BLA 761084

CORRECTED BLA APPROVAL

Kashiv BioSciences, LLC
Attention: John Pakulski
Senior VP, Global Regulatory Affairs
20 New England Avenue
Piscataway, NJ 08854

Dear Mr. Pakulski:

Please refer to your biologics license application (BLA) dated and received August 11, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for Fylnetra (pegfilgrastim-pbbk) injection.

We acknowledge receipt of your resubmission dated November 29, 2021, which constituted a complete response to our August 11, 2021, action letter.

We also refer to our approval letter dated May 26, 2022, which contained the following error:

- The strength was listed as 0.6 mg/0.6 mL injection instead of 6 mg/0.6 mL injection

This corrected action letter incorporates the correction of the error. The effective action date will remain May 26, 2022, the date of the original letter.

LICENSING

We have approved your BLA for Fylnetra (pegfilgrastim-pbbk) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Fylnetra under your existing Department of Health and Human Services U.S. License No. 2131. Fylnetra is 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.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture pegfilgrastim-pbbk drug substance at Kashiv BioSciences, LLC in Chicago, IL. The final formulated drug product will be manufactured and filled at (b) (4) and labeled and packaged at Kashiv BioSciences, LLC. You may label your product with the

proprietary name, Fylnetra, and market it in 6 mg/0.6 mL injection in a single-dose prefilled syringe.

DATING PERIOD

The dating period for Fylnetra shall be 24 months from the date of manufacture when stored at 5 ± 3°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be [redacted] (b) (4) from the date of manufacture when stored at [redacted] (b) (4) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Fylnetra to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Fylnetra, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use). Information on submitting SPL files using

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761084**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We are deferring submission of your pediatric assessments for patients less than 45 kg until October 31, 2025 for this application.

Your deferred pediatric assessments required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are a postmarketing requirement. The status of this postmarketing requirement must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This postmarketing requirement is listed below.

4277-1 Develop an appropriate formulation (presentation) that can be used to directly and accurately administer Fylnetra (pegfilgrastim-pbbk) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conduct any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses.

Final Report Submission: 10/2025

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 120048, with a cross-reference letter to this BLA. Reports of this/these required pediatric assessments must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this/these study(ies). When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4281-1 Perform a real-time drug product (DP) shipping study from the DP manufacturing site to Kashiv BioSciences and to the distribution center to confirm validation of the commercial TPI-120 DP shipping conditions, such as described in protocol PTL-2374 (Section 3.2.P.3.5). The final study report should include assessments for the impact of real-time shipping on (i) product quality (comparison of product pre- and post-shipment), (ii) temperature for the duration of transport, and (iii) physical damage to the DP containers.

The timetable you submitted on April 18, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

4281-2 Perform a study to evaluate the impact of the removal of kanamycin from the (b) (4) manufacturing process. If the data support removal of kanamycin, a plan for the removal of kanamycin from the manufacturing process is expected to be provided. The plan should include an evaluation of consistency of the fermentation process and comparability of the (b) (4) manufactured with and without kanamycin. The results should be reported per 21 CFR 601.12.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on April 18, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4281-3 Reassess the [redacted] (b) (4) acceptance criteria for testing of drug substance (DS) and drug product (DP) at release and on stability when 10 commercial DS and DP batches have been manufactured and tested. The final study report should include sufficient information and data to support the acceptance criteria, and all relevant protocols (e.g., qualification and requalification protocols of reference standards) as well as DS and DP specifications should be updated as needed.

The timetable you submitted on April 18, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call May Zuwannin, Regulatory Project Manager, at 301-796-7775.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Deputy Division Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

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/

ALBERT B DEISSEROTH
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