CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761082Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA Number: 761082
Review of BLA Resubmission (eCTD Sequence: 0060)
Review Date: February 11, 2022

Addendum: The OPQ Executive Summary memorandum uploaded to DARRTS on February 04, 2022 still applies and is valid. This addendum is to provide an assessment of the labeling information provided by the Applicant.

Drug Name/Dosage	Releuko-filgrastim-ayow (theragrastim)/injection
Strength/Potency	i): 300 mcg/mL and 480 mcg/1.6 mL in a single-dose vial 300 mcg/0.5 mL and 480 mcg/0.8 mL in a single-dose prefilled syringe ii): Potency by cell proliferation assay
Route of Administration	IV infusion or SC injection
Rx/OTC dispensed	Rx
Indication	Releuko, referred to by the applicant as theragrastim, proposed indications are: • Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
Applicant/Sponsor	Kashiv Biosciences, LLC

Quality Review Team

Discipline	**Reviewer**	**Division/Office**
Drug Substance	Rong Wang	DBRR-III/OBP/OPQ
Drug Product	Rong Wang	DBRR-III/OBP/OPQ
Comparative Analytics	Rong Wang	DBRR-III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Michael Shanks/Candace Gomez-Broughton (TL)	DBM/OPMA/OPQ
Microbiology	Michael Shanks, Yarery Smith/ Candace Gomez-Broughton (RC)	DMA/OPMA/OPQ
RBPM	Grafton Adams	OPRO/OPQ
Application Technical Lead	Ram Sihag	DBRR-III/OBP/OPQ
Tertiary Reviewer	Susan Kirshner and Frances Namuswe	DBRR-III/OBP/OPQ

ADDENDUM

BACKGROUND

As per CDER 21st Century Review Guidelines, the product quality Executive Summary Memo for BLA761082-0060 was completed and uploaded to DARRTS on February 4, 2022. However, at that time, Kashiv had not provided in-use stability data to support stability of Releuko diluted in 5% dextrose injection with or without human albumin up to 2 mg/mL prior to intravenous infusion.

This **addendum** provides an evaluation of the **lack of in-use stability data** and updates OBP's recommendation regarding the labeling instructions for adminstration by intravenous infusion in Section II, and item G in the Executive Summary Memo submitted on February 4, 2022.

Releuko is a proposed biosimilar to US-licensed Neupogen and Kashiv is requesting approval for strengths, presentations, and indications for which US-licensed Neupogen is approved. Releuko has the same excipients in the same amounts as the corresponding US-licensed Neupogen strengths. According to the current labeling for US-licensed Neupogen[1], it can be administered by subcutaneous injection using the vial or pre-filled syringe strengths, or by intravenous infusion using the vial strengths after dilution from 300 mcg/ml to 5 mcg/ml in 5% dextrose. Final concentrations of Neupogen ranging from 5 mcg/mL to 15 mcg/mL should be diluted in 5% dextrose with the addition of human albumin up to 2 mg/mL.

Kashiv originally requested the same routes of administration and to include the same instructions for dilution for intravenous administration as US-licensed Neupogen. However, as documented in the OPQ Executive Summary Memo dated February 4, 2022, the Applicant did not provide in-use compatibility and stability data to support the product quality of Releuko will be maintained after dilution in 5% dextrose with or without albumin for intravenous infusion. In addition, the Applicant did not provide microbial challenge studies to support storage of diluted Releuko beyond 4 hours at room temperature. (b) (4)

From the product quality perspective, there are two concerns related to diluting a therapeutic protein product into a solution intended for intravenous infusion: that the composition of the diluent might affect product quality (i.e., degrade the protein) or that the excipients used may be incompatible with the diluent.

After further internal OBP discussions, it was determined that because

1) Releuko includes the same excipients in the same amounts as those of US-licensed Neupogen,
2) the proposed administration instructions for intravenous infusion, including the composition of the diluents, are the same as those of US-licensed Neupogen,
3) the comparative analytical assessment data provided in the 351(k) BLA 761082 submission, including the comparative stability profiles between Releuko and US-licensed Neupogen, support that Releuko is highly similar to US-licensed Neupogen, plus adequate information was provided to support that Releuko is compatible with its own vial container closure, and
4) the quality attributes not covered by comparative analytical assessment, such as, subvisible particles and container closure leachables are appropriately controlled in Releuko,

there is no scientific reason to expect Releuko to have a different in-use stability profile when diluted for

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103353s5197lbl.pdf

IV administration from that of US-licensed Neupogen.[2] Therefore, it was concluded that the available data and information provided in BLA 761082 are adequate to support storage of Releuko diluted in 5% dextrose with or without albumin under the same conditions as US-licensed Neupogen for up to 4 hours at room temperature. In addition, in-use compatibility and chemical stability data would not be needed to support storage up to 24-hour at room temperature. However, because the Applicant did not provide microbial assessment data needed to support storage of Releuko at room temperature for longer than 4 hours, the proposed labeling of Releuko for storage for up to 24 hours is not acceptable at this time (see review memo by Dr. Yarery Smith for BLA761082-0055 for details at https://panorama.fda.gov/document/view?ID=60d31d7500294929b1a65ccc226e1781.

CONCLUSION

The available data are adequate to support the current labeling instructions that Releuko 300 mcg/mL in a single-dose vial can be diluted with 5% dextrose with or without human albumin up to 2 mg/mL and stored at room temperature for up to 4 hours. However, because inadequate microbial assessment data was provided to support in-use stability during 24 hours storage, the labeling of storage of Releuko diluted with 5% dextrose with or without human albumin up to 2 mg/mL for a period of more than 4 hour at room temperature is not recommended

[2] We acknowledge that, for other 351(k) applications, applicants have submitted, and the Agency has reviewed, in-use stability data to support use by dilution and subsequent intravenous administration. However, the Agency has concluded that, in this instance, for the reasons described in this review, such data is not necessary.

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/

RAM K SIHAG
02/23/2022 05:50:48 PM

FRANCES NAMUSWE
02/23/2022 07:32:26 PM

Recommendation: Approval

BLA Number: 761082
Review of BLA Resubmission (eCTD Sequence: 0060)
Review Date: February 01, 2022

Drug Name/Dosage Form	Releuko-filgrastim-ayow (theragrastim)/injection
Strength/Potency	i): 300 mcg/mL and 480 mcg/1.6 mL in a single-dose vial 300 mcg/0.5 mL and 480 mcg/0.8 mL in a single-dose prefilled syringe ii): Potency by cell proliferation assay
Route of Administration	IV infusion* or SC injection
Rx/OTC dispensed	Rx
Indication	Releuko, referred to by the applicant as theragrastim[1], proposed indications are: • Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) • *Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
Applicant/Sponsor	Kashiv Biosciences, LLC

** At this time, in-use stability data have not been provided to support stability of theragrastim diluted in dextrose prior to intravenous infusion. Therefore, at this time, the intravenous route of admistration and one of the indications are not supported.*

Product Overview

Theragrastim is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) produced in *E. coli*. It binds to the GCSF receptor (CD114) on the surface of leukocytes and regulates the maturation, proliferation, and differentiation of the precursor cells of neutrophilic granulocytes.

[1] For purposes of this review, we generally refer to Kashiv' s proposed product by the Kashiv-provided descriptor theragrastim, which was the name used to refer to this product during development. On January 29, 2018, FDA found filgrastim-ayow conditionally acceptable as the nonproprietary name for Kashiv's proposed biosimilar to US-licensed Neupogen.

Quality Review Team

Discipline	Reviewer	Division/Office
Drug Substance	Rong Wang	DBRR-III/OBP/OPQ
Drug Product	Rong Wang	DBRR-III/OBP/OPQ
Comparative Analytics	Rong Wang	DBRR-III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Michael Shanks/Candace Gomez-Broughton (TL)	DBM/OPMA/OPQ
Microbiology	Michael Shanks, Yarery Smith/ Candace Gomez-Broughton (RC)	DMA/OPMA/OPQ
RBPM	Grafton Adams	OPRO/OPQ
Application Technical Lead	Ram Sihag	DBRR-III/OBP/OPQ
Tertiary Reviewer	Susan Kirshner and Frances Namuswe	DBRR-III/OBP/OPQ

Multidisciplinary Review Team:

Discipline	Reviewer/TL	Office/Division
RPM	Courtney Hamilton and May Zuwannin	OND/OCHEN/DHN
Signatory	Albert Deisseroth	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OHCHEN/DNH
Clinical Reviewer	Hyon Zu Lee	OND/OHCHEN/DNH
Non-clinical Reviewer	Todd Bourcier	OND/OHCHEN/DPT
Clinical Pharmacology	Anusha Ande/Sudharshan Hariharan	OTS/OCP
Statistics	Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Releuko (proposed)
   b. Nonproprietary name: filgrastim-ayow (conditionally accepted), referred to as theragrastim by the Applicant
   c. CAS name: R-metHuGCSF; Recombinant methionyl human GCSF (CAS Registry number: 121181-53-1)
   d. OBP systematic name: RPROT P09919 (CSF3_HUMAN) Granulocyte colony-stimulating factor [Theragrastim][2]
2. Pharmacologic category: Leukocyte growth factor

Submissions Reviewed:

Submission:	Date Received:	Review Completed (Yes or No)

[2] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

761082-0060	August 27, 2021	Yes
761082-0063	December 17, 2021	Yes
761082-0064	January 10, 2022	Yes
761082-0065	January 13, 2022	Yes
761082-0069	January 22, 2022	Yes

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs: For details on DMFs referenced in this BLA application, refer to the original Executive Summary memo in Panorama dated April 12, 2018.

B. Other documents: OPQ Executive Summary memos from previous submissions for this BLA

Dr. M. Cecilia Tami dated 4/12/2018 in Panorama
Dr. Ramesh Potla dated May 23, 2019 in Panorama
Dr. Ram Sihag dated 7/02/21; 12/21/2020 in DARRTS

3. Consults: No consults were requested during the review cycle for the current resubmission.

4. Environmental Assessment of Claim of Categorical Exclusion: Kashiv requested a categorical exclusion from the preparation of an environmental assessment for Releuko (theragrastim) in accordance with 21 CFR 25.31 (c). Releuko is considered "naturally occurring in the environment" and, when exposed to the environment, is not expected to significantly alter the concentration of the substance, its metabolites, or degradation products in the environment. There are no extraordinary circumstances that may significantly affect the quality of the human environment. The methods employed in the manufacture of the biological product are in compliance with all applicable local, state, and federal environmental regulations. The Applicant's claim of a categorical exclusion is accepted.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ) CDER, recommends approval of BLA 761082 for Releuko (theragrastim) manufactured by Kashiv Biosciences, LLC.

The data submitted in this application are adequate to support the conclusion that the manufacture of Releuko is well-controlled and leads to a product that is pure and potent. The comparative analytical assessment as presented in the BLA supports that:

- The biological product, filgrastim-ayow, is highly similar to U.S.-licensed Neupogen notwithstanding minor differences in clinically inactive components.

As summarized in the following sections of this review, OBP and OPMA reviewers have all concluded that this BLA should be approved. Therefore, I recommend that this product be approved for human use under conditions specified in the package insert.

In a previous review cycle for this BLA, during a pre-license inspection in 2019, the Division of Inspectional Assessment (DIA), now called Division of Biotechnology Manufacturing (DBM), identified deficiencies in the manufacture and control of theragrastim DS, including GMP deficiencies at Kashiv Biosciences, LLC, FEI #3011289655. The product quality data submitted for the BLA application were determined to be insufficient to support a conclusion that the manufacture of theragrastim is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. A Complete Response (CR) letter was issued to Kashiv Biosciences, LLC on June 11, 2019. Based on the deficiencies identified in the CR letter, it was determined that an inspection of the Kashiv Biosciences LLC DS manufacturing facility (FEI 3011289655), Chicago, Illinois, was required before this application may be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with cGMP.

On June 25, 2020, Kashiv submitted BLA761082/0049 in response to the CR letter issued to Kashiv Biosciences, LLC on June 11, 2019. Since Kashiv had not adequately addressed the identified deficiencies related to product quality and the Agency's concerns about good manufacturing practices in place, the Agency issued a CR letter on December 22, 2020. Kashiv submitted a response to this CR letter on February 02, 2021(BLA761082/0055). However, due to U.S. Government and/or Agency-wide restrictions on travel, OPQ could not conduct an inspection of the Kashiv Biosciences LLC facility during the review cycle, and the application could not be approved until the required FDA inspection was conducted and the findings assessed with regard to this application. In addition, a review of the data submitted by Kashiv in BLA 761082/0055 identified deficiencies in the information provided for the new in-house theragrastim working reference standard and the revised potency assay method. On August 02, 2021, the Agency issued a CR letter for BLA 761082/0055.

On August 27, 2021, Kashiv submitted BLA 761082/0060 as a complete response to the deficiencies listed in the Agency's CR letter issued on August 2, 2021. The Applicant satisfactorily addressed the product quality deficiencies identified in the Agency's CR letter issued on August 02, 2021. A pre-license inspection was conducted from January 10, 2022 through January 14, 2022 at the drug substance manufacturing facility for theragrastim located in Chicago, IL (FEI# 3011289655). The inspection

covered the manufacturing process and testing of theragrastim including the following five quality systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. The facility was assessed to be acceptable.

A compliance inspection of the [redacted] (b) (4) manufacturing facility for theragrastim drug product [redacted] (b) (4) was conducted from [redacted] (b) (4) The FDA field investigation team conveyed deficiencies to the representative of the facility. The facility's response to these deficiencies was reviewed and found satisfactory. The current status of this facility is compliant since August 10, 2021.

B. Approval Action Letter Language:

The Applicant satisfactorily addressed the product quality deficiencies identified in the Agency's CR letter issued on August 02, 2021.

- Manufacturing location:
  - Drug Substance: Kashiv Biosciences LLC, 3440 S. Dearborn St., Chicago, IL 60616 USA
  - Drug Product: [redacted] (b) (4)

  Fill size and dosage forms:
  - 300 mcg/mL and 480 mcg/1.6 mL in a single-dose vial
  - 300 mcg/0.5 mL and 480 mcg/0.8 mL in a single-dose prefilled syringe

- Dating period:
  - Drug Product (PFS and Vial): 24 months when stored at 2-8 °C
  - Drug Substance [redacted] (b) (4)
  - For packaged products: Not packaged
- Exempt from lot release:
  - Yes. Releuko is a specified product exempted according to 21 CFR 601.2a.

C. Benefit/Risk Considerations:

Releuko (theragrastim) is a proposed biosimilar to U.S.-licensed Neupogen and proposed for use in same indications approved for Neupogen (see page 1). Releuko is manufactured to the same concentration and presentation. The excipients present in Releuko are the same as those present in the Reference Product

To support a determination that Releuko is highly similar to U.S.-licensed Neupogen, 28 lots of U.S.-licensed Neupogen and 27 lots of Theragrastim DP and 3 lots of Theragrastim DS were evaluated, including lots used in the PK/PD similarity and safety clinical studies and lots manufactured by the proposed commercial manufacturing process. The data provided in the BLA support a determination that Releuko is highly similar to U.S.-licensed Neupogen. The OPQ review of manufacturing has determined that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing as submitted in the BLA submission are sufficient to assure a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The Applicant agreed to a PMC to evaluate the impact of removing kanamycin from the DS manufacturing process to enhance patient safety.

The technical assessments for OBP drug substance and drug product quality and immunogenicity

assay, OPMA microbiological drug substance and drug product and facilities, OBP labeling, and OBP comparative analytical assessment are located as separate documents in the Panorama informatics platform (see Section III- Review documents related to this Executive Summary.

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

PMC: "To perform a study to evaluate the impact of the removal of kanamycin from the theragrastim drug substance manufacturing process. If the data support removal of kanamycin, a plan for the removal of kanamycin from the manufacturing process will be provided. The plan should include an evaluation of consistency of the fermentation process and comparability of the theragrastim drug substance manufactured with and without kanamycin. The results will be reported per 21 CFR 601.12."

Proposed Final Report submission: 12-31-2024

II. Summary of Quality Assessments:

For information relevant to this section, please see the original IQA review memos:

Review by Dr. M. Cecilia Tami for BLA-761082-ORIG-1 dated April 12, 2018 in Panorama
https://panorama.fda.gov/document/view?ID=5acf9d240049771932a754cb02e7edda

Review by Dr. Ramesh Potla for BLA-761082-ORIG-1-RESUB-38 dated May 23, 2019 in Panorama

Review by Dr. Ram Sihag for BLA-761082-ORIG-1-RESUB-55 and 49 dated July 02, 2021 and December 21, 2020 in DARRTS

A. Any Special Product Quality Labeling Recommendations:

- Protect from light
- Avoid freezing
- Avoid shaking

B. Establishment Information:

DRUG SUBSTANCE				
Function	Site Information	DUNS/FEI Number	Inspectional Observations	Final Recommendation
*Manufacture and storage of master and working cell banks *Manufacture of DS *DS release, stability, and in-process testing except for bioburden and HCDNA *DP release and stability testing *Prefilled syringe assembly	Kashiv Biosciences LLC, 3440 S. Dearborn St., Chicago, IL 60616	FEI 3011289655	A pre-license inspection was conducted during this review cycle from January 10, 2022 through January 14, 2022 at the drug substance manufacturing facility for theragrastim. A 5-item Form FDA 483 was issued. Preliminary assessment was VAI. The facility's response to these deficiencies was reviewed and found satisfactory. The current status of this facility is compliant.	Acceptable
DRUG PRODUCT				
*Manufacture of vialed and prefilled syringe DP	(b) (4)		FDA field investigation team inspected the manufacturing facility from (b) (4) The current status of this facility is compliant since August 10, 2021.	Acceptable
*Packaging/ cartoning of Prefilled syringes.			Compliance Assessment was performed.	Acceptable

C. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the DS and DP manufacturing sites. All proposed manufacturing and testing facilities are acceptable based on the inspection reports for the following sites:

i. [redacted] (b) (4) status is acceptable for manufacture of vialed/prefilled syringe theragrastim DP (profile SVS) following an inspection by the Field Office team from [redacted] (b) (4) conducted in support of the subject BLA.
ii. [redacted] (b) (4) is acceptable for packaging/cartoning of the prefilled syringe DP based on compliance history.
iii. Kashiv Biosciences LLC (FEI 3011289655) is acceptable for assembly of theragrastim prefilled syringe assembly (profile IDD) and labeling/secondary packaging of vialed theragrastim DP (profile SVS-repacks) based on a March 2019 PLI conducted in support of the subject BLA.
iv. Kashiv Biosciences LLC (FEI 3011289655) is acceptable for theragrastim DS manufacture (profile CBI) and release/stability testing of theragrastim DS and DP (profile CTX) based on a January 2022 PLI conducted in support of the subject BLA.

D. Lifecycle Knowledge Management:

a. Drug Substance:
   i. Protocols approved: annual stability protocol, qualification protocol of new master cell bank and working cell bank, requalification protocol of master cell bank and working cell bank, stability protocol for EOP cell bank, qualification protocol of in-house working reference standard, annual stability protocols for in-house primary and working reference standards, protocol for verification [redacted] (b) (4)
   ii. Outstanding review issues/residual risk: None
   iii. Future inspection points to consider: None
b. Drug Product
   i. Protocols approved: annual stability protocol and protocol for protocol for microbial challenge test.
   ii. Outstanding review issues/residual risk: None
   iii. Future inspection points to consider: None

E. Biopharmaceutics Considerations: None

F. Novel Approaches/Precedents: No

G. Any Special Product Quality Labeling Recommendations:

At this time, no in-use stability data have been provided to support stability of theragrastim diluted in dextrose prior to intravenous infusion. Therefore, at this time, the intravenous route of administration and one of the proposed indications are not supported.

III. Review documents related to this Executive Summary:

For information relevant to this section, please see the following primary review memos:

BLA-761082-ORIG-1-RESUB-60
https://panorama.fda.gov/project/view?ID=612ea68d001e438d11a06195dd3e7c6f

Dr. Rong Wang on Product Quality Assessment dated January 26, 2022 in Panorama
Dr. Michael Shanks on Drug Substance Microbiology/Facility Assessment dated June 28, 2021 in Panorama
Dr. Yarery Smith on Drug Product Microbiology/Facility Assessment dated December 27, 2021 in Panorama

BLA-761082-ORIG-1-RESUB-55
https://panorama.fda.gov/project/view?ID=601ad7e600210672edef28a906036f34
Dr. Rong Wang on Product Quality Assessment dated July 14, 2021 in Panorama
Dr. Michael Shanks on Drug Substance Microbiology/Facility Assessment dated June 28, 2021 in Panorama
Dr. Yarery Smith on Drug Product Microbiology Assessment dated June 23, 2021 and July 9, 2021 in Panorama

BLA-761082-ORIG-1-RESUB-49
https://panorama.fda.gov/project/view?ID=5ef6314200e7ca015717df0d93104927
Dr. Rong Wang on Product Quality and Comparative Analytical Assessment dated December 1, 2020 in Panorama
Dr. Michael Shanks on Drug Substance Microbiology Assessment dated November 3, 2020 in Panorama
Dr. Yarery Smith on Drug Product Microbiology Assessment dated December 10, 2020 in Panorama

BLA-761082-ORIG-1-RESUB-38
https://panorama.fda.gov/project/view?ID=5c1126cb00b8bfc0114402eba151e743
Dr. Rong Wang on Product Quality and Comparative Analytical Assessment dated May 14, 2019 in Panorama
Dr. Reyes Candau-Chacon on Drug Substance Microbiology Assessment dated April 2, 2019 in Panorama
Dr. Monica Commerford on Drug Product Microbiology Assessment dated May 9, 2019 in Panorama
Dr. Steve Fong on Drug Substance and Drug Product Manufacturing Facility dated June 19, 2019 in Panorama
Dr. Monica M. Commerford on DMF Assessment dated May 9, 2019 in Panorama

BLA-761082-ORIG-1
https://panorama.fda.gov/project/view?ID=596311d701560d8f6c12d055516e8fe2
Drs. Tracy Denison, Fabiola Gomez, Joao Pedras Vasconcel on Drug Substance Assessment dated April 2, 2018 in Panorama
Dr. Tracy Denison on Comparative Analytical Assessment dated April 2, 2018 in Panorama
Dr. Fabiola Gomez on Drug product Assessment dated April 2, 2018 in Panorama
Dr. Joao Pedras Vasconcel on Immunogenicity Assessment dated March 22, 2018 in Panorama
Dr. Kathleen R. Jones on Drug Substance Microbiology Assessment dated April 02, 2018 in Panorama
Dr. Monica Commerford on Drug Product Microbiology Assessment dated April 03, 2018 in Panorama
Dr. Laura Fontan on Drug Substance Manufacturing Facility Assessment dated April 02, 2018 in Panorama
Dr. Laura Fontan on Drug Product Manufacturing Facility Assessment dated April 13, 2018 in Panorama

APPEARS THIS WAY ON ORIGINAL

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/

RAM K SIHAG
02/04/2022 03:22:19 PM

FRANCES NAMUSWE
02/04/2022 03:24:01 PM

Recommendation: Complete Response

BLA Number: 761082
Review of BLA Resubmission (eCTD Sequence: 0055)
Review Date: June 14, 2021

Drug Name/Dosage Form	Releuko/injection
Strength/Potency	300 mcg/mL and 480 mcg/1.6 mL in a single-dose vial 300 mcg/0.5 mL and 480 mcg/0.8 mL in a single-dose prefilled syringe
Route of Administration	IV injection or infusion and SC injection
Rx/OTC dispensed	Rx
Indication	Releuko, referred to by the applicant as theragrastim[1], proposed indications are: • Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
Applicant/Sponsor	Kashiv Biosciences, LLC

Product Overview

Theragrastim is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) produced in *E. coli*. It binds to the GCSF receptor (CD114) on the surface of leukocytes and regulates the maturation, proliferation, and differentiation of the precursor cells of neutrophilic granulocytes.

[1] For purposes of this review, we generally refer to Kashiv' s proposed product by the Kashiv-provided descriptor theragrastim, which was the name used to refer to this product during development. On January 29, 2018, FDA found filgrastim-ayow conditionally acceptable as the nonproprietary name for Kashiv's proposed biosimilar to US-licensed Neupogen.

Quality Review Team

Discipline	Reviewer	Division/Office
Drug Substance	Rong Wang	DBRR-III/OBP/OPQ
Drug Product	Rong Wang	DBRR-III/OBP/OPQ
Comparative Analytics	Rong Wang	DBRR-III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Michael Shanks/Candace Gomez-Broughton (TL)	DBM/OPMA/OPQ
Microbiology	Michael Shanks, Yarery Smith/ Candace Gomez-Broughton (RC)	DMA/OPMA/OPQ
RBPM	Grafton Adams	OPRO/OPQ
Application Technical Lead	Ram Sihag	DBRR-III/OBP/OPQ
Tertiary Reviewer	Susan Kirshner	DBRR-III/OBP/OPQ

Multidisciplinary Review Team:

Discipline	Reviewer/TL	Office/Division
RPM	May Zuwannin	OND/OCHEN/DHN
Signatory	Albert Deisseroth	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OHCHEN/DNH
Clinical Reviewer	Hyon Zu Lee	OND/OHCHEN/DNH
Non-clinical Reviewer	Todd Bourcier	OND/OHCHEN/DPT
Clinical Pharmacology	Anusha Ande/Sudharshan Hariharan	OTS/OCP
Statistics	Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Releuko
   b. Nonproprietary name: filgrastim-ayow (conditionally accepted), referred to as theragrastim by the Applicant
   c. CAS name: R-metHuGCSF; Recombinant methionyl human GCSF (CAS Registry number: 121181-53-1)
   d. OBP systematic name: RPROT P09919 (CSF3_HUMAN) Granulocyte colony-stimulating factor [Theragrastim][2]
2. Pharmacologic category: Leukocyte growth factor

[2] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

Submissions Reviewed:

Submission(s) Reviewed	Document Date
BLA Complete Response Amendment/eCTD Sequence Number: 0055	February 02, 2021
BLA Information Amendment Sequence 59	June 03, 2021

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

   A. DMFs: For details on DMFs referenced in this BLA application, refer to the original Executive Summary memo in Panorama dated April 12, 2018.

   B. Other documents: None

3. Consults: No consults were requested during the review cycle for the current resubmission.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality, OPQ, CDER, has completed review of Complete Response for 351(k) BLA 761082/0049 for theragrastim manufactured by Kashiv Biosciences, LLC (drug substance) and (b) (4) (drug product, a CMO for Kashiv), as a proposed biosimilar to US-licensed Neupogen.

In the previous cycle of review for this BLA, during a pre-BLA inspection in 2019, the Division of Inspectional Assessment (DIA), now called Division of Biotechnology Manufacturing (DBM), identified deficiencies in the manufacture and control of theragrastim DS, including GMP deficiencies at Kashiv Biosciences, LLC, FEI #3011289655. The product quality data submitted for the BLA application were determined to be insufficient to support a conclusion that the manufacture of theragrastim is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. A Complete Response letter was issued to Kashiv Biosciences, LLC on June 11, 2019. Based on the deficiencies identified in the CR letter, it was determined that an inspection of the Kashiv Biosciences LLC DS site (FEI 3011289655), Chicago, Illinois, facility will be required before this application may be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with cGMP.

Due to U.S. Government and/or Agency-wide restrictions on travel, OPQ is unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application.

Furthermore, review of the data submitted by Kashiv in response to the December 22, 2020 issued CR letter, identified deficiencies in the information provided for the new in-house Theragrastim Working Reference Standard and the revised potency assay method.

From a product quality standpoint, OPQ is recommending a Complete Response letter be issued to Kashiv Biosciences, LLC to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues: The following deficiencies were identified during the review cycle for this Complete Response submission:

Deficiencies:

The Agency issued a Complete Response (CR) letter on December 22, 2020 that included product quality deficiencies identified in the previous review cycle of 351(k) BLA 761082/0049 for theragrastim manufactured by Kashiv Biosciences, LLC (DS manufacture facility) and (b) (4) (DP manufacture facility, a CMO for Kashiv), as a proposed biosimilar to US-licensed Neupogen. Kashiv submitted a Complete Response (CR) to Agency's CR letter on February 02, 2021. Kashiv's response to deficiencies presented in the CR letter issued by FDA on December 22, 2020 was reviewed and the deficiencies identified in Kashiv's response are summarized below in section C.

Deficiencies to be Communicated to the Applicant:

See section C. Complete Response Draft Language for deficiencies to be communicated to the Applicant.

Issues Not to be Communicated to the Applicant

(b) (5)

[redacted]

C. Complete Response Draft Language for the Comments to be Communicated to the Applicant:

Comments below are draft comments. Refer to the Complete Response letter for final language.

Please refer to your biologics license application (BLA) dated and received June 25, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for RELEUKO (theragrastim).

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Facilities Inspections

1. An inspection of the Kashiv Biosciences LLC DS manufacture facility (FEI 3011289655), Chicago, Illinois, is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved

until the required FDA inspection is conducted and the findings are assessed with regard to this application.

2. During inspection of the (b) (4) manufacturing facility from (b) (4), FDA field investigation team conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Product Quality

3. In-House Reference Standards

a. In response to FDA Item #4, you updated the stability protocols PTL-1981 "Stability Protocol for Theragrastim Primary Reference Standard Lot (b) (4) "Stability Protocol for Theragrastim Working Reference Standard" for the working reference standards (WRS) (b) (4) include a trending strategy and the acceptance criterion to control for EC50 values in the potency testing. However, there are deficiencies in both stability protocols.

(b) (4)

b. You provided PTL-2306-R "Summary Report for Qualification of Theragrastim In-House Working Reference Standard Lot (b) (4)" as an update to the information request response #3 dated October 08, 2020 (BLA 761082/0053). However, the Agency noted multiple out of specification results (OOS) in this report. Specifically,

(b) (4)

Because of the above OOS results, we do not agree that the current in-house (b) (4) has been qualified appropriately.

To address the above issues, update the stability protocols for the in-house primary and working reference standards to

i. Provide adequate trending analysis strategies for the EC50 values of the RSs. You should evaluate whether there is a EC50 value drift based on the absolute values generated in the potency assay.

ii. Provide an updated qualification report for the adequately qualified in-house WRS. You should use an adequately qualified WRS as the standard in the stability testing for the PRS.

iii. Establish a stability acceptance criterion for the EC50 for the WRS based on a trend analysis of the EC50 values of the WRS obtained during routing release and stability testing.

4. Analytical methods

In section "Additional information related to Module 3", you revised the potency method (STM-0118) based on the change control CC-20-036. However, the summary information you provided to justify the changes made to the potency assay was inadequate because no supporting data were provided to allow assessment of the appropriateness of the proposed change. To ensure that the proposed change has no impact on the potency assay method validation and test article data, provide adequate information to support the proposed change.

Additional Comments

In addition, there are several deficiencies that are not approvability issues, but need to be addressed.

(b) (4)

(b) (4)

[redacted]

3. You have not provided stability data for deliverable volume to support the proposed shelf life of 24 months (accelerated or real time) for your drug product. As stated in our February 7, 2017 teleconference for the Type 4 meeting to discuss the content of format of the BLA, we stated that you should include expellable volume testing at the end of your proposed shelf life. We recommend that you provide results for this essential performance requirement testing to support the proposed 24-month shelf life for your drug product.

D. Benefit/Risk Considerations:

A benefit-risk assessment will be performed upon the receipt and review of the Applicant's complete response information in a future 351(k) BLA resubmission. For additional details, please see the original IQA review memo in Panorama by Dr. Ramesh Potla, dated May 23, 2019.

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

N/A

II. Summary of Quality Assessments:

For information relevant to this section, please see the original IQA review memo uploaded in Panorama by Dr. Ramesh Potla dated May 23, 2019. This section may be updated in future memos depending on the outcome of future CR submissions and inspections.

A. Any Special Product Quality Labeling Recommendations:

- Protect from light
- Avoid freezing
- Avoid shaking

B. Establishment Information

DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
*Manufacture and storage of master and working cell banks *Manufacture of DS *DS release, stability, and in-process testing except for bioburden and HCDNA *DP release and stability testing *Prefilled syringe assembly	Kashiv Biosciences LLC, 3440 S. Dearborn St., Chicago, IL 60616 USA	FEI 3011289655	Pre-license inspection could not be performed due to U.S. Government and/or Agency-wide travel restrictions due to Covid-19 pandemic.	A pre-approval BLA inspection was not performed during this review cycle. However, a pre-license inspection performed during the previous review cycle of this BLA in March 2019 resulted in issuance of a seven-item Form FDA 483. See IQA review memo uploaded in Panorama by Dr. Ramesh Potla dated May 23, 2019. Firm was determined to have NOT adequately addressed these issues.	WITHHOLD
DRUG PRODUCT					
*Manufacture of vialed and prefilled syringe DP.	(b) (4)		Pre-license Inspection	Form FDA 483 was issued citing deficiencies related to manufacture of vialed/prefilled syringes (profile SVS) following an inspection by the Field Office (b) (4)	WITHHOLD
*Packaging/ cartoning of			Compliance Assessment	N/A	Acceptable

APPEARS THIS WAY ON ORIGINAL

C. Facilities:

i. [redacted] (b) (4) is not acceptable for manufacture of vialed/prefilled syringe theragrastim DP (profile SVS) following an inspection by the Field Office from [redacted] (b) (4).

ii. [redacted] (b) (4) is acceptable for packaging/cartoning of the prefilled syringe DP based on compliance history.

iii. Kashiv Biosciences LLC (FEI 3011289655) is acceptable for assembly of theragrastim prefilled syringe assembly (profile IDD) and labeling/secondary packaging of vialed theragrastim DP (profile SVS-repacks) based on a March 2019 PLI conducted in support of the subject BLA.

iv. Kashiv Biosciences LLC (FEI 3011289655) is NOT acceptable for theragrastim DS manufacture (profile CBI) and release/stability testing of theragrastim DP (profile CTX) based on a March 2019 PLI conducted in support of the subject BLA. Significant GMP deficiencies were identified regarding QA oversight of product dispositioning, analytical methods, data integrity, written procedures, and adherence to written procedures. A post-action memo dated June 11, 2019 was issued to the firm to detail the deficiencies. Because of the inability of OPQ to perform a pre-license BLA inspection due to the continuing U.S. Government and/or Agency-wide travel restrictions due to Covid-19 pandemic, a determination cannot be made during this review cycle as to whether or not Kashiv has addressed the CGMP deficiencies identified in Form FDA 483.

D. Lifecycle Knowledge Management:

a. Drug Substance:
   i. Protocols approved: None
   ii. Outstanding review issues/residual risk: See CR comments in Section I. A-C.
   iii. Future inspection points to consider: See establishment information section of this memo and DIA review

b. Drug Product
   i. Protocols approved: None
   ii. Outstanding review issues/residual risk: See CR comments in Section I. A-C.
   iii. Future inspection points to consider: See establishment information section of this memo and DIA review

---

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/

RAM K SIHAG
07/01/2021 05:21:48 PM

SUSAN L KIRSHNER
07/02/2021 12:01:13 AM

Recommendation: Complete Response

BLA Number: 761082
Review of BLA Resubmission (eCTD Sequence: 0049)
Review Date: December 04, 2020

Drug Name/Dosage Form	Releuko/injection
Strength/Potency	300 mcg/mL and 480 mcg/1.6 mL in a single-dose vial 300 mcg/0.5 mL and 480 mcg/0.8 mL in a single-dose prefilled syringe
Route of Administration	IV injection or infusion and SC injection
Rx/OTC dispensed	Rx
Indication	Releuko, referred to by the applicant as theragrastim[1], proposed indications are: • Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
Applicant/Sponsor	Kashiv Biosciences, LLC

Product Overview

Theragrastim is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) produced in *E. coli*. It binds to the GCSF receptor (CD114) on the surface of leukocytes and regulates the maturation, proliferation, and differentiation of the precursor cells of neutrophilic granulocytes.

[1] For purposes of this review, we generally refer to Kashiv' s proposed product by the Kashiv-provided descriptor theragrastim, which was the name used to refer to this product during development. On January 29, 2018, FDA found filgrastim-ayow conditionally acceptable as the nonproprietary name for Kashiv's proposed biosimilar to US-licensed Neupogen.

Quality Review Team

Discipline	Reviewer	Division/Office
Drug Substance	Rong Wang	DBRR-III/OBP/OPQ
Drug Product	Rong Wang	DBRR-III/OBP/OPQ
Comparative Analytics	Rong Wang	DBRR-III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Peter Qui	DBM/OPMA/OPQ
Microbiology	Mike Shanks, Yarery Smith/ Dupeh Palmer (TL) / Peter Qiu (RC)	DMA/OPMA/OPQ
RBPM	Grafton Adams	OPRO/OPQ
Application Technical Lead	Ram Sihag	DBRR-III/OBP/OPQ
Tertiary Reviewer	Susan Kirshner	DBRR-III/OBP/OPQ

Multidisciplinary Review Team:

Discipline	Reviewer/TL	Office/Division
RPM	Metanuj Zuwannin/Charlene Wheeler	OND/OCHEN/DHN
Signatory	Ann Farrell	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Kathy Robie-Suh	OND/OHCHEN/DNH
Clinical Reviewer	Hyon Zu Lee/Kathy Robie-Suh	OND/OHCHEN/DNH
Non-clinical Reviewer	Todd Bourcier	OND/OHCHEN/DPT
Clinical Pharmacology	Anusha Ande/Sudharshan Hariharan	OTS/OCP
Statistics	Yaping Wang/Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Releuko (proposed)
   b. Nonproprietary name: filgrastim-ayow (proposed), referred to as theragrastim by the Applicant
   c. CAS name: R-metHuGCSF; Recombinant methionyl human GCSF (CAS Registry number: 121181-53-1)
   d. OBP systematic name: RPROT P09919 (CSF3_HUMAN) Granulocyte colony-stimulating factor [Theragrastim][2]
2. Pharmacologic category: Leukocyte growth factor

Submissions Reviewed:

Submission(s) Reviewed	Document Date
BLA Complete Response Amendment/eCTD Sequence Number: 0049	June 25, 2020

[2] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

   A. DMFs: For details on DMFs referenced in this BLA application, refer to the original Executive Summary memo in Panorama dated April 12, 2018.

   B. Other documents: None

3. Consults: No consults were requested during the review cycle for the current resubmission.

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality, OPQ, CDER, has completed review of Complete Response for 351(k) BLA 761082/0049 for theragrastim manufactured by Kashiv Biosciences, LLC (drug substance) and (b) (4) (drug product, a CMO for Kashiv), as a proposed biosimilar to US-licensed Neupogen.

In the previous cycle of review for this BLA, during a pre-BLA inspection in 2019, the Division of Inspectional Assessment (DIA), now called Division of Biotechnology Manufacturing (DBM), identified deficiencies in the manufacture and control of theragrastim DS, including GMP deficiencies at Kashiv Biosciences, LLC, FEI #3011289655. The product quality data submitted for the BLA application were determined to be insufficient to support a conclusion that the manufacture of theragrastim is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. A Complete Response letter was issued to Kashiv Biosciences, LLC on June 11, 2019. Based on the deficiencies identified in the CR letter, it was determined that an inspection of the Kashiv Biosciences LLC DS site (FEI 3011289655), Chicago, Illinois, facility will be required before this application may be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with cGMP.

Due to U.S. Government and/or Agency-wide restrictions on travel, OPQ is unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application.

Furthermore, review of the data submitted by Kashiv in response to the CR letter found deficiencies in the reliability of the comparative analytical data and in the product quality data submitted to support control strategy for purity, potency and protein concentration, qualification and requalification program for cell banks, and shipping validation study. The microbiology assessment identified deficiencies in the information provided for media fills (e.g. bulk material vessel size, filling line speed, container size and opening) as well as vial filling and syringe filling lines.

From a product quality standpoint, OPQ is recommending a Complete Response letter be issued to Kashiv Biosciences, LLC to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues: The following deficiencies were identified during the review cycle for this Complete Response submission:

Deficiencies:

The Agency issued a Complete Response (CR) letter on June 11, 2019 that included product quality deficiencies identified in the previous review cycle of 351(k) BLA 761082/0038 for theragrastim manufactured by Kashiv Biosciences, LLC (DS manufacture facility) and (b) (4) (DP manufacture facility, a CMO for Kashiv), as a proposed biosimilar to US-licensed Neupogen. Kashiv

submitted a Complete Response (CR) to Agency's CR letter on June 25, 2020. Kashiv's response to deficiencies presented in the CR letter issued by FDA on June 11, 2019 was reviewed and the deficiencies identified in Kashiv's response are summarized below in section C.

Deficiencies to be Communicated to the Applicant:

See section C. Complete Response Draft Language for deficiencies to be communicated to the Applicant.

Deficiencies Not to be Communicated to the Applicant

(b) (4)

C. Complete Response Draft Language for the Comments to be Communicated to the Applicant:

Comments below are draft comments. Refer to the Complete Response letter for final language.

Please refer to your biologics license application (BLA) dated and received June 25, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for RELEUKO (theragrastim).

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Facilities Inspections

1. An inspection of the Kashiv Biosciences LLC DS manufacture facility (FEI 3011289655), Chicago, Illinois, is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application.

Product Quality

Audit Completeness and Data Traceability

2. We understand that you identified (b) (4) as the third-party to audit your quality data and systems to support BLA 761082. However, it is unclear whether the (b) (4) audit reviewed all the quality data submitted in the BLA because the (b) (4) audit covered data mainly generated during the years 2015-2017 and the clinical DP lots 40-13013 and 45-14042 were manufactured on November 9, 2013 and July 19, 2014, respectively. Also, it is not clear whether there are source data traceability issues in the comparative analytical assessment including lots used in clinical studies submitted in the BLA. The audit team reported (see pages 596-7 of "Response to Retrospective Review of the GMP Systems and Product Quality Data of Theragrastim by (b) (4)"):

a. some HPLC raw data and UV data were not traceable to the source, and
b. SDS-PAGE data for the clinical lot 45-14042 manufactured on July 19, 2014 were not available for review during the audit.

The theragrastim lots for which source data are not traceable should not be included in the comparative analytical assessment. To address this deficiency,

a. Provide a table listing all lots, tests performed with those lots, and the dates of testing that were retrospectively reviewed during the (b) (4) audit.
b. Identify results that were included in the comparative analytical assessment but cannot be traced back to the source.
c. Remove untraceable data from the comparative analytical assessment. If the source of the data is known but the source is unavailable for FDA inspection, then the data are considered untraceable.

Depending on the impact of removing untraceable data from the comparative analytical assessment you may need to conduct additional comparative analytical studies, repeat clinical studies, or both.

Sequence Variants

3. In your response to CR item # 3, you reported the detection of two sequence variants, S77-R77 and G101-R101 from a peak (CEX-P6) separated using the CEX-HPLC method. However, you did not provide an explanation for the etiology of the sequence variants or whether the sequence variants impact the conclusions reached in your comparative analytical assessment. To address this deficiency, provide an explanation for the sequence variants, and whether the variants impact a determination that theragrastim is highly similar to US-licensed Neupogen. Depending on the etiology of the sequence variants and their impact on a determination that theragrastim is highly similar to US-licensed Neupogen,

you may need to develop a strategy to control or remove these sequence variants in theragrastim.

In-House Reference Standards

4. The stability protocols PTL-1981 "Stability Protocol for Theragrastim Primary Reference Standard [redacted] (b) (4) "Stability Protocol for Theragrastim Working Reference Standard" are deficient because there are no acceptance criteria established to control for EC50 values. To address this deficiency, update the stability protocols for in-house primary and working reference standards to include adequate control over EC50. Because you have not established a working reference standard (WRS) and you have been using the primary reference standard (PRS) in QC testing, you should perform a trending analysis of the EC50 values obtained during routine release and stability testing to establish a stability acceptance criterion for the PRS. After a WRS has been established and used in QC testing, you may use a similar strategy to establish a stability acceptance criterion for the WRS. Provide a detailed description of how you propose to perform this trend analysis and how the acceptance criterion is going to be defined.

Post-Approval Stability Protocol

5. We noted deficiencies in your stability specifications and stability protocols for theragrastim DP. The DP stability protocols listed in section 3.2.P.8.2. indicate to test for syringe break loose and glide force determination and follow specifications per SPC-0031 "Theragrastim Drug Product (DP) Specification". However, we noted that SPC-0031 does not list stability specifications for this quality attribute. Also, we noted you schedule to test container closure integrity (CCI) only at the 12-month time-point but not at the 24-month time-point. To address these deficiencies,

a. update the DP stability specifications to assess for syringe break loose and glide force, and
b. modify the DP post-approval stability protocols to include CCI testing at the 24-month time-point.

Shipping Validation Protocol

6. We noted the following deficiencies in the shipping performance qualification protocols PTL 2079 and PTL-2080 for the DP in vials and pre-filled syringes:

a. You proposed to use the lower filling volumes in the shipping validation studies without providing adequate justification that the lower filling volumes represent worst-case scenarios, and it is inconsistent with your response to CR item # 25, that the higher filling volumes will be used in the shipping validation studies.
b. There is no test to examine the primary and secondary packaging systems to ensure that there is no physical damage to the packaging systems after shipment.

To address the above deficiencies, revise the DP shipping validation protocols to
a. provide adequate justification that the lower filling volumes represent worst-case scenarios,
b. update the protocols to include examination of the primary and secondary packaging systems for physical damage.

Additional Comments

In addition, there are several deficiencies that are not approvability issues, but need to be addressed.

7. You did not provide appropriate information to support that there is no impact on the RP-HPLC (STM-0076) and CEX-HPLC (STM-0042) method validation after replacing the United States Pharmacopeia reference standard (USP RS), FOL526, with in-house (b) (4) as a reference standard for the methods. Specifically,

a. Figure 6.6b in PTL-1193-R indicates that USP RS FOL526 and in-house (b) (4) showed differences in RP-HPLC chromatographic patterns, specifically, the reduced peaks did not align.
b. We cannot locate data showing that CEX-HPLC chromatogram profiles for USP RS FOL526 and in-house (b) (4) are comparable.

To address this concern, provide appropriate information supporting the suitable performance of in-house (b) (4) in these methods.

8. We noted deficiencies in the stability protocols for the in-house reference standards:

a. PTL-1981 "Stability Protocol for Theragrastim Primary Reference Standard (b) (4)," does not include adequate replicate runs to robustly test potency. For the primary reference standard, a sufficient number of tests should be performed at the time of stability testing to achieve a statistically significant mean EC50 value. To address this deficiency, update the stability protocol to include sufficient replicates for potency testing.
b. In PTL-2305 "Stability Protocol for Theragrastim Working Reference Standard", your Table 11.1a is entitled "Theragrastim in-house Primary Reference Standard (b) (4) Stability Specifications". It is our understanding that Table 11.1a refers to WRS rather than PRS. Provide the correct reference standard that the table refers to.

9. We noted deficiencies in the protocols for qualification of new cell banks.

a. We noted the following deficiencies in protocol PTL-2168 "Protocol for generation and characterization of new Theragrastim master cell bank and working cell bank":

i. The protocol does not include alert limits, action limits, or criteria for trend analysis of quantitative in-process and release data from the theragrastim DS lots produced using the new working cell banks (WCB) against historical DS lots manufactured using previous WCBs.
ii. The protocol does not include acceptance criteria for cell growth kinetics from fermentation process, including doubling time, growth rate, age at harvest, and percent cell viability and viable cell concentration; and productivity, such as titer.

To address these deficiencies, update the protocol to include adequate acceptance criteria to ensure that new WCB perform comparably to previous WCBs.

(b) (4)

(b) (4)

10. In your response to CR item #24c, you concluded that methods STM-0078 (UV) and STM-0076 (RP-HPLC) produce comparable results for protein concentration by showing a difference of less than (b) (4) in protein concentration values measured by these two methods in the real-time stability studies. However, your justification is not adequate because the stability data in report file PTL-1088-R for the previous in-house (b) (4) indicate that protein concentration values measured by these two methods showed up to (b) (4) difference: (b) (4) using STM-0076 (RP-HPLC) at the 26-month time-point vs. (b) (4) using STM-0078 (UV) at the 49-month time-point. To address this deficiency, provide appropriate justification to demonstrate that the two methods STM-0078 (UV) and STM-0076 (RP-HPLC) will produce comparable results for protein concentration.

11. We acknowledge that you provided data to support that the removal of kanamycin in the (b) (4) fermentation processes does not have an impact on manufacturing process and product quality. However, the final conclusion will be made after the Agency review the final report that you committed to submit.

(b) (4)

D. Benefit/Risk Considerations:

A benefit-risk assessment will be performed upon the receipt and review of the Applicant's complete response information in a future 351(k) BLA resubmission. For additional details, please see the original IQA review memo in Panorama by Dr. Ramesh Potla, dated May 23, 2019.

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

N/A

II. Summary of Quality Assessments:

For information relevant to this section, please see the original IQA review memo uploaded in Panorama by Dr. Ramesh Potla dated May 23, 2019. This section may be updated in future memos depending on the outcome of future CR submissions and inspections.

A. Any Special Product Quality Labeling Recommendations:

- Protect from light
- Avoid freezing
- Avoid shaking

B. Establishment Information

DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
*Manufacture and storage of master and working cell banks *Manufacture of DS *DS release, stability, and in-process testing except for bioburden and HCDNA *DP release and stability testing *Prefilled syringe assembly	Kashiv Biosciences LLC, 3440 S. Dearborn St., Chicago, IL 60616 USA	FEI 3011289655	Pre-license inspection could not be performed due to U.S. Government and/or Agency-wide travel restrictions due to Covid-19 pandemic	A pre-approval BLA inspection was not performed during this review cycle. However, a pre-license inspection performed during the previous review cycle of this BLA in March 2019 resulted in issuance of a seven-item Form FDA 483. See IQA review memo uploaded in Panorama by Dr. Ramesh Potla dated May 23, 2019. Firm was determined to have NOT adequately addressed these issues.	WITHHOLD
(b) (4) UG PRODUCT					
*Manufacture of vialed and prefilled syringe DP.			Pre-license Inspection	Form FDA 483 was issued citing issues with deviation investigations, shipping validation, and clean hold time validation. Firm was determined to have adequately addressed these issues.	Acceptable
*Packaging/ cartoning of Prefilled syringes.			Compliance Assessment	N/A	Acceptable

C. Facilities:

i. [redacted] (b) (4) is acceptable for manufacture of vialed/prefilled syringe theragrastim DP (profile SVS) based on a [redacted] (b) (4) PLI conducted in support of the subject BLA.

ii. [redacted] (b) (4) is acceptable for packaging/cartoning of the prefilled syringe DP based on compliance history.

iii. Kashiv Biosciences LLC (FEI 3011289655) is acceptable for assembly of theragrastim prefilled syringe assembly (profile IDD) and labeling/secondary packaging of vialed theragrastim DP (profile SVS-repacks) based on a March 2019 PLI conducted in support of the subject BLA.

iv. Kashiv Biosciences LLC (FEI 3011289655) is NOT acceptable for theragrastim DS manufacture (profile CBI) and release/stability testing of theragrastim DP (profile CTX) based on a March 2019 PLI conducted in support of the subject BLA. Significant GMP deficiencies were identified regarding QA oversight of product dispositioning, analytical methods, data integrity, written procedures, and adherence to written procedures. A post-action memo dated June 11, 2019 was issued to the firm to detail the deficiencies. Because of the inability of OPQ to perform a pre-license BLA inspection due to the continuing U.S. Government and/or Agency-wide travel restrictions due to Covid-19 pandemic, a determination cannot be made during this review cycle as to whether or not Kashiv has addressed the CGMP deficiencies identified in Form FDA 483.

D. Lifecycle Knowledge Management:

a. Drug Substance:
   i. Protocols approved: None
   ii. Outstanding review issues/residual risk: See CR comments in Section I. A-C.
   iii. Future inspection points to consider: See establishment information section of this memo and DIA review

b. Drug Product
   i. Protocols approved: None
   ii. Outstanding review issues/residual risk: See CR comments in Section I. A-C.
   iii. Future inspection points to consider: See establishment information section of this memo and DIA review

---

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/

RAM K SIHAG
12/18/2020 03:00:25 PM

SUSAN L KIRSHNER
12/21/2020 12:34:26 PM