 95% confidence interval obtained for the difference in means with a pre-defined equivalence margin of $2\sigma_R$ (σ_R is the variability of reference product) is derived from 12 US-licensed Neulasta batches. For the QR testing approach, upper and lower limit of QR is defined from 12 US-licensed Neulasta batches and derived as Mean $\pm 2SD$ (standard deviation). For the selected quality attributes with moderate to high criticality, the QR testing approach was applied where upper and lower limit of QR is defined from 6-10 US-licensed Neulasta batches and derived as Mean $\pm 2SD$. For quality attributes with low criticality, tested with orthogonal tests or tested with qualitative test methods, raw data or graphical data were presented. The selected approaches for comparative analytical assessment are consistent with FDA Draft Guidance: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019). The selected multiplier as 2 used in the QR testing approach, which is based on the criticality of the quality attributes, sensitivity of the analytical methods, abundance of the quality attributes, the distribution of the quality attributes and the type of the analytical methods, is justified. Results from method

validation or qualification studies support the suitability of the methods used in the comparative analytical assessment.

The Applicant compared 18 independent batches of LUBT 004 and 12 batches of US-licensed Neulasta by using both the equivalence testing approach and the QR testing approach for the selected quality attributes with highest criticality. The Applicant compared 11-18 independent batches of LUBT 004 and 6-10 batches of US-licensed Neulasta by using the QR testing approach for the selected quality attributes with moderate to high criticality. The Applicant compared 1-12 independent batches of LUBT 004 and 1-6 batches of US-licensed Neulasta by using the raw data or graphical data approach for the selected quality attributes with low criticality. The 18 LUBT 004 batches included the batches used in the PK/PD similarity study ARL/18/360/LBC-19-146 and the comparative clinical study LRP/PegG-CSF/2016/004 evaluating safety/immunogenicity as well as the process performance qualification (PPQ) batches manufactured by the proposed commercial manufacturing process. The Applicant tested LUBT 004 and US-licensed Neulasta using multiple orthogonal methods to adequately evaluate the necessary quality attributes of the products.

The expiry dates of the US-licensed Neulasta batches ranged from May 2019 to January 2023, which span the shelf-life of US-licensed Neulasta and were adequate to capture potential product differences over time. The Applicant also performed comparative forced degradation studies under agitation, pH, photo, thermal and oxidative stress conditions. The comparative forced degradation studies support that LUBT 004 and US-licensed Neulasta have a similar degradation profile.

Two types of bioactivity assays reflecting the mechanism of action of US-licensed Neulasta and LUBT 004 were conducted. In vitro potency was determined using a murine myelogenous leukemia cell line (M-NFS-60 cell line) to evaluate the receptor-activated hematopoietic cell proliferation induced by the products. The Applicant chose to evaluate results from the in vitro cell-based assay for both relative activity and specific activity with an equivalence testing approach as well as a QR testing approach because of the high-risk level for this critical quality attribute. A SPR assay with a Biacore instrument to measure G-CSF receptor binding affinity was conducted. The comparison of G-CSF receptor binding affinity (equilibrium dissociation constant, KD) by a QR testing approach and an equivalence testing approach as well as the association constant (Ka) and dissociation constant (Kd) by a raw data testing approach support a determination in that the higher order structure required for binding to the receptor and response binding kinetics are similar between LUBT 004 and US-licensed Neulasta. The two bioactivity assays support LUBT 004's proposed mechanism of action.

Our assessment of the LUBT 004 and US-licensed Neulasta data supports that LUBT 004 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. LUBT 004 has the same strength, dosage form, and route of administration as US-licensed Neulasta. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of LUBT 004 and US-licensed Neulasta to support a demonstration in that the products are highly similar. Numbers of batches tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. Observed differences do not preclude a demonstration in that LUBT 004 is highly similar to US-licensed Neulasta.

B. Results of Comparative Analytical Assessment

The results of the analytical comparisons that support LUBT 004 is highly similar to US-licensed Neulasta are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
<i>Primary Structure</i>	<i>Amino acid sequence and comparison</i>	<i>Yes</i>
	<i>mPEG attachment site</i>	<i>Yes</i>
	<i>Extinction coefficient</i>	<i>Yes</i>
	<i>Intact mass and molecular weight</i>	<i>Yes</i>
	<i>Polydispersity of molecular weights distribution</i>	<i>Yes</i>
<i>Higher Order Structure</i>	<i>Disulfide bonds analysis</i>	<i>Yes</i>
	<i>Secondary structure (far-UV Circular Dichroism (CD), fourier-transform infrared spectroscopy (FTIR))</i>	<i>Yes</i>
	<i>Tertiary structure (near UV CD, intrinsic fluorescence spectroscopy, second derivative UV-Vis spectroscopy)</i>	<i>Yes</i>
	<i>Differential scanning calorimetry (DSC) for thermal stability</i>	<i>Yes</i>
<i>Product-Related Substance and Impurities</i>	<i>Size variants and impurities</i>	<i>Monomer/purity (size exclusion high performance liquid chromatography (SE-HPLC), analytical ultra centrifugation (AUC), size exclusion chromatography multiple angle laser light scattering (SEC-MALS) and sodium dodecyl sulphate polyacrylamide gel (SDS-PAGE))</i>
		<i>High molecular weight (HMW) impurities (e.g., aggregates, dimer & Di-Peg/HMW) (SE-HPLC, AUC, SEC-MALS, SDS-PAGE and reverse phase high performance liquid chromatography (RP-HPLC))</i>
		<i>Low molecular weight (LMW) impurities (e.g., fragments, free G-CSF, and free mPEG) (SE-HPLC, AUC, SDS-PAGE, RP-HPLC) and RP-HPLC with charged aerosol detector (CAD))</i>
	<i>Charge variants</i>	<i>Pre-peaks (cation-exchange high performance liquid chromatography (CEX-HPLC))</i>
		<i>Main peak (CEX-HPLC)</i>
	<i>Hydrophobic variants</i>	<i>Pre-peaks (RP-HPLC)</i>
		<i>Main peak (RP-HPLC)</i>
		<i>Post-peaks (RP-HPLC)</i>
	<i>Post translational modifications</i>	<i>Oxidation and deamidation (peptide mapping with mass spectrometry (MS) detection, LC-MS/MS and RP-HPLC))</i>
	<i>Bioactivity</i>	<i>G-CSF receptor binding (SPR)</i>
<i>Binding kinetics Ka</i>		
<i>Binding kinetics Kd</i>		
<i>M-NFS-60 cell proliferation</i>		<i>Relative potency</i>
		<i>Specific activity</i>
<i>Drug Product Attributes</i>	<i>Protein concentration</i>	

C. Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

D. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all quality attributes with the exception for aggregates determined by SE-HPLC between LUBT 004 and US-licensed Neulasta.

The aggregates measured by SE-HPLC in LUBT 004 (0.07-0.22%) is outside the QR of US-licensed Neulasta (0.09-0.20%) although the aggregates are low abundance impurities in both LUBT 004 and US-licensed Neulasta. Based on differences in the age of the batches of LUBT 004 and US-licensed Neulasta and the results from comparative forced degradation stability studies, consideration was given to whether these differences in aggregates are due to the age of the products as the aggregate is a stability indicating quality attribute. At the time of analysis, LUBT 004 batches were 1-35 months old while US-licensed Neulasta batches were 1-29 months old. The differences in aggregates might theoretically impact bioactivity. However, based on the bioactivity data, the observed bioactivity is similar between LUBT 004 and US-licensed Neulasta despite the small differences in levels of the aggregates. In addition, when the LUBT 004 and US-licensed Neulasta batches are in a similar age, the aggregates measured by AUC and SEC-MALS in LUBT 004 are within the QR of US-licensed Neulasta measured by AUC and SEC-MALS. Based on the data and information provided, the observed differences between LUBT 004 and US-license Neulasta in the low abundance aggregates determined by SE-HPLC are due to differences in the ages of the products tested.

In summary, based on the above data and assessment, there are no residual uncertainties regarding the comparative analytical assessment that would preclude a demonstration in that LUBT 004 is highly similar to US-licensed Neulasta.

E. Same Strength(s)

LUBT 004 has the same dosage form and route of administration as US-licensed Neulasta. Lupin Pharmaceuticals, Inc. is seeking approval of 6.0 mg/0.6 mL LUBT 004 in a single-dose prefilled syringe. US-licensed Neulasta is available at this strength as 6.0 mg/0.6 mL in a single-dose prefilled syringe¹. Lupin Pharmaceuticals, Inc. is seeking approval of LUBT 004 for the same strength as US-licensed Neulasta. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. (b) (4)

manufacturing process controls. The proposed presentation of LUBT 004 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Neulasta (6 mg/0.6 mL). The strength of LUBT 004 prefilled syringe is the same as that of US-licensed Neulasta.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for LUBT 004

U.S. Prescribing Information, U.S.-Licensed Neulasta. Accessed 1/21/22 from <https://www.accessdata.fda.gov/scripts/cder/daf>

Table B: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
<i>In vitro</i> cell-based bioassay (potency)	Efficacy	Intrinsic to the molecule, impacted by exposure UV light stress	(b) (4)	(b) (4)
Receptor binding	Efficacy	Intrinsic to the molecule		
Identity	Efficacy and Safety	Intrinsic to the molecule		
HMW species (product-related impurity)	PK and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, oxidation reagent stress, and UV light stress		
LMW species/Fragments (product-related impurity)	Efficacy, PK and Safety (Immunogenicity)	Manufacturing process and storage		
Hydrophobic variants (include product-related impurities)	Efficacy and safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, oxidation reagent, high pH and light stress		

Charge variants (include product-related impurities)	Efficacy and PK	Manufacturing process, storage and exposure to low pH, high pH, heat and UV light stress	(b) (4)	(b) (4)

B. Drug Substance (LUBT 004) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy
Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process	(b) (4)
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process	(b) (4)
Quantity	Efficacy	Manufacturing process	(b) (4)
pH (General)	Efficacy and Stability	Formulation components and stability	(b) (4)
Osmolality (General)	Stability	Composition of the DS	(b) (4)
Appearance (General)	Stability	Formulation components and stability	(b) (4)
Degree of coloration (General)	Stability	Formulation components and stability	(b) (4)
Clarity and degree of opalescence (General)	Stability	Formulation components and stability	(b) (4)

Host cell DNA (Process-related impurity)	Safety	Production cell line, (b) (4)	(b) (4)
Host cell protein (Process-related impurity)	Safety (Immunogenicity) and Purity	Production cell line, (b) (4)	(b) (4)
Residual mPEG	Safety and Purity	(b) (4)	(b) (4)
(b) (4) Process-related impurity)	Safety and Purity	Cell banks, raw materials	(b) (4)
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material, (b) (4)	(b) (4)
Additives (b) (4)	Safety and Purity	(b) (4)	(b) (4)

- Description:
G-CSF intermediate, (b) (4)

- Mechanism of Action (MoA):

G-CSF binds to G-CSF receptors and stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, reduce the maturation time of non-mitotic cells in the bone marrow, and increase functional longevity of mature neutrophils. Pegylated G-CSF has the same MoA as G-CSF.

- Potency Assays:

The *in vitro* cell based bioassay for testing the potency of LUBT 004 is a cell proliferation assay, which utilizes the ability of G-CSF adapted M-NFS-60 cells undergoing active proliferation upon LUBT 004 treatment in a dose dependent manner. The cells are incubated with varying concentrations of LUBT 004 in-house reference standard and test sample. After a timed incubation, a detection reagent (monitoring a bioluminescent response) is added to the cell cultures in a 96 well plate to measure cell viability in the wells. The degree of cell viability is directly proportional to the LUBT 004 concentration applied and is used to monitor cell proliferation activity. The potency of test samples is determined by comparing luminescent signals from the test sample treated M-NFS-60 cells to that from in-house reference standard treated M-NFS-60 cells.

- Reference Materials:

-

-

(b) (4)

- **Critical Starting Materials or Intermediates:**

(b) (4)



- **Manufacturing Process Summary:**

(b) (4)



(b) (4)





- **Dating Period and Storage Conditions:**
The dating period for the G-CSF intermediate is (b) (4) months when stored at (b) (4)
The dating period for the (b) (4) months when stored at (b) (4)

C. Drug Product (LUBT 004) Quality Summary:

Table D provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

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

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process, failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process	(b) (4)	N/A
Container Closure Integrity (sterility assurance)	Safety and efficacy	Breach during manufacture or storage	(b) (4)	N/A
Quantity	Efficacy	Manufacturing process	(b) (4)	N/A
pH (General)	Efficacy and Stability	Formulation components and stability	(b) (4)	N/A
Osmolality (General)	Stability	Composition of the DP	(b) (4)	N/A
Appearance of visible particles (General)	Stability	Formulation components and stability	(b) (4)	N/A

Degree of coloration (General)	Stability	Formulation components and stability	(b) (4)	N/A
Clarity and degree of opalescence (General)	Stability	Formulation components and stability	(b) (4)	N/A
Particulate matter for subvisible particles (Product- or process-related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles.	(b) (4)	N/A
Extractable volume (General)	Efficacy/Dosing	Fill process	(b) (4)	N/A
Polysorbate 20 concentration	Stability	Formulation components and stability	(b) (4)	N/A
Device functionality (Break loose, gliding force, safety needle shield activation, needle safety activation force, needle safety lockout force/override force and needle safety pre-activation)	Efficacy and Safety	Device performance	(b) (4)	Assessed also by CDRH team
Leachables (Process-related impurities)	Safety and product quality	Manufacturing equipment and CCS	(b) (4)	Annual report after completion of the protocols

- Potency and Strength:**
 LUBT 004 is supplied in a PFS at a strength of 6 mg/0.6 mL. LUBT 004 was developed to have the same strength as US-licensed Neulasta. Potency is defined as the percent activity relative to the current LUBT IRRS. The potency assays are the same as described in the DS section of this memo.
- Summary of Product Design:**
 LUBT 004 is supplied as a sterile, single-dose, clear, colorless, and preservative-free solution for subcutaneous injection in one strength. LUBT 004 was developed as a biosimilar to US-licensed Neulasta and targets the quality profile of US-licensed Neulasta.
- List of Excipients:**
 Each mL of solution contains (b) (4) mg (b) (4) sorbitol, (b) (4) (b) (4) mg glacial acetic acid, (b) (4) mg polysorbate 20 and water-for-injection, pH 4.0.
- Reference Materials:**
 (b) (4)
- Manufacturing Process Summary:**

The DP manufacturing process involves (b) (4)

Microbial control and sterility assurance of the DP is acceptable; (b) (4)

endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

- **Container Closure System:**
 The primary packaging components of LUBT 004 DP are Type (b) (4) glass syringe with a 27 G 1/2 inch fixed injection needle, a rigid needle shield and (b) (4) rubber stopper (b) (4). The final DP is assembled with (b) (4) Ultrasafe® plus passive needle safety guard. The needle shield contains natural rubber which has been reflected in the final prescribing information.
- **Dating Period and Storage Conditions:**
 The dating period for the LUBT 004 DP is 12 months when stored at 2-8°C (pending on final stability updates committed to be submitted in March 2022)
- **List of Co-Package Components (if applicable):** None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2-8°C in the original carton
- Protect from light
- Do not shake
- Avoid freezing
- Discard syringe if frozen more than once
- Discard syringes stored at room temperature for more than 48 hours

F. Establishment Information:

Overall Recommendation: Pending pre-license inspection (PLI) due to Travel Restrictions					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS intermediate manufacturing and in-process, QC and	Lupin Ltd. (Biotech Division), Pune, India	DUNS: 915787052	PLI required	N/A	Pending PLI

stability testing, DS manufacturing, QC, and stability testing		FEI: 3010977634			
Master Cell Bank Production	(b) (4)				
Cell bank storage	Lupin Ltd, Tarapur, India	FEI: 3005343934	No Evaluation Necessary	No Evaluation Necessary	No Evaluation Necessary
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture, QC, and stability testing, device assembly, labeling and secondary packaging	Lupin Ltd. (Biotech Division), Pune, India	DUNS: 915787052 FEI: 3010977634	PLI required	N/A	Pending PLI

G. Facilities:

An inspection of the G-CSF intermediate, LUBT 004 DS and DP facilities as well as the quality control testing and comparative analytical assessment site at Lupin Limited, Pune India (FEI 3010977634) is required before this application can be approved. Due to restrictions on travel, OPQ may be unable to conduct inspections of these facilities prior to the User Fee Date.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
(b) (4)			
[Redacted Content]			



- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.2.6	Real-time and accelerated DP leachable protocols	At 5 ± 3°C, one DP batch at initial, 3, 6, 12, 24 and 36 months; at 25 ± 2 °C & 60± 5%RH, one DP batch at initial, 3 and 6 months.	Results will be reported in Annual Report after the protocol has been executed
3.2.P.8.2	Annual stability protocol for LUBT 004 DP with shelf-life extension	At 5 ± 3°C, at least one bath per year at initial, 3, 6, 9, 12, 18, 24, 36 months, according to the tests and AC listed in 3.2.P.8.2.	Stability updates will be provided annually as a part of the Annual Report

- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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

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/s/

YAN WANG
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