DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF NONMALIGNANT HEMATOLOGY

MEMORANDUM TO FILE

DATE: November 28, 2025

FROM: Margaret Thompson, CDTL and Team Lead, Division of Nonmalignant Hematology

SUBJECT: BLA 761212 Class 2 Resubmission #2

1. Executive Summary:

The Division of Nonmalignant Hematology (DNH) recommends for approval, under BLA 761212, LUBT004 (proprietary name: Armlupeg; nonproprietary name: pegfilgrastim-unne), a biosimilar to US-licensed Neulasta, for all indications approved for US-licensed Neulasta, specifically:

- 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.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

With the same limitation of use as US-licensed Neulasta:

Armlupeg is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Approval will be issued with the following postmarketing requirement (PMR):

4932-1 Develop a presentation that can be used to accurately administer Armlupeg (pegfilgrastim-unne) to pediatric patients who weigh less than 45 kg.

Final Report Submission: 04/2028

2. Background of Application:

Applicant	Lupin Limited
Product Code Name	LUBT 004
Submission	**Date Received**

Original Application	04/02/2021
Original CRL	02/01/2024
Resubmission#1	05/14/2024
CRL #2	11/14/2024
Resubmission #2	5/30/2025

Original Submission:

On 4/2/2021, Lupin Limited submitted an original BLA 761212 for LUBT 004, 6mg/0.6mL solution in a single dose prefilled syringe (PFS) as a proposed biosimilar to US-licensed Neulasta. During the review of this submission, the Agency has determined that:

- LUBT004 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between LUBT004 and US-licensed Neulasta in terms of the safety, purity, and potency of the product.
- LUBT004 6mg/0.6mL injection in a single-dose PFS has the same strength, dosage form and route of administration as US-licensed Neulasta 6mg/0.6mL injection in a single-dose PFS.
- The Applicant has provided adequate scientific justification for extrapolation of data and information submitted to support licensure of LUBT004 as a biosimilar, for the following indication for which US-Licensed Neulasta has been previously approved and for which the Applicant is seeking:
    - 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.

However, based on the findings of the on-site manufacturing facilities inspection and the product quality deficiency, there is insufficient information to demonstrate that the manufacturing process and control strategy of LUBT004 is well-controlled and leads to a product that is safe, pure, and potent. The Agency issued a complete response letter (CRL) for this application based on recommendations of the Office of Pharmaceutical Quality (OPQ) due to deficiencies identified related to Lupin Limited (Biotech Division), Pune, India (FEI: 3010977634) facility and microbiology.

The conclusions for offices/divisions other than OPQ are summarized below. For full details of the review of the original submission see the biosimilar multidisciplinary evaluation and review (BMER) uploaded to DARRTS 2/1/2024.

Nonclinical

Animal studies with LUBT004 and US-Neulasta were not required to support this 351(k) application. There were no nonclinical residual uncertainties.

Office of Clinical Pharmacology
The clinical studies including a PK/PD similarity study in healthy subjects and a comparative immunogenicity study in breast cancer patients adequately showed PK and PD similarity between LUBT004 and U.S.- licensed Neulasta and showed no increase in immunogenicity risk for LUBT004 when compared to U.S-license Neulasta. There are no residual uncertainties from the clinical pharmacology assessment. The clinical studies support that there are no clinically meaningful differences between LUB004 and US-licensed Neulasta.

Clinical
Based on the review of the safety results, the overall safety profile of LUBT004 was similar to that of US-licensed Neulasta. The safety results from the comparative immunogenicity studies in breast cancer patients support a demonstration of no clinically meaningful differences between LUBT004 and US- licensed Neulasta.

Center for Devices and Radiological Health (CDRH)
LUBT004 is supplied as a single-use, disposable, fix dose (6mg/mL) pre-filled syringe (PFS) with a 27G ½ inch fixed injection needle and a rigid needle shield. PFS is assembled with (b) (4) Ultrasafe plus passive needle safety guard.

CDRH consult review included an assessment of needle safety device constituent performance, needle safety stability, and needle safety control strategy. CDRH concluded that the LUBT004 pre-filled syringe from a device perspective was approvable.

Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA reviewed the user-related risk analysis (URRA) that the sponsor submitted under IND 131463. The review concluded that a human factor validation study is not needed for the proposed LUBT004 PFS. See the DMEPA review memo for IND 131463 dated on July 28, 2020 in DARRTS.

DMEPA performed a risk assessment of the proposed LUBT004 container label, carton labeling, Prescriber Information (PI), Patient Information (PPO), and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors. DMEPA concluded that the proposed PI, PPI, IFU, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. See the Label and Labeling Review dated 10/05/2021 in DARRTS. Due to the recommendation of the Complete Response action, the final labeling review was deferred until the next review cycle.

Resubmission #1:

On May 14, 2024, the Applicant submitted resubmission #1 to the BLA, which included additional Chemistry, Manufacturing, and Controls (CMC) and safety update information submitted in response to the February 1, 2024, complete response letter.

After review of the resubmission, the Agency issued a CRL on November 14, 2024, due to ongoing deficiencies in manufacturing facility identified during the pre-license inspection of Lupin Limited (Biotech Division), Pune, Maharashtra, India (FEI 3010977634).

No other Office/Division had ongoing deficiencies for this application. Request for safety update was included in the CRL.

Clinical

Included in this resubmission, the Applicant submitted safety data from the following study:

> An Open label, Balanced, Randomized, Single-Dose, Single-Period, Two-Treatment, Parallel Comparative Pharmacokinetics Study of Lupin's Test Product Pegfilgrastim On Body Injector 6 mg/0.6 mL with Lupin's Test Product Pegfilgrastim Pre-filled Syringe injection 6 mg/0.6 mL in Healthy, Adult, Human Subjects.

The safety information included adverse events reported from the study. This information was consistent with safety data submitted with the original BLA. Labeling was updated accordingly.

In addition, the Applicant requested licensure for, and inclusion of the draft USPI with the following indication:

> Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome (H-ARS)).

This indication was not included in the original BLA because at the time, US-Neulasta was eligible for orphan-drug exclusivity for the indication, "to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)." US-Neulasta's orphan-drug exclusivity for this indication expired on March 30, 2022. Based on the data and information provided in the original BLA and in this resubmission, the Applicant has provided adequate scientific justification for extrapolation of data and information to support licensure of LUBT004 as a biosimilar, for the following indication for which US-Licensed Neulasta has been previously approved and for which the Applicant is seeking:

- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

3. Review of Current Submission

On May 30, 2025, the Applicant submitted resubmission #2 in response to the CRL issued on November 14, 2024.

OPQ

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761212 for Armlupeg manufactured by Lupin Limited (Biotech Division). The data submitted in the original BLA 761212, the resubmission submitted on May 14, 2024, and this current submission 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.

The OPQ Executive Summary was signed and uploaded to DARRTS on 11/10/2025.

Clinical and Clinical Pharmacology

No new clinical studies or safety data was submitted with the submission. There are no clinical and clinical pharmacology issues that would preclude approval. Refer to the BMER uploaded in DARRTS on 2/1/2024.

Proprietary Name and Non-Proprietary Name

DMEPA has completed the review of proprietary name and non-proprietary name for LUBT004. DMEPA has concluded that the proposed proprietary name, Armlupeg, and non-proprietary name, pegfilgrastim-unne, are approved for BLA 761212. Refer to the approval letter and DMEPA's review memoranda dated on 8/14/2025, 9/11/2025 in DARRTS.

Labeling

It has been determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Applicant is seeking licensure for the same indications for which US-licensed Neulasta is currently approved. The proposed Armlupeg labeling incorporated relevant data and information from US licensed Neulasta labeling, with appropriate modifications.

On August 18, 2025, US-licensed Neulasta was approved for a new 4 mg/0.4 mL single-dose vial presentation for dosing in pediatric patients weighing less than 45 kg, and the

Prescribing Information states that the Neulasta 6 mg/0.6 mL PFS should be used for adult patients of any weight and pediatric patients weighing 45 kg and greater. Since LUBT004 is proposed as a 6 mg/0.6 mL PFS, the review team concluded that (b) (4) should be removed from the labeling. In addition, the team concluded that Section 2.3 should contain a statement that clearly states there is no presentation of Armlupeg that allows weight-based dosing for pediatric patients below 45 kg. The revised Armlupeg labeling incorporated these recommendations in the relevant sections.

Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

The Applicant submitted the initial Pediatric Study Plan (iPSP) under IND 131463 on January 13, 2020, and an agreement letter was issued on June 30, 2020.

The applicant submitted pediatric assessments for the two indications listed below based on a demonstration of biosimilarity and by providing adequate scientific justification to support extrapolation of data and information to support licensure:

- 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, and
- (b) (4) acutely exposed to myelosuppressive doses of radiation (b) (4)

At the time of original BLA submission, US-licensed Neulasta had a PREA post-marketing requirement (PMR) to develop of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. The Applicant requested a deferral of the requirement to develop an "appropriate formulation" (presentation) to accurately administer LUBT004 to pediatric patients who weigh less than 45 kg and require doses

that are less than 0.6 mL (6 mg) until after the pediatric presentation for US-licensed Neulasta becomes available. PeRC discussed this application on 3/8/2022 and concurred with the Division to grant a deferral for development a presentation to allow accurately administration of LUBT004 in pediatric patients less than 45mg until the timeline for the PREA-PMR is available. However, in view of the recommendation for a Complete Response, a PREA PMR was not applicable at the time of initial BLA review.

On August 18, 2025, FDA approved a new 4 mg/0.4 mL single-dose vial presentation of Neulasta which fulfilled the PMR for the sponsor of Neulasta (Amgen) to develop an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta (pegfilgrastim) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg). A PREA PMR is required for the Applicant's deferred pediatric assessment to develop an appropriate presentation that can be accurately administered LUBT004 to pediatric patients who weigh less than 45mg.

Post-Marketing Requirement

The following PREA PMR description should be included in the Approval letter for the LUBT004 single-dose prefilled glass syringe presentation.

> PMR-4932: Develop a presentation that can be used to accurately administer Armlupeg (pegfilgrastim-unne) to pediatric patients who weigh less than 45 kg.
>
> Final Report Submission: 04/2028

Regulatory Action

In considering the totality of the evidence submitted, the data and information submitted by the Applicant demonstrates that LUBT 004 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between LUBT004 and US-licensed Neulasta in terms of the safety, purity and potency. The Applicant has provided adequate scientific justification for extrapolation of data and information, demonstrated that:

- LUBT 004, 6mg/0.6mL injection for subcutaneous use in a single-dose PFS is biosimilar to US-licensed Neulasta 6mg/0.6mL injection for subcutaneous use in a single-dose PFS

for the following indications for which US-Licensed Neulasta has been previously approved and for which the Applicant is seeking:

- In adults and pediatric patients aged newborn and older to 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.
- Increase survival in in adults and pediatric patients aged newborn and older acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

The recommended regulatory action is approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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11/28/2025 11:44:49 AM