

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761084Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 26, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761084
Product Name and Strength:	TPI-120 ^a Fylnetra (pegfilgrastim-pbbk) Injection, 6 mg/0.6 mL
Applicant/Sponsor Name:	Kashiv BioSciences LLC (Kashiv)
OSE RCM #:	2020-1691-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 11, 2022 and May 24, 2022 for TPI-120 Fylnetra. We reviewed the revised container label and carton labeling for TPI-120 Fylnetra (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^b and additional recommendations from the Office of Biotechnology Products (OBP) labeling, such as removal of the standard potency statement.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a TPI-120 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name Fylnetra, was found conditionally acceptable on April 6, 2022. The nonproprietary name, pegfilgrastim-pbbk, was found conditionally acceptable on February 17, 2022.

^b Iverson, N. Label and Labeling Review for TPI-120 Fylnetra (BLA 761084). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 26. RCM No.: 2020-1691-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON May 11, 2022 and May 24, 2022
Container label (syringe)

(b) (4)



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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 17, 2022

To: May Zuwannin
Regulatory Project Manager
Division of Nonmalignant Hematology (DNH)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Melissa Khashei, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (nonproprietary name): [TPI-120] FYLNETRA (pegfilgrastim-pbbk)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761084

Applicant: Kashiv Biosciences, LLC

¹ TPI-120 has been developed as a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim). The Applicant withdrew the proposed proprietary name (b) (4) on February 11, 2022. The proposed proprietary name FYLNETRA was found to be conditionally acceptable by DMEPA on April 6, 2022. The proposed nonproprietary name “pegfilgrastim-pbbk” was found to be conditionally acceptable by DMEPA on May 10, 2021 and is used throughout this document.

1 INTRODUCTION

On November 29, 2021, Kashiv Biosciences, LLC submitted a Complete Response to the Agency's Complete Response Letter dated August 11, 2021, for their original Biologics License Application (BLA) 761084 for [TPI-120] FYLNETRA (pegfilgrastim-pbbk) injection, a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim). The proposed indication for [TPI-120] FYLNETRA (pegfilgrastim-pbbk) injection is 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on December 6, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert and Instructions for Use (IFU) for [TPI-120] FYLNETRA (pegfilgrastim-pbbk) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft [TPI-120] FYLNETRA (pegfilgrastim-pbbk) injection PPI received on November 29, 2021, and received by DMPP and OPDP on March 2, 2022.
- Draft [TPI-120] FYLNETRA (pegfilgrastim-pbbk) injection IFU received on November 29, 2021, revised on February 28, 2022, and received by DMPP and OPDP on March 2, 2022.
- Draft [TPI-120] FYLNETRA (pegfilgrastim-pbbk) injection Prescribing Information (PI) received on November 29, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 2, 2022.
- Approved US-licensed NEULASTA (pegfilgrastim) labeling dated February 2, 2021, January 5, 2021 and April 28, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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DIVISION OF NONMALIGNANT HEMATOLOGY

Associate Director for Labeling Review of the Prescribing Information

Product Title	FYLNETRA (pegfilgrastim-pbbk) injection, for subcutaneous use
Applicant	Kashiv Biosciences
Application/Supplement Number	BLA 761084
Type of Application/Submission ¹	Biosimilar to Neulasta
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	FYLNETRA is a leukocyte growth factor indicated 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. (1.1) <u>Limitations of Use</u> FYLNETRA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.
Approved Indication(s) (if applicable)	FYLNETRA is a leukocyte growth factor indicated 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. (1.1) <u>Limitations of Use</u> FYLNETRA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.
Date FDA Received Application	11/29/21
Review Classification (Priority/Standard)	Class I resubmission; response to CR Letter
Action Goal Date	05/27/22
Review Date	05/16/2022
Reviewer	Virginia E. Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements²
- Is consistent with labeling guidance recommendations³ and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers

¹ Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(e\)](#) and [201.80](#).

³ See [PLR Requirements for PI](#) website for PLR labeling guidances.

- Is consistent with the reference drug PI (Neulasta)

The applicant is seeking approval of Fylnetra (pegfilgrastim-pbbk), a proposed biosimilar to Neulasta. This review is being completed just prior to action, with final agreed upon labeling.

This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant's draft PI and currently approved PI.

Labeling was nearly finalized during the last submission (prior to the CR). Labeling had been reviewed by the Biosimilar group (OTBB).

During this cycle, the labeling was reviewed by the multi-disciplinary team, labeling consultants (DMEPA, DMPP, OPDP), as well as OTBB.

Since the last submission, the Agency has been asking Biosimilar applicants to align their Instructions for Use documents more closely with the innovator labeling.

The Applicant proposed the following changes which FDA agreed with:

1. Updated the Proprietary Name from (b) (4) to Fylnetra.
2. Revised Applicant name from Amneal Biosciencies to Amneal Pharmaceuticals with a revised phone number of 877-835-5472, option 3.
3. Throughout the USPI, when providing a range, used the word "to" instead of "-"

In summary, during this review cycle, the following changes were suggested by the FDA:

1. This Information Request was sent to the Applicant regarding their proposed IFU.
 - a. To Applicant: We have reviewed your draft IFU, which has language and positional differences (including additional images) compared to the IFU for US-licensed Neulasta PFS. In the Labeling for Biosimilar Products Guidance, it is recommended that if the FDA-approved patient labeling for the reference product includes IFU, the IFU for the proposed biosimilar product should incorporate relevant information from the IFU for the reference product and present the information in a similar manner. This guidance describes certain differences between biosimilar and reference product labeling, including the IFU, that may be appropriate. Please edit the draft IFU text in accordance with the FDA guidance referenced above and resubmit so that your IFU aligns with the IFU for US-licensed Neulasta PFS. If any differences continue to exist between the updated IFU and the IFU for the reference product, please provide a rationale for why those particular elements differ.
2. In Highlights, updated revision dates to 05/2022 and Initial U.S. Approval Date to 2022.
3. To Section 11:
 - a. Added the text "Kanamycin is used during the manufacturing process but is undetectable in the final product." Along with the explanation: "We added the type and calculated amount of antibiotics added during manufacture (See 21 CFR 610.61(m))".
 - b. We added the dosage form "injection" as required by regulation.
 - c. We asked the Applicant to revise the inactive ingredients to compendial names.
4. To Section 16: Added the room temperature storage conditions "[68oF to 77oF (20oC to 25oC)]"

Regulatory Recommendation: Labeling is considered final and ready for action.

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/s/

VIRGINIA E KWITKOWSKI
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 26, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761084
Product Name, Dosage Form, and Strength:	TPI-120 ^a Fylnetra (pegfilgrastim-pbbk) Injection, 6 mg/0.6 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kashiv BioSciences LLC (Kashiv)
FDA Received Date:	November 29, 2021, February 28, 2022, and March 2, 2022
OSE RCM #:	2020-1691-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

^a TPI-120 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name Fylnetra, was found conditionally acceptable on April 6, 2022. The nonproprietary name, pegfilgrastim-pbbk, was found conditionally acceptable on February 17, 2022.

1. REASON FOR REVIEW

As part of the approval process for Fylnetra (pegfilgrastim-pbbk) Injection, this review evaluates proposed Fylnetra container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

US-licensed Neulasta (pegfilgrastim) was approved on January 31, 2002 under BLA 125031. Fylnetra is being proposed for the indication 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. Like US-licensed Neulasta, the proposed strength is a 6 mg/0.6 mL in a single-dose, ungraduated prefilled syringe (PFS); however it contains a passive needle guard.

Kashiv submitted BLA 761084 on August 11, 2020. We previously completed a review of the proposed container label, carton labeling, PI, Patient Information, and IFU on April 20, 2021. As part of that review, we also evaluated a use-related risk analysis (URRA) and comparative analyses submitted by Kashiv on August 11, 2020. Our review of the URRA did not identify any new or unique risks for the TPI-120 PFS as compared to the US-licensed Neulasta PFS. However, we note that users are not required to activate the needle guard manually (as compared to the US-licensed Neulasta PFS). Our review of the comparative analyses noted differences in plunger rod color, plunger head diameter, and needle guard between TPI-120 and US-licensed Neulasta. The critical tasks for TPI-120 align with the critical tasks for US-licensed Neulasta, with one exception that users of the US-licensed Neulasta PFS are required to activate the needle guard manually (i.e., the user slides the needle guard over the needle), whereas the TPI-120 PFS has a passive needle guard which does not require manual activation. We found the elimination of manual activation of the needle guard in TPI-120 acceptable. Additionally, a review of the TPI-120 IFU noted it follows similar steps and injection technique as US-licensed Neulasta. As such, we determined that the Sponsor did not need to submit a human factors validation study for our review at that time.^b

The application received a Complete Response (CR) letter on August 11, 2021 due to microbiology, product quality, and facility inspection issues. Kashiv submitted a response to the CR letter for Fylnetra on November 29, 2021.

^b DeGraw, S. Use-Related Risk Analysis, Comparative Analyses, Label and Labeling Review for TPI-120 (BLA 761084). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 20. RCM No.: 2020-1691 and 2020-1705.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Kashiv BioSciences LLC (Kashiv) submitted a 351(k) application to obtain marketing approval of Fylnetra (pegfilgrastim-pbbk) Injection. Fylnetra is proposed to be indicated 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.

We performed a risk assessment of the proposed container label, carton labeling, PI, Patient Information, and IFU to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. For the Division, we note the proprietary name, (b) (4) was withdrawn, and the name, “Fylnetra” was found conditionally acceptable on April 4, 2022. Therefore, we recommend replacing (b) (4) with the conditionally acceptable name, “Fylnetra”. For the Applicant, we note the Rx only statement is missing on the container label, the net quantity statement on the carton labeling has the incorrect unit of measure statement and missing product identifiers. In addition, we recommend replacing (b) (4) with the conditionally acceptable name, “Fylnetra” wherever it appears on the label and labeling. These factors may confuse the user

and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4. CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container label, carton labeling, PI, Patient Information, and IFU that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Kashiv BioSciences LLC (Kashiv) to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. General Comments

- a. We note your submission received February 11, 2022 requesting a withdrawal for the proposed proprietary name “(b) (4)”. Replace the proprietary name “(b) (4)” in the Prescribing Information with the conditionally acceptable name “Fynetra”.

B. Patient Information

1. We note your submission received February 11, 2022 requesting a withdrawal for the proposed proprietary name “(b) (4)”. Replace the proprietary name “(b) (4)” in the Patient Information with the conditionally acceptable name “Fynetra”.

C. Instructions for Use

1. We note your submission received February 11, 2022 requesting a withdrawal for the proposed proprietary name “(b) (4)”. Replace the proprietary name “(b) (4)” in the Instructions for Use with the conditionally acceptable name “Fynetra”.

4.2 RECOMMENDATIONS FOR KASHIV BIOSCIENCES LLC (KASHIV)

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. We note your submission received February 11, 2022 requesting a withdrawal for the proposed proprietary name “(b) (4)”. Replace the proprietary name

“(b) (4)” in the Prescribing Information with the conditionally acceptable name “Fynetra”.

B. Container Label

1. Add the required ‘Rx Only’ statement to the syringe container label.

C. Carton Labeling (inner tray (b) (4) label)

1. We recommend revising the net quantity statement, “1 x 6 mL/0.6 mL single-dose syringe” to “1 x 6 mg/0.6 mL single-dose syringe” to reflect the correct unit of measure for this product.

D. Carton Labeling (outer)

1. As currently presented, the inclusion of a product identifier is not indicated. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the guidance to determine if the product identifier requirements apply to your product’s labeling.

¹The guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fylnetra received on November 29, 2021 from Kashiv BioSciences LLC (Kashiv), and the US-licensed Neulasta.

Table 2. Relevant Product Information for Fylnetra and US-licensed Neulasta		
Product Name	Fylnetra	US-licensed Neulasta ^c
Initial Approval Date	N/A	January 31, 2002
Nonproprietary Name	pegfilgrastim-pbbk	pegfilgrastim
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.	- 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)
Route of Administration	Subcutaneous	
Dosage Form	Injection	
Strength	6 mg/0.6 mL	

^c Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 FEB 02. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125031s203lbl.pdf.

Dose and Frequency	Cancer patients receiving myelosuppressive chemotherapy: 6 mg administered subcutaneously once per chemotherapy cycle. - Do not administer between 14 days before and 24 hours after cytotoxic chemotherapy. - Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1. Table 1. Dosing of (b) (4) for pediatric patients weighing less than 45 kg <table border="1"> <tr> <th>Body Weight</th><th>(b) (4) Dose</th><th>Volume to Administer</th></tr> <tr> <td>Less than 10 kg*</td><td>See below*</td><td>See below*</td></tr> <tr> <td>10 -20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr> <tr> <td>21 -30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr> <tr> <td>31 -44 kg</td><td>4 mg</td><td>0.4 mL</td></tr> </table> *For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of (b) (4)	Body Weight	(b) (4) Dose	Volume to Administer	Less than 10 kg*	See below*	See below*	10 -20 kg	1.5 mg	0.15 mL	21 -30 kg	2.5 mg	0.25 mL	31 -44 kg	4 mg	0.4 mL	Cancer patients receiving myelosuppressive chemotherapy: 6 mg administered subcutaneously once per chemotherapy cycle. - Do not administer between 14 days before and 24 hours after cytotoxic chemotherapy. - Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1. Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome: - Give 6 mg subcutaneously for adult victims with body weight $\geq$ 45 kg for two doses given two weeks apart; for pediatric patients weighing less than 45 kg, use weight-based dosing. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1. Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg <table border="1"> <tr> <th>Body weight</th><th>Neulasta Dose</th><th>Volume to administer</th></tr> <tr> <td>Less than 10 kg*</td><td>See below*</td><td>See below*</td></tr> <tr> <td>10 – 20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr> <tr> <td>21 – 30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr> <tr> <td>31 – 44 kg</td><td>4 mg</td><td>0.4 mL</td></tr> </table> *For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta	Body weight	Neulasta Dose	Volume to administer	Less than 10 kg*	See below*	See below*	10 – 20 kg	1.5 mg	0.15 mL	21 – 30 kg	2.5 mg	0.25 mL	31 – 44 kg	4 mg	0.4 mL
Body Weight	(b) (4) Dose	Volume to Administer																														
Less than 10 kg*	See below*	See below*																														
10 -20 kg	1.5 mg	0.15 mL																														
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Body weight	Neulasta Dose	Volume to administer																														
Less than 10 kg*	See below*	See below*																														
10 – 20 kg	1.5 mg	0.15 mL																														
21 – 30 kg	2.5 mg	0.25 mL																														
31 – 44 kg	4 mg	0.4 mL																														

How Supplied	(b) (4) (pegfilgrastim-pbbk) injection is a clear, colorless to slightly yellow, preservative-free solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-pbbk, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe Plus™ Passive Needle Guard. (b) (4) is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 70121-1627-1).	Neulasta injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. Neulasta is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 55513-190-01).
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 28, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Fynetra', '(b) (4)', 'TX01', 'BLA 761084' and 'IND 120048'. Our search identified one previous review^d, and we considered our previous recommendations to see if they are applicable for this current review.

^d DeGraw, S. Use-Related Risk Analysis, Comparative Analyses, Label and Labeling Review for TPI-120 (BLA 761084). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 20. RCM No.: 2020-1691 and 2020-1705.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Fylnetra labels and labeling submitted by Kashiv BioSciences LLC (Kashiv).

- Container label (syringe) received on November 29, 2021
- Carton labeling (inner tray (b) (4) label) received on November 29, 2021
- Carton labeling (outer) received on November 29, 2021
- Instructions for Use received on March 2, 2022, available from <\\CDSESUB1\evsprod\bla761084\0041\m1\us\114-labeling\draft-labeling\draft-label-text\draft-ifu-word-track-change.docx>
- Patient Information received on November 29, 2021, available from <\\CDSESUB1\evsprod\bla761084\0036\m1\us\114-labeling\draft-labeling\draft-label-text\draft-patient-information.pdf>
- Prescribing Information (Image not shown) received on November 29, 2021, available from <\\CDSESUB1\evsprod\bla761084\0036\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-prescr-info.pdf>

G.2 Label and Labeling Images

Container label (syringe)

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^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MEMORANDUM

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

DATE: July 28, 2021

TO: Ann T. Farrell, MD
Director
Division of Nonmalignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology, and
Nephrology (OCHEN)

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
DGDSI, OSIS

SUBJECT: Clinical FOR CAUSE Inspection of WCCT Global, Inc.,
Cypress, CA

1. Inspection Summary

At the request of DNH/OCHEN and DGDSI/OSIS, the Office of Regulatory Affairs (ORA) conducted a FOR CAUSE inspection of clinical portions of study TPI-CL-109A submitted as part of BLA 761084, (b) (4) conducted at WCCT Global. In part the inspection pursued allegations made in a complaint about bonus payments given to some study participants.

(b) (4)

Significant objectionable conditions were observed during the inspection and Form FDA 483 was issued at the inspection closeout. The objectionable conditions impact the reliability of the data from study TPI-CL-109A.

After reviewing the inspectional findings, I recommend that clinical data from study TPI-CL-109A not be accepted for agency review, and note several observations that should be considered by DNH/OCHEN reviewers.

The final inspection classification is Voluntary Action
Indicated (VAI).

2. Inspected Studies:

BLA 761084

Study Number: TPI-CL-109A

Study Title: "A randomized, double-blind, single-dose, two-period crossover comparative pharmacology study comparing TPI-120 and Neulasta® administered through subcutaneous route in healthy adult subjects"

Dates of conduct: February 2017 - January 2018

(b) (4)

Clinical site: WCCT Global, Inc.
5630 Cerritos Ave.
Cypress, CA 90630

3. Inspectional Findings

ORA investigators Andrea A. Branche and Kaitlyn T. Dang inspected WCCT Global, Inc. 5630 Cerritos Ave., Cypress, CA between 6/7/2021 and 6/18/2021.

The previous OSIS inspection of WCCT Global was conducted in August 2019. At the conclusion of the inspection, Form FDA 483 was not issued. The final classification was NAI. However, the two items below were discussed during the inspection closeout.

- ☐ A subject with a positive urine drug screen test was enrolled in the study in violation of the protocol.
- ☐ Several end-of-study physical examinations were performed outside the allowable timeframe.

Firm management made corrections by dismissing a physician, adjusting laboratory email notifications, and retraining another physician. The current inspection confirmed these corrections.

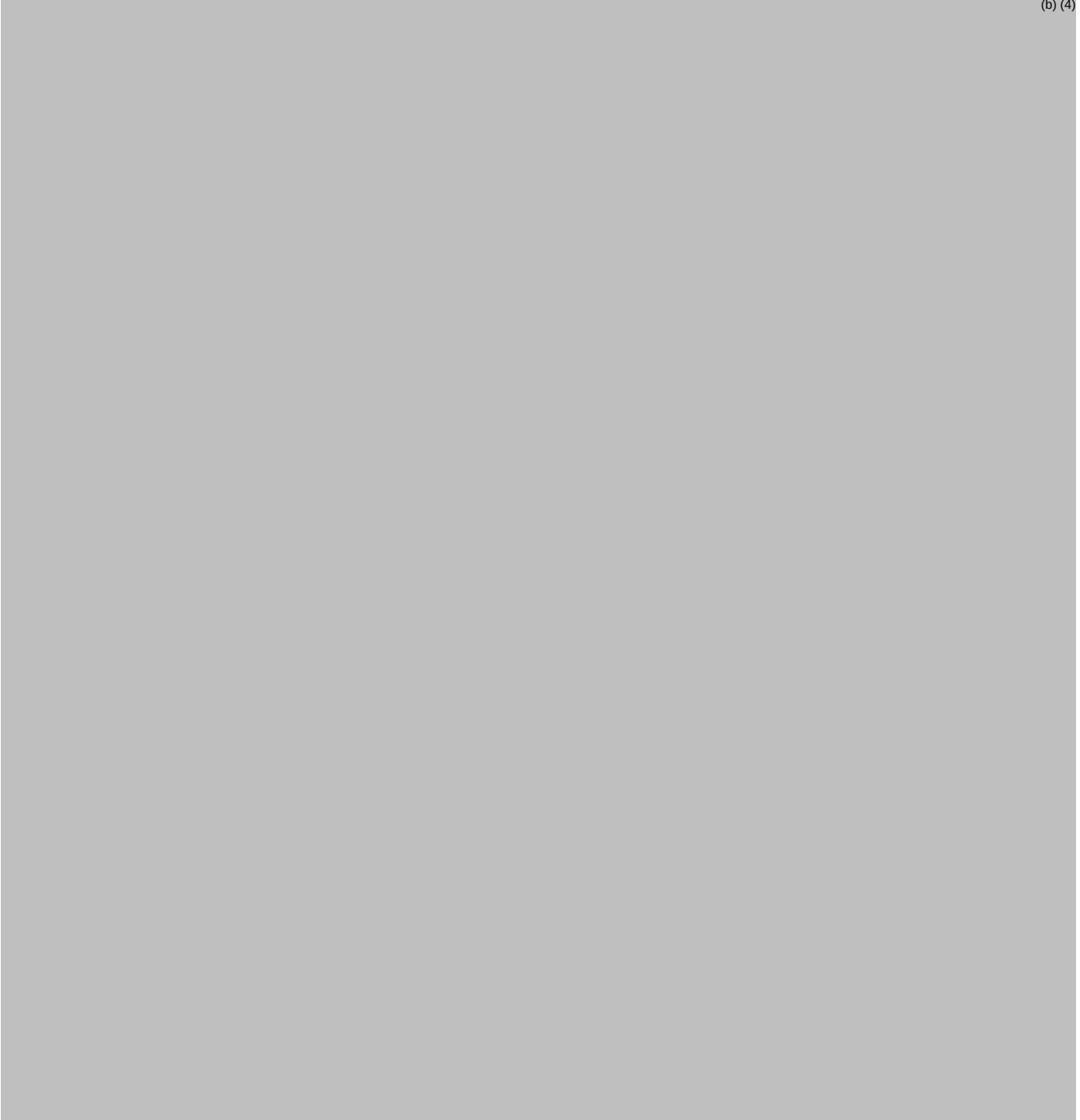
The current inspection included auditing the following items: informed consent forms (ICFs), subject CRFs, documentation of inclusion/exclusion criteria for all subjects randomized into the studies, dosing records, adverse event reporting-evaluation, IRB approval of the study protocols, amendments, and ICFs, Investigator and Sub-Investigator CVs, drug accountability and reserve sample control, and monitoring visits and reports.

At the conclusion of the inspection, investigators Branche and Dang observed objectionable conditions and issued Form FDA 483 to WCCT Global. The observations on Form FDA 483 (**Attachment 1**), the WCCT response dated 07/09/2021 (**Attachment 2**), and my evaluations are presented below.

3.1 FDA 483 Observations



(b) (4)



OBSERVATION 2:

Lack of adequate records covering of an investigational drug.

Specifically,

For the study TPI-CL-109A:

The blinding of this study could not be verified and/or recreated. The site did not maintain any copies of finished labeling for dosing of subjects, nor did they maintain sealed randomization codes. There was no record of destruction or disposition of the randomization codes.

Firm's Response:

In their written response, WCCT acknowledges that some records requested to demonstrate blinding practices during this study were not produced during the inspection, while other substantial information was provided in a timely manner.

WCCT recognizes that the pharmacy labels and correspondence sections of the Investigator Site File (ISF) were not easily accessible and that controls should be added to their processes for managing these materials.

WCCT analyzed the root cause, which is a lack of internal processes outlining the handling of unblinding records and related documentation.

WCCT stated in their response to Form FDA 483 that quality control measures were added to the management of the ISF in April of 2019, however this study was conducted prior to implementation of those measures.

For observation 2 above, WCCT has taken the following corrective actions:

- ☐ Ensured that information requested, but not available during the time of the inspection, has been appropriately archived with the study records.
- ☐ In April of 2019, WCCT implemented mandatory QC checks for the ISF at specified intervals for each study. These additional QC checks have helped to ensure that essential documents and relevant correspondence are accounted for prior to study closeout.

To ensure that the observation does not recur in the future, WCCT has taken the preventive actions detailed in **Attachment 2**.

OSIS Evaluation:

After the evaluation of the response to Form FDA 483, I conclude that the above observation has impact on reliability of data from study TPI-CL-109A. The response to Form FDA 483 stated that WCCT has taken preventive actions to ensure that this

observation does not recur in future studies. However, these procedures were not in use at the time of the study TPI-CL-109A.

Based on the study protocol, study TPI-CL-109A was a randomized, double-blind study. One set of sealed envelopes containing the randomization code for each subject was provided to the WCCT PI at the start of the study. At the end of the study, these sealed envelopes should have been retained or destroyed according to site procedures, unless specified otherwise by the sponsor. Breaking of these sealed envelopes was forbidden in the protocol except in the event of a medical emergency. During the inspection, these sealed envelopes were requested by ORA investigators to verify subjects' dosing materials. The sealed envelopes were the only way for the ORA investigators to confirm that subjects received the correct treatments. However, during the inspection, the sealed envelopes were not provided to them. The explanation provided by WCCT in response to Form FDA 483 does not resolve the concerns, and correct dosing of the subjects in study TPI-CL-109A cannot be confirmed.

Without the ORA investigator confirming during inspection that subjects received the correct (blinded) treatments, data from study TPI-CL-109A are not reliable to support agency review.

3.2 Additional general discussion with management

(b) (4)

Final Classification:

VAI - WCCT Global, Inc.
5630 Cerritos Ave.
Cypress, CA 90630
FEI#: 3006237846

CC:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Lewin/Li
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XFL 07/23/2021, 07/27/2021, 07/28/2021
Edits: MFS 07/23/2021, 07/27/2021, 07/28/2021; KAB 07/27/2021,
07/28/2021

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/West Coast Clinical
Trials (WCCT-Global 5630 Cerritos), Cypress, CA, USA

OSIS File #: BE8987

FACTS: 12095120
OP ID: 10957793

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 18, 2021

To: May Zuwannin
Regulatory Project Manager
Division of Nonmalignant Hematology

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Rebecca Falter, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name [TPI-120] TRADENAME (pegfilgrastim-pbbk)¹
(nonproprietary name):

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761084

Applicant: Kashiv Biosciences, LLC

¹ TPI-120 has been developed as a biosimilar to US-licensed NEULASTA. At the time of our review, the proposed proprietary name has not yet been determined. In this document, we refer to Kashiv Biosciences LLCs proposed product by the company code “TPI-120” and TRADENAME. The proposed nonproprietary name “pegfilgrastim-pbbk” was found to be conditionally acceptable by DMEPA on May 10, 2021 and is used throughout this document.

1 INTRODUCTION

On August 11, 2020, Kashiv Biosciences, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761084 for [TPI-120] TRADENAME (pegfilgrastim-pbbk) injection, a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim) injection (BLA 125031). The proposed indication for [TPI-120] TRADENAME (pegfilgrastim-pbbk) injection is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on August 20, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for [TPO-120] TRADENAME (pegfilgrastim-pbbk) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft [TPO-120] TRADENAME (pegfilgrastim-pbbk) injection PPI and IFU received on August 11, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on March 30, 2021.
- Draft [TPO-120] TRADENAME (pegfilgrastim-pbbk) injection Prescribing Information (PI) received on August 11, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on March 30, 2021.
- Approved US-licensed NEULASTA (pegfilgrastim) injection (BLA 125031) labeling dated February 2, 2021, January 5, 2021 and April 28, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using Arial font, size 11 and the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

- ☐ simplified wording and clarified concepts where possible
- ☐ ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- ☐ removed unnecessary or redundant information
- ☐ ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ☐ ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- ☐ Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- ☐ Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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USE-RELATED RISK ANALYSIS, COMPARATIVE ANALYSES, LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 20, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761084
Product Name and Strength:	TPI-120 ^a (pegfilgrastim-xxxx) ^b 6 mg/0.6 mL
Product Type:	Biologic-Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Kashiv BioSciences, LLC (Kashiv)
Submission Date:	August 11, 2020
OSE RCM #:	2020-1691 and 2020-1705
DMEPA Primary Reviewer:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD

^a TPI-120 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name for this BLA has not yet been determined; therefore, the placeholder, TPI-120, is used throughout this review to refer to the proprietary name for this product.

^b The nonproprietary name suffix for this BLA has not yet been determined; therefore, the placeholder, pegfilgrastim-xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1 REASON FOR REVIEW

Kashiv BioSciences, LLC (Kashiv) submitted BLA 761084 for TPI-120 (pegfilgrastim-xxxx) on August 11, 2020. This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for TPI-120 (pegfilgrastim-xxxx) for areas of vulnerability that could lead to medication errors. In addition, we evaluated the use-related risk analysis and comparative analyses submitted by Kashiv on August 11, 2020.

1.1 PRODUCT BACKGROUND

On August 11, 2020, Kashiv submitted 351(k) BLA 761084 seeking licensure for TPI-120 as a biosimilar to US-licensed Neulasta. TPI-120 is being proposed for the indication of decreasing 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. TPI-120 is being proposed as a 6 mg/0.6 mL solution in a single-dose, ungraduated prefilled syringe with a passive needle guard.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Requests	F – N/A
Labels and Labeling	G
Pediatric Considerations	H

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The BLA submission included a use-related risk analysis, comparative analyses, proposed container label, carton labeling, Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU). Kashiv is pursuing only one of the indications of US-licensed Neulasta (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).

3.1 USE-RELATED RISK ANALYSIS ASSESSMENT

We note that TPI-120 has the same intended users, use environments, dosing, and route of administration as US-licensed Neulasta (BLA 125031) for its febrile neutropenia indication.

The sponsor submitted a URRAs, which identified and evaluated the tasks involved in the use of the TPI-120 prefilled syringe (PFS), the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors.

We reviewed the URRAs for the proposed product. We did not identify any new or unique risks for the TPI-120 PFS as compared to the US-licensed Neulasta PFS. However, we note that users are not required to activate the needle guard manually (as compared to the US-licensed Neulasta PFS). We describe our evaluation of this difference below (see Section 3.2).

3.2 COMPARATIVE ANALYSIS ASSESSMENT

Physical Comparison

TPI-120 is supplied as a single-dose, ungraduated PFS with an UltraSafe Plus Passive needle guard. US-licensed Neulasta is supplied as a single-dose, ungraduated PFS with a manual needle guard.^c Both products are supplied in a carton containing one PFS.

We note in the physical comparison that the TPI-120 PFS plunger rod is white whereas the plunger rod in the US-licensed Neulasta PFS is dark blue. The TPI-120 PFS has a larger plunger head diameter as compared to the plunger head in the US-licensed Neulasta PFS. Additionally, TPI-120 PFS has a clear (transparent) UltraSafe Plus Passive needle guard while US-licensed Neulasta has a translucent blue UltraSafe Active needle guard. In this particular instance, our evaluation of the physical comparison determined the physical differences should not affect critical tasks; therefore, these differences are acceptable.

Task Comparison

We note in the task comparison, that the critical tasks for TPI-120 align with the critical tasks for US-licensed Neulasta, with one exception that users of the US-licensed Neulasta PFS are required to activate the needle guard manually (i.e., the user slides the needle guard over the needle), whereas, the TPI-120 PFS has a passive needle guard which does not require manual activation. The passive needle guard automatically activates after the user presses the plunger all the way down to administer the injection and then allows their finger to release pressure, which causes the needle to retract into the body and lock the guard in place. We find the elimination of manual activation of the needle guard in TPI-120 acceptable.

^c US-licensed Neulasta is also available as an OnPro Kit, which contains the same PFS and an on-body delivery device.

Labeling Comparison: Side-by-Side IFU Comparison

The TPI-120 IFU follows similar steps and injection technique as US-licensed Neulasta. However, we note the following differences:

- The TPI-120 IFU does not contain a figure depicting the syringe after use in the introduction to the syringe parts.
- Like US-licensed Neulasta, the TPI-120 PFS does not have graduation marks, and therefore, doses less than 6 mg (0.6 mL) cannot be accurately measured or directly administered without manipulation of the PFS content or dose approximation. Due to the potential for dosing errors, direct administration to patients requiring doses less than 0.6 mL (6 mg) is not recommended. We note that information regarding dosing limitations of the PFS is not conveyed in the IFU.
- Figure G in the TPI-120 IFU does not include labels for the appropriate injection sites, unlike the US-licensed Neulasta IFU.
- Additionally, we identified other aspects of the IFU that should be revised to add and/or relocate important information regarding the administration of TPI-120.

We provide all recommendations for the IFU in Section 4.1 below.

Labeling Comparison: Carton and Container Labels

Our review of the comparison of the carton and container labels determined that differences identified in the comparative analysis of the carton and container labels were product-specific information (e.g., tradename and trade dress). As such, we find these differences acceptable.

However, from a medication error perspective, we identified several areas that may be improved to increase the readability and prominence of important information on the carton and container labels. We provide our recommendations in Section 4.2 below.

3.3 LABELING: PRESCRIBING INFORMATION AND PATIENT INFORMATION

We performed a risk assessment of the proposed PI and PPI to evaluate the potential for medication errors. Our evaluation of the proposed TPI-120 PI and PPI did not identify any new or unique areas of vulnerability that may lead to medication errors for the TPI-120 PFS as compared to the US-licensed Neulasta PFS; however, we note the proprietary name, Fylnetra was found unacceptable, therefore, we recommend replacing “Fylnetra” with the placeholder “Tradename” wherever it appears until a proprietary name is found conditionally acceptable. We provide our recommendation for the division below.

4 CONCLUSION & RECOMMENDATIONS

Our review of the URRAs for the proposed TPI-120 concluded that there were no new or unique risks when compared to US-licensed Neulasta. We also note that the intended user group, intended uses, and use environments for TPI-120 align with US-licensed Neulasta for the febrile neutropenia indication.

We determined that the sponsor does not need to submit a human factors validation study for our review at this time. Any changes to the URRAs would warrant further review.

Additionally, as a biosimilar, the proposed labeling for TPI-120 is, in relevant part, substantially the same as the labeling for US-licensed Neulasta regarding administration of doses less than 0.6 mL (6 mg). We have no comments or recommendations for the PPI at this time. However, we conclude that the proposed PI, IFU, container label, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Kashiv in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DNH

A. Prescribing Information

1. General Comments

- a. We note the proposed proprietary name “Fylnetra” was found unacceptable as communicated in the Proprietary Name Review Denial letter dated September 6, 2019 under IND 120048. Therefore, we recommend replacing “Fylnetra” in the Prescribing Information with “Tradename” as a placeholder until a proprietary name is found conditionally acceptable.

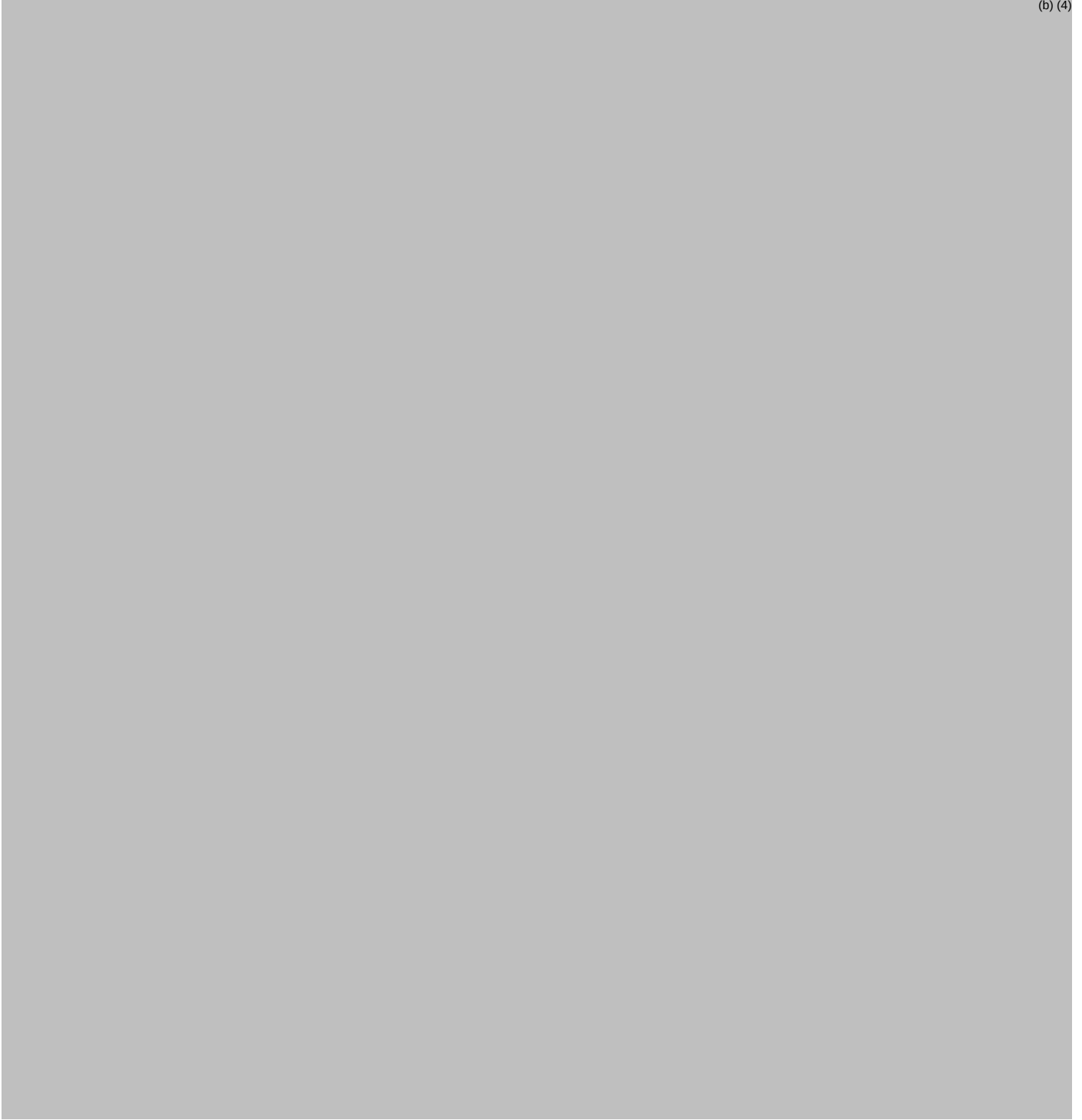
B. Instructions for Use (IFU)

We provide the following IFU recommendations to increase the clarity of the information presented and to more closely align with the US-license Neulasta IFU.

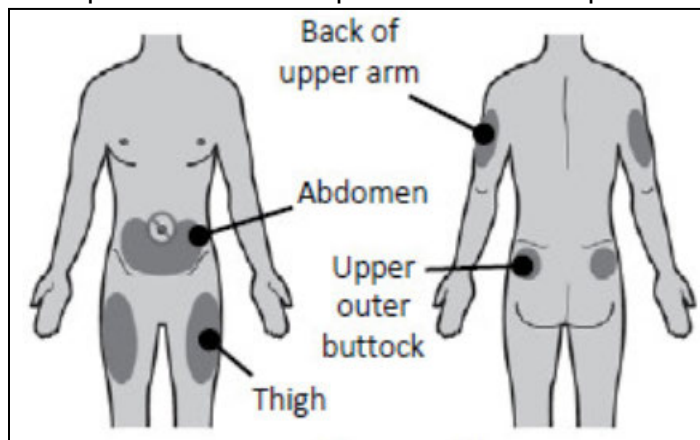
1. We note the proposed proprietary name “Fylnetra” was found unacceptable as communicated in the Proprietary Name Review Denial letter dated September 6, 2019 under IND 120048. Therefore, we recommend replacing “Fylnetra” in the Prescribing Information with “Tradename” as a placeholder until a proprietary name is found conditionally acceptable.
2. We recommend creating a “Guide to Parts” section as the first section of the IFU.
3. We recommend moving Figure A, which shows the syringe parts, to the Guide to Parts section and labeling this figure “Before Use”.
4. We recommend including a second figure in the “Guide to Parts” section which depicts the syringe after the injection is complete and the needle guard has been activated and labeling this figure “After Use”.

5. We recommend revising the “IMPORTANT” and “Section A” sections to include all pertinent warnings and device information. For example, revise as follows:

(b) (4)



6. We recommend moving the “What you need for your injection” section so that it appears under the “Preparing to Inject with the Prefilled Syringe” heading.
7. We recommend revising “(b) (4)” to read “Step 1: Gather Supplies”. Re-number all subsequent steps accordingly.
8. We recommend adding “adhesive bandage” as an item that should be gathered that is not included in the pack. A corresponding image of an adhesive bandage should also be added to the current Figure B which depicts the supplies.
9. We recommend deleting Figure (b) (4) syringe will be included in the Guide to Parts section.
10. We recommend labeling the current Figure G with the appropriate injection sites to correspond with the text provided. For example:



11. We recommend revising “Choose a different site for each injection of FYLNETRA” to read, “Choose a different injection site for each injection of TRADENAME. If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.”
12. Under the “Remove the needle cap” step, the image used in the current Figure I does not match the accompanying text. The text states to “pull the needle cap straight off”, however, the image shows the needle cap is removed at an angle. Please reorient the image used in Figure I to show the needle cap being pulled straight up to provide congruency with the text and the image.
13. Under the “Remove the needle cap” section, we recommend including additional warning statements about removal of the needle cap. For example, revise as follows:

- Carefully pull the needle cap straight off.
- Do not remove the needle cap from the prefilled syringe until you are ready to inject.
- Do not twist or bend the needle cap.
- Do not hold the prefilled syringe by the plunger rod

14. We recommend revising the “Pinch the skin” language to read “...gently pinch the skin around the injection site to create a firm surface.”

15. We recommend removing the instructions “(b) (4)” as the dose should be fully administered once the plunger is fully depressed and does not need to be held afterward.

16. As currently presented, step 15 which instructs users to “Treat injection site as needed” appears after the syringe disposal step. We recommend moving the “treat the injection site” step so that it appears immediately after the “Allow safety mechanism to activate and retract the needle” step.

4.2 RECOMMENDATIONS FOR KASHIV

A. General Comments for the Container Label and Carton Labeling

1. The proposed proprietary name “Fylnetra” was found unacceptable as communicated in the Proprietary Name Review Denial letter dated September 6, 2019 under IND 120048. Therefore, we recommend replacing “Fylnetra” in the with “Tradename” as a placeholder until a proprietary name is found conditionally acceptable.
2. As currently presented, the format of the expiration date is not indicated. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3. We note that the labels and labeling submitted on August 11, 2020 state the nonproprietary name and dosage form as “(pegfilgrastim-xxxx) Injection” whereas the samples provided state “pegfilgrastim-xxxx” without parenthesis and do not

include the dosage form. Please confirm you intend to present the nonproprietary name and dosage form as “(pegfilgrastim-xxxx) Injection”.

B. Container Label

1. To decrease the risk of wrong route medication errors, we recommend adding the route of administration “For subcutaneous use only” on the principal display panel if space will allow.

C. Carton Labeling – Inner Tray

1. We recommend revising the “6 mg” strength in the teal rectangle to state the amount per total volume, “6 mg/0.6 mL”.
2. As currently presented, the location and format for the lot and expiration date are not described. Please confirm the inclusion and location of these items so that we may review the acceptability of how it is presented in relation to other important product information. See recommendation A.2 for FDA recommended expiration date formats.
3. As currently presented, the inclusion and location of a linear barcode is not indicated. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label. Add the product’s linear barcode to each individual carton (tray) labeling in accordance with 21 CFR 201.25(c)(2).
4. Revise “Read the full prescribing information before use” to read “Dosage: See Prescribing Information” in alignment with 21 CFR 201.55 to ensure consistency with all doses described in the prescribing information.
5. We recommend revising the storage statement to present the storage temperature in Fahrenheit first which is more familiar to lay persons, and to present the information all in black font to improve readability. Revise to read, “Refrigerate at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do Not Freeze. Do Not Shake.”

D. Carton Labeling – Outer Carton

1. We recommend revising the “6 mg” strength in the circle to state the amount per total volume, “6 mg/0.6 mL”.
2. As currently presented, the location and format for the lot and expiration date are not described. Please confirm the inclusion and location of these items. See recommendation A.2 for FDA recommended expiration date formats.
3. As currently presented, the inclusion and location of a linear barcode is not indicated. The drug barcode is often used as an additional verification during the

medication use process; therefore, it is an important safety feature that should be part of the label. Add the product's linear barcode to each individual carton (outer carton) labeling in accordance with 21CFR 201.25(c)(2).

4. Add the statement "Dosage: See Prescribing Information" to a side panel in alignment with 21 CFR 201.55 to ensure consistency with all doses described in the prescribing information.
5. The numbers in the contents statement are printed in a light teal color on a white background. This color contrast appears difficult to read. Low contrast is a common cause of unreadable text. Therefore, we recommend revising the text color (i.e., black) to improve the contrast and readability of this information.
6. We recommend revising the storage statement to present the storage temperature in Fahrenheit first which is more familiar to lay persons, and to present the information all in black font to improve readability. Revise to read, "Refrigerate at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do Not Freeze. Do Not Shake." Additionally, the storage statement on the principal display panel (PDP) may be removed as it is stated on the side panel.
7. We recommend removing the trailing zero that appears in the contents list (i.e., 30.0 mg) to avoid misinterpretation of the number (i.e., 30 versus 300).
8. As currently presented, the inclusion of a product identifier is not indicated. In September 2018, FDA released draft guidance, which, when finalized will represent the agency's current thinking on the topics therein, on product identifiers required under the Drug Supply Chain Security Act.^d The Act requires manufacturers and re-packagers, respectively, to affix or imprint a human-readable and machine-readable product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. Therefore, please confirm the inclusion and location of this information.

^d Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for TPI-120 that Sandoz submitted on August 11, 2020 and US-licensed Neulasta.

Table 2. Relevant Product Information for Udenyca and US-Licensed Neulasta		
Product Name	TPI-120	US-licensed Neulasta ^e
Initial Approval Date	N/A	January 31, 2002
Nonproprietary or Proper Name	Pegfilgrastim-xxxx	Pegfilgrastim
Indication	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.	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. Neulasta is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection	Injection
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	Cancer patients receiving myelosuppressive chemotherapy: 6 mg administered subcutaneously once per chemotherapy cycle. - Do not administer TPI-120 between 14 days before and 24 hours after administration of cytotoxic chemotherapy. - Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1.	Cancer patients receiving myelosuppressive chemotherapy: 6 mg administered subcutaneously once per chemotherapy cycle. - Do not administer between 14 days before and 24 hours after cytotoxic chemotherapy. - Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1. Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome: - Give 6 mg subcutaneously for adult victims with body weight $\geq$ 45 kg for two doses given two weeks apart; for

^e Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Apr 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125031s198lbl.pdf

	The TPI-120 prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of TPI-120 less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1. Table 1. Dosing of TPI-120 for pediatric patients weighing less than 45 kg <table> <tr> <th>Body weight</th><th>TPI-120 Dose</th><th>Volume to administer</th></tr> <tr> <td>Less than 10kg*</td><td>See below*</td><td>See below*</td></tr> <tr> <td>10-20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr> <tr> <td>21-30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr> <tr> <td>31-44 kg</td><td>4 mg</td><td>0.4 mL</td></tr> </table> *For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of TPI-120	Body weight	TPI-120 Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL	pediatric patients weighing less than 45 kg, use weight-based dosing. The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1. Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg <table> <tr> <th>Body weight</th><th>Neulasta Dose</th><th>Volume to administer</th></tr> <tr> <td>Less than 10kg*</td><td>See below*</td><td>See below*</td></tr> <tr> <td>10-20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr> <tr> <td>21-30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr> <tr> <td>31-44 kg</td><td>4 mg</td><td>0.4 mL</td></tr> </table> *For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta	Body weight	Neulasta Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL
Body weight	TPI-120 Dose	Volume to administer																														
Less than 10kg*	See below*	See below*																														
10-20 kg	1.5 mg	0.15 mL																														
21-30 kg	2.5 mg	0.25 mL																														
31-44 kg	4 mg	0.4 mL																														
Body weight	Neulasta Dose	Volume to administer																														
Less than 10kg*	See below*	See below*																														
10-20 kg	1.5 mg	0.15 mL																														
21-30 kg	2.5 mg	0.25 mL																														
31-44 kg	4 mg	0.4 mL																														
How Supplied	TPI-120 injection is a clear, colorless to slightly yellowish solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-xxxx, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe Plus™ Passive Needle Guard. TPI-120 is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 70121-1627-1).	Neulasta is a clear, colorless, preservative-free solution available as single dose prefilled syringe with an UltraSafe® Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim as well as an OnPro kit which contains 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the on-body Injector for Neulasta.																														
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Store refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.																														

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 12, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, (b) (4), 'Fylnetra', 'TX01', 'BLA 761084' and 'IND 120048'. Our search identified no previous human factors or label and labeling reviews.

APPENDIX C. HUMAN FACTORS

We received the following Human Factors documents submitted by Kashiv on August 11, 2020.

Use-Related Risk Analysis (Product Hazard Analysis)

<\\CDSESUB1\evsprod\bla761084\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\human-factor-report\product-hazard-ana-dcp-0041.pdf>

Threshold Analysis

<\\CDSESUB1\evsprod\bla761084\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\human-factor-report\threshold-analy-report-iaa-cmo-0085.pdf>

HF Summary Report

<\\CDSESUB1\evsprod\bla761084\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\human-factor-report\human-factor-summary-report-dcp-0042.pdf>

HF Formative Study Report

<\\CDSESUB1\evsprod\bla761084\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\human-factor-report\human-factor-formative-stud-report-iaa-cmo-0078.pdf>

HF Formative Study Protocol

<\\CDSESUB1\evsprod\bla761084\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\human-factor-report\human-factor-formative-stud-protocol-iaa-cmo-0077.pdf>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following TPI-120 labels and labeling submitted by Kashiv on August 11, 2020.

- Container label (syringe)
- Carton labeling (inner tray (b) (4) label)
- Carton labeling (outer)
- Prescribing Information, Patient Information, Instructions for Use (image not shown)
<\\CDSESUB1\evsprod\bla761084\0001\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-word.docx>

G.2 Label and Labeling Images

Container label (syringe)



^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX H. PEDIATRIC CONSIDERATIONS

As part of the submission for BLA 761084, Kashiv submitted a request for deferral for its pediatric assessments. We note the following:

- October 4, 2019, DMEPA memorandum (archived to BLA 125031). On October 4, 2019, DMEPA finalized a memorandum of a comprehensive review and analysis of medication errors associated with doses of pegfilgrastim products less than 0.6 mL (6 mg) in pediatric patients. TPI-120 has the same strength, dosage form, and route of administration as US-licensed Neulasta, and, like US-licensed Neulasta, would only be available in a prefilled syringe without graduation marks. Additionally, the proposed labeling for TPI-120, in relevant part, is substantially the same as US-licensed Neulasta's labeling, including with respect to pediatric use information and the statements that the prefilled syringe is not designed to allow for direct administration and cannot accurately measure doses less than 0.6 mL (6 mg). Therefore, if the requirements for biosimilarity are met, TPI-120 would be expected to be associated with the same type of dosing error and potential consequences as US-licensed Neulasta. See also October 10, 2019, Memorandum on Requirements for Pediatric Assessments Pursuant to Section 505B(b)(1) of the FD&C Act.
- Order letter to sponsor of US-licensed Neulasta. On October 10, 2019, FDA issued an order letter pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to the sponsor of US-licensed Neulasta, requiring it to submit pediatric assessments as described in section 505B(a)(2)(A) of the FD&C Act. As described in the letter, the sponsor of U.S.-licensed Neulasta is subject to a postmarketing requirement referred to as submission of pediatric assessments for Neulasta (pegfilgrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of 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), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. In the letter, FDA stated it expected that a pediatric presentation – such as a vial or a pediatric-sized pre-filled syringe (with an appropriate concentration of product) – that can be used to directly and accurately deliver doses of less than 0.6 mL (6 mg) of pegfilgrastim to pediatric patients could be an "appropriate formulation" as described in section 505B(a)(2)(A). FDA issued similar letters to sponsors of the licensed pegfilgrastim biosimilars, Udenyca (BLA 761039) and Fulphila (BLA 761075). FDA licensed Ziextenzo (BLA 761045) on November 4, 2019 and Nyvepria (BLA 761111) on June 10, 2020, which are also subject to a similar postmarketing requirement.

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/

STEPHANIE L DEGRAW
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LOLITA G WHITE on behalf of CHI-MING TU
04/21/2021 04:43:38 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: April 8, 2021

To: May Zuwannin, Regulatory Project Manager, Division of
Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for FYLNETRA (pegfilgrastim-xxxx) injection,
for subcutaneous use

BLA: 761084

In response to DNH's consult request dated August 18, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU) for the original BLA submission for Fylnetra. Per communications by electronic mail with May Zuwannin on April 7, 2021, OPDP has reviewed the proposed carton and container labeling as well.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (May Zuwannin) on March 30, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 11, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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immediately following this page

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