CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761173Orig1s000

PRODUCT QUALITY REVIEW(S)

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

Recommendation: Approval

BLA Number: 761173
Review Number: 1
Review Date: August 1, 2022

Drug Name/Dosage Form	Stimufend (pegfilgrastim-fpgk) (company code: MSB11455), injection (1 mL single dose pre-filled syringe)
Strength/Potency	6 mg/0.6 mL
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	MSB11455 is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Applicant/Sponsor	Fresenius Kabi USA, LLC

Product Overview

MSB11455 is a covalent conjugate of recombinant methionyl human granulocyte-colony stimulating factor (G-CSF) produced in *Escherichia coli* (*E. coli*) (b) (4) cells and a 20 kDa monomethoxypolyethylene glycol propionaldehyde (mPEG). MSB11455 is a proposed biosimilar to the US-licensed Neulasta. Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. MSB11455 drug product (DP) is a sterile, clear, colorless, preservative-free solution in 1 mL single dose pre-filled syringe. Each DP pre-filled syringe contains 6 mg/0.6 mL of MSB11455 at concentration of 10 mg/mL with pH of 4.0. Each mL of solution contains 10.0 mg MSB11455, 50.0 mg (b) (4) sorbitol, (b) (4) 0.03 mg polysorbate 20 and water for injection. The recommended dose for MSB11455 is same as the US-licensed Neulasta (i.e., 6 mg administered subcutaneously once per chemotherapy cycle).

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Pick-Wei Lau	OPQ/OBP/DBRRII
Product Quality (DS)	Prabuddha Sengupta	OPQ/OBP/DBRRII
Product Quality (small molecule - mPEG and pegylation aspects of DS)	Rohit V. Tiwari	OPQ/ONDP/DNDAPI/NDB1
Labeling	James Barlow/Scott Dallas Pick-Wei Lau	OPQ/OBP OPQ/OBP/DBRRII
Facility	Yun Wu (DS) Yarery Smith (DP)	OPQ/OPMA/DBM
Microbiology	Yun Wu (DS) Yarery Smith (DP)	OPQ/OPMA/DBM
Team Lead	Yan Wang (product quality) Dupeh Palmer (microbiology DP)	OPQ/OBP/DBRRII OPQ/OPMA/DBM

	Peter Qiu /Candace Gomez-Broughton (microbiology DS and facilities) Ali Al Hakim (small molecule)	OPQ/OPMA/DBM OPQ/ONDP/DNDAPI
Inspection team	Richard Ledwidge/Yun Wu/Zhong Li	OPQ/OPMA/DBM
	Chen Sun	OPQ/OBP/DBRRII
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing/ Patrick Lynch	OPQ/OBP/DBRRII
OBP Biosimilar Policy	Marlene Schultz-DePalo	OPQ/OBP
OBP Associate Director of Biosimilar and Biologic Policy	Joel Welch	OPQ/OBP
RBPM	Florence Aisida/Hamet Toure/Melinda Bauerlien	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Courtney Hamilton	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Julie Weisman	OND/OCHEN/DNH
Pharm/Tox	David Carlson; Todd Bourcier	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Kunal Jhunjhunwala; Anusha Ande; Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Jiaxi Zhou; Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Stimufend
   b. Trade Name: Stimufend
   c. Non-Proprietary Name/USAN: pegfilgrastim
   d. Chemical Abstract Service (CAS) Registry Number: 208265-92-3
   e. International Union of Pure and Applied Chemistry (IUPAC) Number: N-(3-hydroxypropyl) methionyl colony-stimulating factor (human), 1-ether with alpha-methylomega-hydroxypoly (oxyethylene)
   f. INN Name: pegfilgrastim
   g. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [MSB11455]
   h. Other name(s): MSB11455 and B3114 for pegfilgrastim, S152 for G-CSF (company code)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761173/SN0045 (IR response)	April 23, 2021 (OBP)
STN 761173/SN0046 (IR response)	July 9, 2021 (CDRH)
STN 761173/SN0047 (IR response)	July 30, 2021 (OPMA)
STN 761173/SN0048 (IR response)	August 5, 2021 (OPMA)
STN 761173/SN0049 (IR response)	August 30, 2021 (OPMA)
STN 761173/SN0050 (IR response)	November 23, 2021 (OBP)
STN 761173/SN0051 (IR response)	January 21, 2022 (OPMA)
STN 761173/SN0053 (IR response)	July 7, 2022 (OBP and OPMA)
STN 761173/SN0054 (IR response)	July 18, 2022 (OBP)
STN 761173/SN0055 (IR response)	July 20, 2022 (OBP)
STN 761173/SN0056 (IR response)	July 25, 2022 (OBP)

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

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:
Refer to the Integrated Quality Assessment (Also referred to as Executive Summary) for BLA 761173 dated February 4, 2021 in DARRTS for an assessment of Drug Master Files (DMF), which is attached as Appendix 1 in the current Executive Summary addendum, and supporting documents referenced in the original BLA.

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH-OPEQ-OHT3/DHT3C	June 24, 2022	Complete (July 14, 2022)	Approvable and a post-marking commitment which was previously communicated with the Applicant is not needed	Kathleen Fitzgerald/ Courtney Evans

4. Environmental Assessment:
Fresenius Kabi USA, LLC claimed a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (b), action on a BLA when the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Fresenius Kabi claims that to their knowledge there are no extraordinary circumstances as described in 21 CFR 25.15(d). Thus, no environmental assessment is required.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761173 for Stimufend (pegfilgrastim-fpgk) manufactured by Fresenius Kabi USA, LLC. This memo documents the review after missing the BsUFA date as of March 27, 2021 due to inability to perform an inspection during the review cycle. After the pre-licensed inspections of the G-CSF intermediate manufacturing facility (b) (4) and the quality control testing site (b) (4) as well as the 704(a)(4) records review of the MSB11455 DS manufacturing facility (b) (4) the OPQ, CDER, recommends approval from a facilities perspective based on the manufacturing facility assessment. The pre-approval inspection at the major comparative analytical testing site at (b) (4) verified that the tests generated to support a demonstration of highly similar are scientifically sound, fit for their intended use, and provide

results that are reproducible and reliable. The data submitted in this application are adequate to support the conclusion that the manufacture of Stimufend (pegfilgrastim-fpgk) is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Stimufend (pegfilgrastim-fpgk) is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - G-CSF intermediate (uppegylated G-CSF): (b) (4)
    - MSB11455 drug substance (pegylated G-CSF): (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 6 mg in 0.6 mL (10 mg/mL) solution in a pre-filled syringe
- Dating period:
  - Drug Product: 24 months at 2-8°C
  - Drug Substance: (b) (4) months at (b) (4) °C
  - G-CSF intermediate: (b) (4) months at (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols: We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.
- Exempt from lot release in accordance with 21 CFR 601.2a. MSB11455 is a specified product.

C. Benefit/Risk Considerations:

Refer to the Executive Summary memo for BLA 761173 dated February 4, 2021 in DARRTS for Benefit/Risk Considerations assessed, which is attached in Appendix 1 in the current Executive Summary addendum.

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

The following post-marketing commitments (PMCs) have been discussed and agreed by the Applicant during the BLA review.

OBP-1: To complete method development and implement a method [redacted] (b) (4) for a [redacted] (b) (4) in-process control.

Final report submission date: July 2023

OBP-2: To complete a viral inactivation study [redacted] (b) (4) and to demonstrate that it is an effective step for inactivation of viruses that may be present.

Final report submission date: March 2023

OBP-3: To complete a real-time leachables study using the final container closure system [redacted] (b) (4) to identify any potential leachables at initial, 6 and 12 months under storage condition [redacted] (b) (4)

Final report submission date: March 2023

OBP-4: To complete a real-time leachables study using the final container closure system with MSB11455 drug substance to identify any potential leachables at initial, 6 and 12 months under storage condition [redacted] (b) (4)

Final report submission date: March 2023

OBP-5: To complete a real-time leachables study using the final container closure system with MSB11455 drug product to identify any potential leachables at initial, 6, 12, 24 and 36 months under storage condition between 2°C -8°C.

Final report submission date: March 2025

II. Summary of Quality Assessments:

Refer to the Executive Summary memo for BLA 761173 dated February 4, 2021 in DARRTS for assessments of comparative analytical assessment, critical quality attributes, risks, lifecycle management, and establishment information. The original February 4, 2021 Executive Summary memo is also attached as Appendix 1 in the current Executive Summary addendum. The OBP product quality and immunogenicity assay, the OPMA facility, microbiological DS and DP, as well as the OBP labeling technical assessments are located as separate documents in Panorama.

Appendix 1

Recommendation: pending final assessment of facilities compliance

BLA Number: 761173
Review Number: 1
Review Date: February 3, 2021

Drug Name/Dosage Form	MSB11455 injection (pre-filled syringe for single dose injection)
Strength/Potency	6 mg/0.6 mL
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	MSB11455 is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Applicant/Sponsor	Fresenius Kabi USA, LLC

Product Overview

MSB11455 is a covalent conjugate of recombinant methionyl human granulocyte-colony stimulating factor (G-CSF) produced in *Escherichia coli* (*E. coli*) (b) (4) and a 20 kDa monomethoxypolyethylene glycol propionaldehyde (mPEG). MSB11455 is a proposed biosimilar to the US-licensed Neulasta. Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. MSB11455 drug product (DP) is a sterile, clear, colorless, preservative-free solution. Each DP pre-filled syringe contains 6 mg/0.6 mL of MSB11455 at concentration of 10 mg/mL with pH of 4.0. Each mL of solution contains 10.0 mg MSB11455, 50.0 mg (b) (4) sorbitol, (b) (4) 0.03 mg polysorbate 20 and water for injection. The recommended dose for MSB11455 is same as the US-licensed Neulasta (i.e., 6 mg administered subcutaneously once per chemotherapy cycle).

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Pick-Wei Lau	OPQ/OBP/DBRRII
Product Quality (small molecule - mPEG and pegylation aspects of DS)	Rohit V. Tiwari	OPQ/ONDP/DNDAPI/NDB1
Labeling	James Barlow Pick-Wei Lau	OPQ/OBP OPQ/OBP/DBRRII
Facility	Yun Wu (DS) Yarery Smith (DP)	OPQ/OPMA/DBM/BMB2
Microbiology	Yun Wu (DS) Yarery Smith (DP)	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Team Lead	Yan Wang (product quality) Dupeh Palmer (microbiology DP) Peter Qiu (microbiology DS and facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB1 OPQ/OPMA/DBM

	Ali Al Hakim (small molecule)	OPQ/ONDP/DNDAPI
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
OBP Biosimilar Policy	Marlene Schultz-DePalo	OPQ/OBP
OBP Associate Director of Biosimilar and Biologic Policy	Joel Welch	OPQ/OBP
RBPM	Florence Aisida/Hamet Toure	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Courtney Hamilton	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Julie Weisman	OND/OCHEN/DNH
Pharm/Tox	David Carlson; Todd Bourcier	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Kunal Jhunjhunwala; Anusha Ande; Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Jiaxi Zhou; Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   i. Proprietary Name: Stimufend (proposed)
   j. Trade Name: Stimufend (proposed)
   k. Non-Proprietary Name/USAN: pegfilgrastim
   l. Chemical Abstract Service (CAS) Registry Number: 208265-92-3
   m. International Union of Pure and Applied Chemistry (IUPAC) Number: N-(3-hydroxypropyl) methionyl colony-stimulating factor (human), 1-ether with alpha-methylomega-hydroxypoly (oxyethylene)
   n. INN Name: pegfilgrastim
   o. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [MSB11455]
   p. Other name(s): MSB11455 and B3114 for pegfilgrastim, S152 for G-CSF (company code)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761173/SN0001 (Original submission)	March 27, 2020 (OBP and OPMA)
STN 761173/SN0002 (Information request (IR) response)	May 19, 2020 (OPMA-DP)
STN 761173/SN0004 (IR response)	June 29, 2020 (OPMA-DS)
STN 761173/SN0006 (IR response)	August 4, 2020 (ONDP)
STN 761173/SN0007 (IR response)	August 6, 2020 (OPMA-DS)
STN 761173/SN0008 (IR response)	August 13, 2020 (OBP-IR1)
STN 761173/SN0010 (IR response)	August 28, 2020 (OPMA-facility)
STN 761173/SN0013 (IR response)	September 15, 2020 (OPMA-DP)
STN 761173/SN0015 (IR response)	October 2, 2020 (OBP-IR2)
STN 761173/SN0017 (IR response)	October 13, 2020 (OPMA-DP)
STN 761173/SN0019 (IR response)	October 30, 2020 (OPMA-DS)
STN 761173/SN0020 (IR response)	November 9, 2020 (OBP-IR3)
STN 761173/SN0021 (IR response)	November 13, 2020 (CDRH)
STN 761173/SN0022 (IR response)	November 19, 2020 (CDRH)
STN 761173/SN0023 (IR response)	November 20, 2020 (OBP-IR5-1)
STN 761173/SN0024 (IR response)	November 24, 2020 (OBP-IR4)
STN 761173/SN0025 (IR response)	December 7, 2020 (OBP-IR3-follow up)

STN 761173/SN0026 (IR response)	December 7, 2020 (OBP-IR5-2)
STN 761173/SN0027 (IR response)	December 9, 2020 (OBP-IR6)
STN 761173/SN0029 (IR response)	December 9, 2020 (CDRH)
STN 761173/SN0030 (IR response)	December 11, 2020 (OBP-IR5-2-follow up)
STN 761173/SN0032 (Late cycle meeting minutes)	December 18, 2020 (revised timeline for microbiology DS PMCs)
STN 761173/SN0033 (IR response)	December 23, 2020 (OBP-IR7)
STN 761173/SN0035 (IR response)	January 8, 2021 (OBP-IR8)
STN 761173/SN0037 (IR response)	February 1, 2021 (CDRH)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	3	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A
	N/A			3	Adequate	N/A	Defer to CDRH
	II			1	Adequate	10/22/20	Reviewed by CDER/OPQ/ ONDP

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

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	113717	Parent IND

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH-OPEQ-OHTIII/DHTIIIC	May 19, 2020	Complete (2/3/2021)	Approvable	Gang Peng/Rumi Young

4. Environmental Assessment:

Fresenius Kabi USA, LLC claimed a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (b), action on a BLA when the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Fresenius Kabi claims that to their knowledge there are no extraordinary circumstances as described in 21 CFR 25.15(d). Thus, no environmental assessment is required.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

B. Recommendation and Conclusion on Approvability:

Recommendation:

The recommendation for STN 761173 from the Office of Pharmaceutical Quality (OPQ), CDER, is pending on the final assessment of facilities compliance. Inspections of the G-CSF intermediate manufacturing facility (b) (4) the MSB11455 DS manufacturing facility (b) (4) as well as the quality control testing and comparative analytical assessment site (b) (4) are required before the application can be approved. The Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER must assess the ability of the facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, OPQ may be unable to conduct inspections of these facilities prior to the User Fee Date. OPMA will continue to monitor the public health situation as well as travel restrictions. OPMA is actively working to define an approach for scheduling outstanding inspections once safe travel may resume based on public health need and other factors.

From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER as well as OPMA, OPQ, CDER do not note any product quality deficiencies that would preclude approval of STN 761173 for MSB11455 manufactured by Fresenius Kabi USA, LLC at this time. The analytical similarity data submitted in the application demonstrate that MSB11455 is highly similar to US-licensed Neulasta. If Fresenius Kabi USA, LLC submits additional manufacturing information during this review cycle, additional assessment may be needed during the current assessment cycle.

E. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - G-CSF intermediate (uppegylated G-CSF): (b) (4)
    - MSB11455 drug substance (pegylated G-CSF): (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 6 mg in 0.6 mL (10 mg/mL) solution in a pre-filled syringe

- Dating period:
    - Drug Product: 24 months at 2-8°C (pending on final stability updates committed to be submitted in February 2021)
    - Drug Substance: (b) (4) months at (b) (4) °C
    - G-CSF intermediate: (b) (4) months at (b) (4) °C
    - Stability Option:
        - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
        - For stability protocols: We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.

- Exempt from lot release in accordance with 21 CFR 601.2a. MSB11455 is a specified product.

F. Benefit/Risk Considerations:

MSB11455 is a proposed biosimilar to US-licensed Neulasta. The applicant requested the neutropenia indication for which US-licensed Neulasta is approved.

Review of manufacturing has identified that the methodologies used for G-CSF intermediate, MSB11455 DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. In addition, the microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product.

Inspections of the G-CSF intermediate and MSB11455 DS facilities as well as the quality control testing and comparative analytical assessment site are required before this application can be approved as OPMA must assess the ability of the facility to conduct the listed manufacturing operations in compliance with cGMP. However, due to US Government and/or Agency-wide restrictions on international travel under COVID-19 pandemic, OPQ may be unable to conduct inspections prior to the User Fee Date.

The data provided in the BLA support a determination that MSB11455 is highly similar to U.S.-licensed Neulasta.

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

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

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

Quality - (b) (4)

OPMA-1: Complete bioburden and endotoxin method verification (b) (4)

Final report submission date: April 2021

OPMA-2: Complete microbial purity method verification with a total of 3 commercial-scale batches and provide the final method verification report.

Final report submission date: April 2021

Quality - (b) (4)

OPMA-3: Review and adjust microbial control limits of in-process pools based on process capability.

Final report submission date: April 2021

OBP-1: To complete a real-time leachables study using the final container closure system (b) (4) to identify any potential leachables at initial, 6 and 12 months under storage condition (b) (4)

Final report submission date: December 2022

OBP-2: To complete a real-time leachables study using the final container closure system with MSB11455 drug substance to identify any potential leachables at initial, 6 and 12 months under storage condition (b) (4)

Final report submission date: December 2022

OBP-3: To complete a real-time leachables study using the final container closure system with MSB11455 drug product to identify any potential leachables at initial, 6, 12, 24 and 36 months under storage condition between 2°C -8°C.

Final report submission date: December 2024

OBP-4: To complete method development and implement a method (b) (4) for a (b) (4) in-process control.

Final report submission date: November 2021

OBP-5: To complete a viral inactivation study (b) (4) and to demonstrate that it is an effective step for inactivation of viruses that may be present.

Final report submission date: December 2021

CDRH-1: To update the design verification package which will include the needle safety activation, needle safety override, resistance to pre-activation after shipping simulation and resistance to pre-activation after drop testing. The verification will be performed using the final finished combination product from the final commercial manufacturing process using a sample size of n=299 in order to meet 99% reliability (at 95% of confidence level) for each verification test.

Final report submission date: June 2021 (pending on the final commitment from the Applicant)

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

A. Summary of Comparative Analytical Assessment

a. Analytical Assessment Overview and Conclusions

The Applicant provided results of the comparative analytical assessment to support a demonstration that MSB11455 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. The Applicant ranked the criticality of the quality attributes based on their potential impact on activity, pharmacokinetic (PK)/ pharmacodynamic (PD), safety and immunogenicity.

For the selected quality attributes with highest criticality (i.e., protein concentration as well as pegfilgrastim induced M-NFS-60 cell proliferation of relative potency and specific activity), both an equivalence test approach where the pre-determined equivalence margin for demonstrating similarity was defined as ± 1.5 X standard deviation (SD), and a quality range (QR) approach where the QR was set based on the range of the values obtained from US-licensed Neulasta lot variations expressed as ± XSD (the multiplier X=2 was used), were applied. For the selected quality attributes with moderate to very high criticality, the QR approach with multiplier as X=3 was applied. For quality attributes with low criticality, tested with orthogonal tests or tested with qualitative test methods, raw data (RD) or graphical data were presented. The selected approaches for comparative analytical assessment are consistent with FDA Draft Guidance: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019). The selected multiplier X used in the QR approach, which are based on the criticality of the quality attributes, sensitivity of the analytical methods, abundance of the quality attributes, the distribution of the quality attributes and the type of the analytical methods, is justified. Results from method validation or qualification studies support the suitability of the methods used in the comparative analytical assessment.

The Applicant compared 16 independent lots of MSB11455 and 28 lots of US-licensed Neulasta. The 16 MSB11455 lots included the lots used in the PK/PD similarity study EMR200621-001 and the comparative clinical study EMR200621-003 evaluating safety/immunogenicity as well as the process performance qualification (PPQ) lots manufactured by the proposed commercial manufacturing process. The Applicant tested MSB11455 and US-licensed Neulasta using multiple orthogonal methods to adequately evaluate the necessary quality attributes of the products.

The expiry dates of the US-licensed Neulasta lots ranged from June 2015 to June 2020, which spans the shelf-life of US-licensed Neulasta and were adequate to capture potential reference product differences over time. The Applicant also performed comparative forced degradation studies under mechanical, pH, light, thermal and oxidative stress conditions. The comparative forced degradation studies support that MSB11455 and US-licensed Neulasta have a similar degradation profile.

Two types of bioactivity assays reflecting the mechanism of action of US-licensed Neulasta and MSB11455 were conducted. In vitro potency was determined using a murine myelogenous leukemia cell line (M-NFS-60 cell line) to evaluate the receptor-activated hematopoietic cell proliferation induced by the products. The Applicant chose to evaluate results from the in vitro cell-based assay for both relative activity and specific activity with an equivalence test as well as a QR approach because of the high risk level for this critical quality attribute. A surface plasmon resonance (SPR) assay with a Biacore instrument to measure G-CSF receptor binding affinity was conducted. The comparison of G-CSF receptor binding affinity (equilibrium dissociation constant-KD) by a QR approach as well as the association constant (Ka) and dissociation constant (Kd) by a RD approach support a determination that the higher order structure required for binding to the receptor and response binding kinetics are similar between MSB11455 and US-licensed Neulasta. The two bioactivity assays support the proposed mechanism of action of MSB11455.

Our assessment of the MSB11455 and US-licensed Neulasta data supports a demonstration that MSB11455 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. MSB11455 has the same strength, dosage form, and route of administration as US-licensed Neulasta. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of MSB11455 and US-licensed Neulasta to support a demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. Observed differences do not preclude a demonstration that MSB11455 is highly Similar to US-licensed Neulasta.

b. Results of Comparative Analytical Assessment

The results of the analytical comparisons that support a demonstration that MSB11455 is highly similar to US-licensed Neulasta are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
Primary Structure	Amino acid sequence	Yes
	Comparison of levels of post translational modifications (oxidation at Met122, Met127, Met138; total oxidation; deamidation at Gln26; succinimide at Asp28)	Yes
	mPEG attachment site	Yes
	Extinction coefficient	Yes
	Molecular weight	Yes*
	Polydispersity of molecular weights distribution	Yes
Higher Order Structure	Disulfide bonds and free sulfhydryl groups	Yes
	Secondary structure (fluorescence spectroscopy, Far-UV CD & 2D NMR spectra)	Yes
	Tertiary structure (near UV CD & 2D NMR spectra)	Yes
	Thermal stability (DSC)	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed		Supports a Demonstration of Highly Similar
Product-Related Substance and Impurities	Size variants and impurities	Monomer/purity (SE-HPLC, AUC, SEC-MALLS and reduced CGE-SDS)	Yes*
		High molecular weight (HMW) species (e.g., aggregates, dimer & Di-Peg/HMW) (SE-HPLC, AUC and SEC-MALLS)	Yes*
		Low molecular weight (LMW) species (e.g., fragments, free G-CSF and free mPEG) (SE-HPLC, AUC, SEC-MALLS, reduced CGE-SDS, SDS-PAGE and RP-HPLC)	Yes
	Charge variants	Acidic variants (icIEF and SCX-HPLC)	Yes
		Main species (icIEF and SCX-HPLC)	Yes*
		Basic variants (icIEF and SCX-HPLC)	Yes
	Hydrophobic variants	Pre-peak groups (RP-HPLC) (M-1, M-2 and M-3)	Yes*
		Main species (RP-HPLC)	Yes*
		Post peak groups (RP-HPLC) (M+1, M+2 and M+3)	Yes*
Bioactivity	G-CSF receptor binding (SPR)	Binding affinity KD	Yes
		Binding kinetics Ka	Yes
		Binding kinetics Kd	Yes
	M-NFS-60 cell proliferation	Relative potency	Yes
		Specific activity	Yes
Drug Product Attributes	Protein concentration		Yes

"Yes*": Differences were noted, but do not preclude a determination of highly similar and will be explained further below.

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

Not applicable.

Data generated from studies using EU-approved Neulasta were not used to support a demonstration of biosimilarity. Therefore, the analytical testing results from 24 lots of EU-approved Neulasta submitted in the BLA in section 3.2.R Regional Information were not assessed, as there was no need to establish an adequate scientific bridge.

d. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all quality attributes with the following exceptions between MSB11455 and US-licensed Neulasta:

- Molecular weight: the molecular weight (MW) measured by MALDI-TOF analysis is from 39767.8 to 40950.0 Da for MSB11455 and is from 39999.9 to 40264.7 Da for US-licensed Neulasta, respectively. The data showed that the MW of mPEG used to manufacture MSB11455 drug substance is in a good alignment with the mass of MSB11455 indicating that the MW differences are due to the different sizes of mPEG used during manufacture. LC-MS/MS results suggest that the mPEG used for US-licensed Neulasta is centered at an average MW of ~20.9 kDa, whereas the mPEG used for these MSB11455 lots is centered at an average MW of ~21.7 kDa. However, the polydispersity index determined by LC-MS used as a measure of MW distribution of mPEG is similar between MSB11455 (1.0003) and US-licensed Neulasta (1.0003-1.0004) suggesting the similar mPEG quality and MW distribution. In addition, the size of the mPEG used in the manufacture of MSB11455 is controlled in the specification with the

acceptance criterion as (b) (4) kDa. The highly flexible mPEG molecule is predicted to form a thick, flexible layer across the surface of the protein and thereby increase the hydrodynamic radius of pegylated protein which impacts its in vivo residence time, the half-life and bioactivity. The hydrodynamic radius (by SEC-MALLS) ranges of all tested MSB11455 lots (5.3 nm - 6.1 nm) are within the hydrodynamic radius ranges of US-licensed Neulasta (5.3 nm - 8.9 nm) lots. The bioactivity ranges of all tested MSB11455 lots are within the bioactivity QR of US-licensed Neulasta. These data suggest that the differences in MW between MSB11455 and US-licensed Neulasta have a minimal impact on the PK and bioactivity. We consulted with the clinical pharmacology reviewers, who reviewed this PK/PD similarity study EMR200621-001 and found the results corroborate with the analytical finding, and the data suggested that the minor difference in MW would not differentially impact the PK/PD profiles. Therefore, the differences in MW between MSB11455 and US-Neulasta do not preclude a demonstration of highly similar.

- Size variants and impurities: all size variants and impurities detected by SE-HPLC, AUC, SEC-MALLS, and reduced SDS-PAGE in MSB11455 lots are also observed in US-licensed Neulasta with similar level with exception of % Di-Peg/HMW and % monomer determined by SE-HPLC. % Di-Peg/HMW (~62.7 kDa) measured by SE-HPLC in MSB11455 (0.48-1.67%) is outside the QR of US-licensed Neulasta (0.85-1.58%). The differences in % Di-Peg/HMW might theoretically impact the PK and bioactivity. Due to the differences in the % Di-Peg/HMW determined by SE-HPLC, the %monomer (~39 kDa) in MSB11455 (97.89-99.30%) is slightly outside the QR of US-licensed Neulasta (97.91-98.86%) although the aggregates including dimer and other HMW determined by SE-HPLC are similar. However, based on the bioactivity data, the bioactivity is similar between MSB11455 and US-licensed Neulasta despite the small differences in levels of % Di-Peg/HMW. Overall, the slight differences in % Di-Peg/HMW do not impact the bioactivity as evidenced by results showing similar bioactivity between MSB11455 and US-licensed Neulasta. Furthermore, the small difference in the maximum levels of % Di-Peg/HMW for MSB11455 of 0.2% compared to US-licensed Neulasta is not expected to impact PK. We consulted with the clinical pharmacology reviewers, and the PK data are consistent with the conclusion that similar PK and PD profiles were obtained from MSB11455 and US-licensed Neulasta lots used in the PK/PD similarity study EMR200621-001 (refer to the Biosimilar Multi-Disciplinary Evaluation and Review (BMER) for details) despite the % Di-Peg/HMW contents from the MSB11455 (1.09 %) and US-licensed Neulasta (1.5 %) lots being slightly different. Therefore, the small differences in % Di-Peg/HMW and %monomer do not preclude a demonstration of highly similar.

- Charge variants: the charge variants evaluated by icIEF were further assessed by SCX-HPLC. The acidic groups of Cluster 1, Cluster 2 and Cluster 3 by icIEF contain positional isomers of mono-pegylated protein (Lys 35 or Lys 41) and forms with deamidation at Gln68 or Gln174, and Cluster 2 also contains dimer and dipegylated (Met 1 and Lys 35 or Lys 41) forms. The major isoform (Cluster 4 and Cluster 5) by icIEF were identified by SCX-HPLC as native mono-pegylated MSB11455 (correlated to Cluster 4) and basic isoforms with oxidation at Met122, Met127 or Met138 (correlated to Cluster 5).

  For native mono-pegylated pegfilgrastim (Cluster 4), 85% of MSB11455 lots were within the QR of US-licensed Neulasta (52.82 – 65.36%). One lot of MSB11455, BA052548P had the level of Cluster 4 (65.78%) above, but very close to, the upper QR of US-licensed Neulasta (65.36 %) lots. One lot of MSB11455, BA051607P, had the level of Cluster 4 (52.73%) below, but very close to, the lower QR of US-licensed Neulasta (52.82%). However, MSB11455 and US-licensed

Neulasta lots contain similar levels of Cluster 1, Cluster 2, Cluster 3 and Cluster 5 (more than 90% of MSB11455 lots within the QR of US-licensed Neulasta). In addition, the bioactivity is similar between MSB11455 and US-licensed Neulasta. Therefore, the slightly higher level of Cluster 4 observed in BA052548P and slightly lower level of Cluster 4 observed in BA051607P are highly unlikely to be clinically significant and do not preclude a demonstration of highly similar.

- Hydrophobic variants: RP-HPLC is used to separate variants based on their capacity to create hydrophobic interaction. Peak characterization studies suggest that main peak corresponds to the molecule intact form; all pre-peaks (M-3, M-2 and M-1) have positional isomers of mono-pegylated species where M-1 also contains variants with oxidation at Met138, but M-2 and M-3 contain variants with oxidation at Met122 and Met127; post peaks M+1 and M+2 contain di-pegylated forms (Met1 and Lys35 or Lys41) and/or positional isomers of mono-pegylated forms (Lys35 or Lys41) where M+1 also contains variants with deamidation at Gln68 and Gln174 as well reduced variants, but M+2 contains variants with deamidation at Gln108 and species related to G-CSF as well as pegylation variants, and post peak M+3 contains dimer.

  The differences were observed for main species, M-1 peak, overall total oxidation levels, M+2 peak and overall total deamidation levels between MSB11455 and US-licensed Neulasta. Specifically, for main species 77% of MSB11455 lots (min-max: 95.16-97.37%) is within the QR of US-licensed Neulasta (94.43 – 97.24%); for M-1 54% of MSB11455 lots (min-max: 0.98-1.28%) is within the QR of US-licensed Neulasta (0.56 - 1.07%); for total oxidation 77% of MSB11455 lots (min-max: 1.27 - 1.62%) is within the QR of US-licensed Neulasta (0.82 - 1.48%); for M+2 54% of MSB11455 lots (min-max: 0.13 - 1.65%) is within the QR of US-licensed Neulasta (0.16 - 1.24%); for total deamidation 54% of MSB11455 lots (min-max: 1.24 - 3.53%) is within the QR of US-licensed Neulasta (1.66 - 4.36%). The difference for M-1 is mainly due to the Met138 oxidation. However, the small differences in total oxidation have minimal impact on potency based on the characterization data where up to 12.25% total oxidation by RP-HPLC does not impact binding affinity to G-CSF-R or G-CSF-mediated cell proliferation. In addition, similar levels of Met122, Met127, Met138 and total oxidation were observed between MSB11455 and US-licensed Neulasta by peptide mapping LC-ESI-MS/MS. The difference for M+2 is mainly due to the Gln108 deamidation. But the levels of total deamidated forms in MSB11455 lots are the same or lower than those present in US-licensed Neulasta, and lower levels would not be expected to have an adverse impact on clinical efficacy or safety. The differences for main species are due to the differences for M-1 peak, overall total oxidation levels, M+2 peak and overall total deamidation levels. Overall, the differences in hydrophobic variants do not impact the bioactivity because the bioactivity is similar between MSB11455 and US-licensed Neulasta. Therefore, these differences in hydrophobic impurities do not preclude a demonstration of highly similar.

  In summary, based on the above, there are no residual uncertainties regarding the comparative analytical assessment that would preclude a demonstration that MSB11455 is highly similar to US-licensed Neulasta.

B. Same Strength(s)

MSB11455 has the same dosage form and route of administration as US-licensed Neulasta. Fresenius Kabi USA, LLC (Fresenius Kabi) is seeking approval of 6.0 mg/0.6 mL MSB11455 in a prefilled syringe.

US-licensed Neulasta is available at this strength as 6.0 mg/0.6 mL in a prefilled syringe. Fresenius Kabi is seeking approval of MSB11455 for the same strength as US-licensed Neulasta. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. (b) (4) The proposed presentation of MSB11455 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Neulasta (6 mg/0.6 mL). The strength of MSB11455 prefilled syringe is the same as that of US-licensed Neulasta.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for MSB11455

Table 1: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
In vitro cell-based bioassay (potency)	Efficacy	Intrinsic to the molecule, impacted by exposure to heat, oxidation reagent stress and light stress	(b) (4)	(b) (4)
Receptor binding	Efficacy	Intrinsic to the molecule		Binding kinetics are characterized by binding affinity (equilibrium dissociation constant-KD), the association constant (Ka) and dissociation constant (Kd)
Identity	Efficacy and Safety	Intrinsic to the molecule		N/A

(b) (4)

HMW species (Product related impurity)	PK and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, low pH, mechanical stress, oxidation reagent stress, and light stress	
LMW species/Fragments (Product related impurity)	Efficacy, PK and Safety (Immunogenicity)	Manufacturing process, and exposure to low pH, heat, mechanical stress, and light stress	
Hydrophobic variants including oxidized, deamidated and reduced impurities as well as positional mono-pegylated isomers)	Efficacy and safety (Immunogenicity)	Manufacturing process and exposure to heat, oxidation reagent stress and light stress	
Charge variants including oxidized impurity, Di-Peg/HMW and positional mono-pegylated isomers	Efficacy and PK	Manufacturing process and exposure to heat, oxidation reagent stress and light stress	

B. Drug Substance (MSB11455) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process	(b) (4)	Assessed by CDER/OPQ/OPMA team (b) (4)
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process		Assessed by CDER/OPQ/OPMA team
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Appearance (General)	Stability	Formulation components and stability		N/A
Degree of coloration (General)	Stability	Formulation components and stability		N/A
Clarity and degree of opalescence (General)	Stability	Formulation components and stability		N/A
(b) (4)	Stability	Formulation component and stability		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line, bioreactor and harvest, cell viability and % viable cell density		(b) (4)

				(b) (4)
Host cell protein (Process related impurity)	Safety (Immunogenicity) and Purity	Production cell line, bioreactor and harvest cell viability and % viable cell density	(b) (4)	
(b) (4)	Safety and Purity	(b) (4)		Assessed also by CDER/OPQ/ONDP team
Residual (b) (4)	Safety and Purity			Assessed also by CDER/OPQ/ONDP team
(b) (4) (Process related impurity)	Safety and Purity	Cell banks, raw materials		(b) (4)
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material (b) (4) and DS container closure system (CCS)		PMCs to complete a real time leachables study using the final CCS for (b) (4) DS through the shelf-life
Culture medium additives, buffer components and other added materials (b) (4)	Safety and Purity	(b) (4)		Levels are below toxicological concern based on the risk assessment for non-animal derived materials

			(b) (4)	

- Description:
  G-CSF intermediate, a non-glycosylated recombinant methionyl human granulocyte colony stimulating factor, is produced in E. coli. The G-CSF intermediate is composed of 175 amino acids which is identical to natural G-CSF, except for an additional methionine residue at the N-terminus. G-CSF intermediate is an antiparallel, four α-helix bundle arranged in an up-up and down-down topology with a left-handed twist. To produce MSB11455, a 20 kDa mPEG-PAL molecule is covalently bound to the N-terminal methionyl residue of G-CSF intermediate. MSB11455 possesses two disulfide bonds between cysteine residues Cys37 and Cys43, and between Cys65 and Cys75, maintaining the biologically active conformation of G-CSF. The average molecular weight of MSB11455 is approximately 39 kDa. MSB11455 is a proposed biosimilar to US-licensed Neulasta.

- Mechanism of Action (MoA):
  G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. Pegylated G-CSF has the same MOA as G-CSF.

- Potency Assays:
  A cell-based bioassay is used to determine the potency of G-CSF intermediate or MDB11455 DS based on its ability to stimulate the G-CSF dependent proliferation of G-CSF-adapted M-NFS-60 murine myelogenous leukemia cells. Specifically, after incubation of M-NFS-60 cells with 30 ng/mL G-CSF intermediate or MDB11455 DS, a cell-permeable resazurin-based dye, that is reduced to fluorescent resorufin in viable cells, is added. The resulting fluorescence is then read at an excitation wavelength of 560 nm and an emission wavelength of 590 nm. The fluorescence measured is proportional to cell proliferation. The potency of G-CSF intermediate or MSB11455 DS test samples is determined in comparison to the EC50 of the relevant G-CSF intermediate reference standard or MSB11455 DS reference standard, respectively.

- Reference Materials:
  - (b) (4)

(b) (4)

- For MSB11455 DS: A two-tiered reference material system is in place. The current primary reference standard - (b) (4) and working reference standard - (b) (4) The Applicant has provided sufficient data to bridge the current primary reference standard with the clinical reference standard used in the clinical studies and the reference standards used in the comparative analytical assessment. Therefore, the current primary and working reference standards are representative of the clinical and manufacturing experiences as well as materials used to support a demonstration of analytical similarity with US-licensed Neulasta. A protocol is provided for the qualification of future primary and working reference standards. The protocol contains adequate testing and acceptance criteria. The procedures (i.e., requalification) to monitor the potential changes and stability of the primary and working reference standards are appropriate.

- Critical Starting Materials or Intermediates:

(b) (4)

- Manufacturing Process Summary:

(b) (4)

(b) (4)

- Container Closure System:

(b) (4)

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

  The dating period for the (b) (4) is (b) (4) months when stored at (b) (4) °C.

C. Drug Product (MSB11455) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process	(b) (4)	Assessed by CDER/OPQ/OPMA team
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		Assessed by CDER/OPQ/OPMA team
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DP		N/A
Appearance (General)	Stability	Formulation components and stability		N/A
Degree of coloration (General)	Stability	Formulation components and stability		N/A
Clarity and degree of opalescence (General)	Stability	Formulation components and stability		N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Extractable volume (General)	Efficacy/Dosing	Fill process		N/A
Polysorbate 20 Concentration	Stability	Formulation component and stability		N/A
(b) (4)	Safety and Purity	(b) (4)		Assessed also by CDER/OPQ/ONDP team
Break loose and gliding force	Efficacy and Safety	Device performance		Assessed also by CDRH team
(b) (4)	Safety	CCS		the Maximum Daily Exposure (MDE) of

			(b) (4)
(b) (4)	Safety	CCS	(b) (4)
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	PMC to complete a real time leachables study using the final CCS for DP through the shelf-life

- Potency and Strength:
  MSB11455 is supplied in a pre-filled syringe (PFS) at a strength of 6 mg/0.6 mL. MSB11455 was developed to have the same strength as US-licensed Neulasta. Potency is defined as the percent activity relative to the current MSB11455 primary reference standard. The potency assays are the same as described in the DS section of this memo.

- Summary of Product Design:
  MSB11455 is supplied as a sterile, single-dose, clear, colorless, preservative-free solution for subcutaneous injection in one strength. MSB11455 was developed as a biosimilar to US-licensed Neulasta and targets the quality profile of US-licensed Neulasta.

- List of Excipients:
  Each mL of solution contains 50.0 mg (b) (4) sorbitol, (b) (4) 0.03 mg polysorbate 20 and water for injection, pH 4.0.

- Reference Materials:
  The same reference standards are used for (b) (4) and DP.

- Manufacturing Process Summary:
  (b) (4)

- Container Closure System:
  The MSB11455 DP primary container closure system is a single-dose PFS consisting of a 1 mL [(b) (4)] glass syringe closed with a [(b) (4)] plunger stopper and combined with a 27 Gauge, [(b) (4)] steel needle protected by a rigid needle shield. The needle shield [(b) (4)] contains [(b) (4)] Dry natural rubber which has been reflected in the final prescribing information.

- Dating Period and Storage Conditions:
  The dating period for the DP is 24 months when stored at 2-8°C (pending on final stability updates committed to be submitted in February 2021)

- List of Co-Package Components (if applicable): None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C in the original carton
- Protect from light
- Do not shake
- Do not freeze
- Discard syringe if frozen
- Discard syringes stored at room temperature for more than 72 hours

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS intermediate manufacturing and QC testing (except potency), cell bank preparation and storage	[redacted]	[(b) (4)]	Pending PLI	N/A	Deferred – Travel Restrictions - COVID
DS manufacturing, in-process control, and QC testing [(b) (4)]			Pending PLI	N/A	Deferred – Travel Restrictions - COVID
DS intermediate and DS QC and stability testing			Pending PLI	N/A	Deferred – Travel Restrictions - COVID
Cell bank testing and storage			No Evaluation Necessary	N/A	N/A

	(b) (4)				
DRUG PRODUT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture and device assembly	(b) (4)		The inspection of the DP facility has been waived based on inspection history	N/A	Approved
DP QC and stability testing			Inspection is needed before approval	N/A	Deferred – Travel Restrictions - COVID
Labeling and secondary packaging	Fresenius Kabi USA, LLC 5200 Corporate Parkway West Wilson, NC 27893-9412 United States of America	FEI: 3008887707	No evaluation necessary	N/A	N/A
	Fresenius Kabi Austria GmbH Am Gewerbepark 6 8402 Werndorf Austria	FEI: 3003708554	No evaluation necessary	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for MSB11455 DP manufacture. The proposed manufacturing for this facility is acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

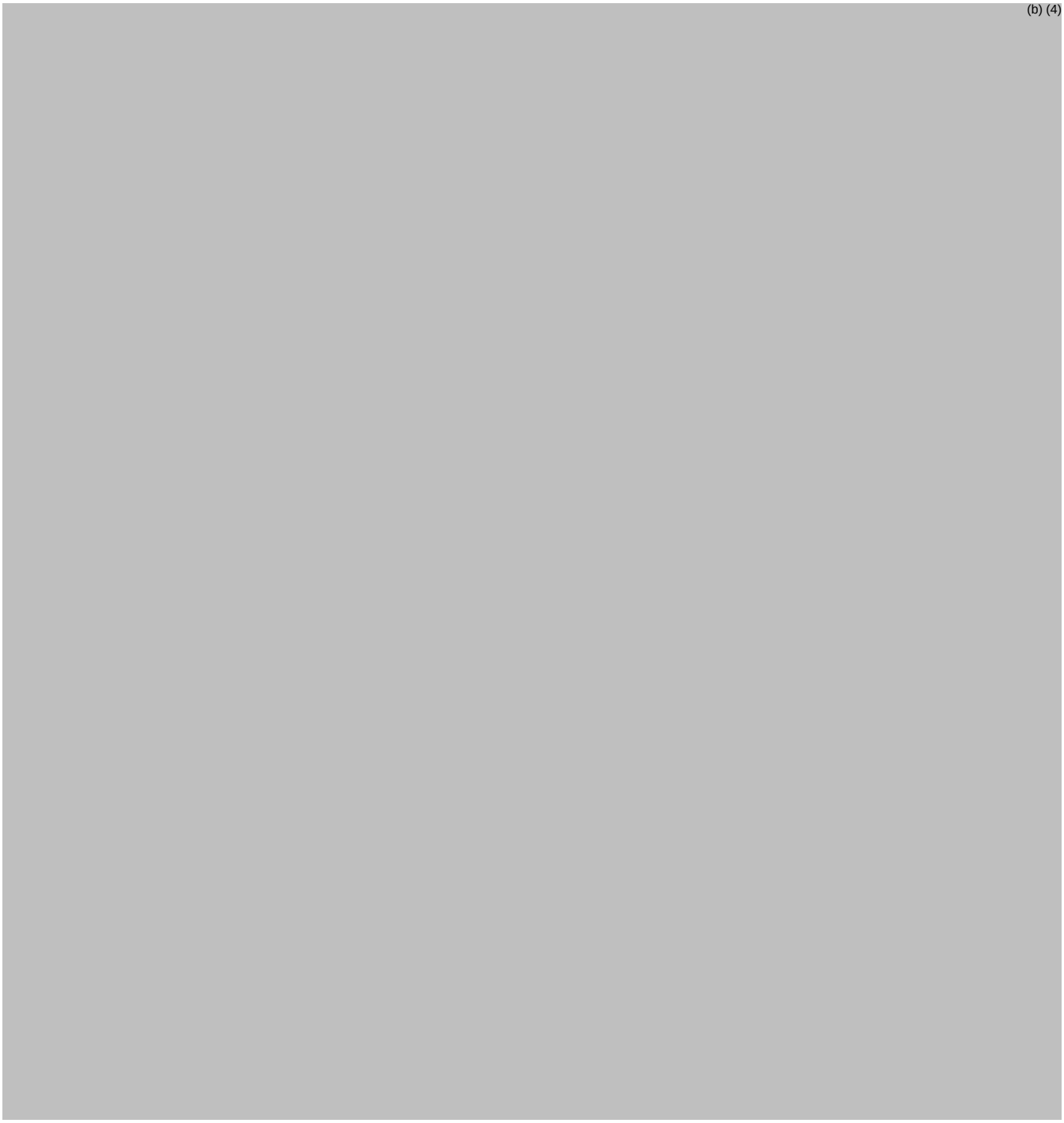
Inspections of the G-CSF intermediate manufacturing facility (b) (4) MSB11455 DS manufacturing facility (b) (4) as well as quality control testing and comparative analytical assessment site (b) (4) are required before the application can be approved. Due to restrictions on travel, OPQ may be unable to conduct inspections of these facilities prior to the User Fee Date.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

(b) (4)



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

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category

3.2.P.8.2	Annual stability protocol for MCB11455 DP with shelf-life extension	At 5 ± 3°C at least one bath per year at initial, 3, 6, 12, 18, 24, 30, 36 months, according to the tests and AC listed in 3.2.P.5.1 Specification.	Stability updates will be provided annually as part of the Annual Report

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

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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

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/s/

YAN WANG
08/01/2022 05:26:17 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Submission Tracking Number:	761173/0000
Subject:	New Biologics License Application
Review/Revision Date:	10/02/2020
Primary Reviewer:	Yarery Smith, Ph.D., Microbiologist
Secondary Reviewer:	Dupeh Palmer-Ochieng, Ph.D., Microbiologist
Applicant:	Fresenius Kabi USA, LLC
US License Number:	2146
Product:	pegfilgrastim-xxxx (MSB11455)
Manufacturing Sites:	(b) (4)
Indication:	Reduce the chance of infection due to a low white blood cell count
Dosage Form:	Solution for Injection, 6 mg/0.6 mL
FDA Receipt Date:	03/27/2020, 05/19/2020, 09/15/2020, and 10/13/2020
Action Date:	03/26/2021

Recommendation for Approvability: (STN) The drug product BLA 761173/0000 was reviewed from a product quality microbiology/sterility assurance and/or cross-contamination control perspective and is recommended for approval.

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT: DRUG PRODUCT

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	03/27/2020	Original BLA
0002	05/19/2020	IR-1 response
0013	09/15/2020	IR-2 Response
0017	10/13/2020	IR-3 Response

The following DMF was additionally reviewed for this submission:

DMF #	Dates Reviewed	Finding	Document Name
501	03/26/2020	Adequate	D501M76R01.doc
	06/01/2020		
	06/17/2020		
	09/15/2020		
	10/14/2020		

MODULE 1
1.14 LABELING

The drug product is administered subcutaneously via a single-dose pre-filled syringe (PFS) for manual use.

The suggested dose for patients with cancer receiving myelosuppressive chemotherapy and some directions for administration are as follows:

- 6 mg administered subcutaneously once per chemotherapy cycle.
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.
- Use weight-based dosing for pediatric patients weighing less than 45 kg:

Body Weight	Stimufend 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

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Stimufend.

Reviewer's Comment: There are no reconstitution and/or dilution procedures recommended for this drug product.

SATISFACTORY

MODULE 3.2.P – DRUG PRODUCT

P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Reviewer's comment: The drug product is a sterile, preservative-free solution for injection intended for subcutaneous administration.

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.4 Container Closure System

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/s/

YARERY C SMITH
02/10/2021 09:09:14 AM

Recommendation: pending final assessment of facilities compliance

BLA Number: 761173
Review Number: 1
Review Date: February 3, 2021

Drug Name/Dosage Form	MSB11455 injection (pre-filled syringe for single dose injection)
Strength/Potency	6 mg/0.6 mL
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	MSB11455 is a proposed biosimilar to US-licensed Neulasta for the following indication: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Applicant/Sponsor	Fresenius Kabi USA, LLC

Product Overview

MSB11455 is a covalent conjugate of recombinant methionyl human granulocyte-colony stimulating factor (G-CSF) produce in *Escherichia coli* (*E. coli*) (b) (4) and a 20 kDa monomethoxypolyethylene glycol propionaldehyde (mPEG). MSB11455 is a proposed biosimilar to the US-licensed Neulasta. Endogenous G-CSF is the primary regulating factor for neutrophils. G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. MSB11455 drug product (DP) is a sterile, clear, colorless, preservative-free solution. Each DP vial contains 6 mg/0.6 mL of MSB11455 at concentration of 10 mg/mL with pH of 4.0. Each mL of solution contains 10.0 mg MSB11455, 50.0 mg (b) (4) sorbitol, (b) (4) 0.03 mg polysorbate 20 and water for injection. The recommended dose for MSB11455 is same as the US-licensed Neulasta (i.e., 6 mg administered subcutaneously once per chemotherapy cycle).

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Pick-Wei Lau	OPQ/OBP/DBRRII
Product Quality (small molecule - mPEG and pegylation aspects of DS)	Rohit V. Tiwari	OPQ/ONDP/DNDAPI/NDB1
Labeling	James Barlow Pick-Wei Lau	OPQ/OBP OPQ/OBP/DBRRII
Facility	Yun Wu (DS) Yarery Smith (DP)	OPQ/OPMA/DBM/BMB2
Microbiology	Yun Wu (DS) Yarery Smith (DP)	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Team Lead	Yan Wang (product quality) Dupeh Palmer (microbiology DP) Peter Qiu (microbiology DS and facility) Ali Al Hakim (small molecule)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB1 OPQ/OPMA/DBM OPQ/ONDP/DNDAPI
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII

OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
OBP Biosimilar Policy	Marlene Schultz-DePalo	OPQ/OBP
OBP Associate Director of Biosimilar and Biologic Policy	Joel Welch	OPQ/OBP
RBPM	Florence Aisida/Hamet Toure	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Courtney Hamilton	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Julie Weisman	OND/OCHEN/DNH
Pharm/Tox	David Carlson; Todd Bourcier	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Kunal Jhunjhunwala; Anusha Ande; Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Jiaxi Zhou; Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Stimufend (proposed)
   b. Trade Name: Stimufend (proposed)
   c. Non-Proprietary Name/USAN: pegfilgrastim
   d. Chemical Abstract Service (CAS) Registry Number: 208265-92-3
   e. International Union of Pure and Applied Chemistry (IUPAC) Number: N-(3-hydroxypropyl) methionyl colony-stimulating factor (human), 1-ether with alpha-methylomega-hydroxypoly (oxyethylene)
   f. INN Name: pegfilgrastim
   g. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [MSB11455]
   h. Other name(s): MSB11455 and B3114 for pegfilgrastim, S152 for G-CSF (company code)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761173/SN0001 (Original submission)	March 27, 2020 (OBP and OPMA)
STN 761173/SN0002 (Information request (IR) response)	May 19, 2020 (OPMA-DP)
STN 761173/SN0004 (IR response)	June 29, 2020 (OPMA-DS)
STN 761173/SN0006 (IR response)	August 4, 2020 (ONDP)
STN 761173/SN0007 (IR response)	August 6, 2020 (OPMA-DS)
STN 761173/SN0008 (IR response)	August 13, 2020 (OBP-IR1)
STN 761173/SN0010 (IR response)	August 28, 2020 (OPMA-facility)
STN 761173/SN0013 (IR response)	September 15, 2020 (OPMA-DP)
STN 761173/SN0015 (IR response)	October 2, 2020 (OBP-IR2)
STN 761173/SN0017 (IR response)	October 13, 2020 (OPMA-DP)
STN 761173/SN0019 (IR response)	October 30, 2020 (OPMA-DS)
STN 761173/SN0020 (IR response)	November 9, 2020 (OBP-IR3)
STN 761173/SN0021 (IR response)	November 13, 2020 (CDRH)
STN 761173/SN0022 (IR response)	November 19, 2020 (CDRH)
STN 761173/SN0023 (IR response)	November 20, 2020 (OBP-IR5-1)
STN 761173/SN0024 (IR response)	November 24, 2020 (OBP-IR4)
STN 761173/SN0025 (IR response)	December 7, 2020 (OBP-IR3-follow up)
STN 761173/SN0026 (IR response)	December 7, 2020 (OBP-IR5-2)
STN 761173/SN0027 (IR response)	December 9, 2020 (OBP-IR6)

STN 761173/SN0029 (IR response)	December 9, 2020 (CDRH)
STN 761173/SN0030 (IR response)	December 11, 2020 (OBP-IR5-2-follow up)
STN 761173/SN0032 (Late cycle meeting minutes)	December 18, 2020 (revised timeline for microbiology DS PMCs)
STN 761173/SN0033 (IR response)	December 23, 2020 (OBP-IR7)
STN 761173/SN0035 (IR response)	January 8, 2021 (OBP-IR8)
STN 761173/SN0037 (IR response)	February 1, 2021 (CDRH)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	3	Adequate	N/A	N/A
	III			3	Adequate	N/A	N/A
	N/A			3	Adequate	N/A	Defer to CDRH
	II			1	Adequate	10/22/20	Reviewed by CDER/OPQ/ ONDP

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

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	113717	Parent IND

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH-OPEQ-OHTIII/DHTIIIC	May 19, 2020	Complete (2/3/2021)	Approvable	Gang Peng/Rumi Young

4. Environmental Assessment:

   Fresenius Kabi USA, LLC claimed a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (b), action on a BLA when the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Fresenius Kabi claims that to their knowledge there are no extraordinary circumstances as described in 21 CFR 25.15(d). Thus, no environmental assessment is required.

   The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The recommendation for STN 761173 from the Office of Pharmaceutical Quality (OPQ), CDER, is pending on the final assessment of facilities compliance. Inspections of the G-CSF intermediate manufacturing facility (b) (4) , the MSB11455 DS manufacturing facility (b) (4) as well as the quality control testing and comparative analytical assessment site (b) (4) are required before the application can be approved. The Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER must assess the ability of the facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, OPQ may be unable to conduct inspections of these facilities prior to the User Fee Date. OPMA will continue to monitor the public health situation as well as travel restrictions. OPMA is actively working to define an approach for scheduling outstanding inspections once safe travel may resume based on public health need and other factors.

From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER as well as OPMA, OPQ, CDER do not note any product quality deficiencies that would preclude approval of STN 761173 for MSB11455 manufactured by Fresenius Kabi USA, LLC at this time. The analytical similarity data submitted in the application demonstrate that MSB11455 is highly similar to US-licensed Neulasta. If Fresenius Kabi USA, LLC submits additional manufacturing information during this review cycle, additional assessment may be needed during the current assessment cycle.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - G-CSF intermediate (uppegylated G-CSF): (b) (4)
    - MSB11455 drug substance (pegylated G-CSF): (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 6 mg in 0.6 mL (10 mg/mL) solution in a pre-filled syringe

- Dating period:
  - Drug Product: 24 months at 2-8°C (pending on final stability updates committed to be submitted in February 2021)
  - Drug Substance: (b) (4) months at (b) (4) °C
  - G-CSF intermediate: (b) (4) months at (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols: We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.

- Exempt from lot release in accordance with 21 CFR 601.2a. MSB11455 is a specified product.

C. Benefit/Risk Considerations:

MSB11455 is a proposed biosimilar to US-licensed Neulasta. The applicant requested the neutropenia indication for which US-licensed Neulasta is approved.

Review of manufacturing has identified that the methodologies used for G-CSF intermediate, MSB11455 DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. In addition, the microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product.

Inspections of the G-CSF intermediate and MSB11455 DS facilities as well as the quality control testing and comparative analytical assessment site are required before this application can be approved as OPMA must assess the ability of the facility to conduct the listed manufacturing operations in compliance with cGMP. However, due to US Government and/or Agency-wide restrictions on international travel under COVID-19 pandemic, OPQ may be unable to conduct inspections prior to the User Fee Date.

The data provided in the BLA support a determination that MSB11455 is highly similar to U.S.-licensed Neulasta.

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

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

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

Quality - (b) (4)

OPMA-1: Complete bioburden and endotoxin method verification (b) (4)

Final report submission date: April 2021

OPMA-2: Complete microbial purity method verification with a total of 3 commercial-scale batches and provide the final method verification report.

Final report submission date: April 2021

Quality - (b) (4)

OPMA-3: Review and adjust microbial control limits of in-process pools based on process capability.

Final report submission date: April 2021

OBP-1: To complete a real-time leachables study using the final container closure system (b) (4) to identify any potential leachables at initial, 6 and 12 months under storage condition (b) (4)

Final report submission date: December 2022

OBP-2: To complete a real-time leachables study using the final container closure system with MSB11455 drug substance to identify any potential leachables at initial, 6 and 12 months under storage condition (b) (4)

Final report submission date: December 2022

OBP-3: To complete a real-time leachables study using the final container closure system with MSB11455 drug product to identify any potential leachables at initial, 6, 12, 24 and 36 months under storage condition between 2°C -8°C.

Final report submission date: December 2024

OBP-4: To complete method development and implement a method (b) (4) for a (b) (4) in-process control.

Final report submission date: November 2021

OBP-5: To complete a viral inactivation study (b) (4) and to demonstrate that it is an effective step for inactivation of viruses that may be present.

Final report submission date: December 2021

CDRH-1: To update the design verification package which will include the needle safety activation, needle safety override, resistence to pre-activation after shipping simulation and resistence to pre-activation after droptesting. The verification will be performed using the final finished combination product from the final commercial manufacturing process using a sample size of n=299 in order to meet 99% reliability (at 95% of confidence level) for each verification test.

Final report submission date: June 2021 (pending on the final commitment from the Applicant)

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

A. Summary of Comparative Analytical Assessment

a. Analytical Assessment Overview and Conclusions

The Applicant provided results of the comparative analytical assessment to support a demonstration that MSB11455 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. The Applicant ranked the criticality of the quality attributes based on their potential impact on activity, pharmacokinetic (PK)/ pharmacodynamic (PD), safety and immunogenicity.

For the selected quality attributes with highest criticality (i.e., protein concentration as well as pegfilgrastim induced M-NFS-60 cell proliferation of relative potency and specific activity), both an equivalence test approach where the pre-determined equivalence margin for demonstrating similarity was defined as ± 1.5 X standard deviation (SD), and a quality range (QR) approach where the QR was set based on the range of the values obtained from US-licensed Neulasta lot variations expressed as ± XSD (the multiplier X=2 was used), were applied. For the selected quality attributes with moderate to very high criticality, the QR approach with multiplier as X=3 was applied. For quality attributes with low criticality, tested with orthogonal tests or tested with qualitative test methods, raw data (RD) or graphical data were presented. The selected approaches for comparative analytical assessment are consistent with FDA Draft Guidance: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019). The selected multiplier X used in the QR approach, which are based on the criticality of the quality attributes, sensitivity of the analytical methods, abundance of the quality attributes, the distribution of the quality attributes and the type of the analytical methods, is justified. Results from method validation or qualification studies support the suitability of the methods used in the comparative analytical assessment.

The Applicant compared 16 independent lots of MSB11455 and 28 lots of US-licensed Neulasta. The 16 MSB11455 lots included the lots used in the PK/PD similarity study EMR200621-001 and the comparative clinical study EMR200621-003 evaluating safety/immunogenicity as well as the process performance qualification (PPQ) lots manufactured by the proposed commercial manufacturing process. The Applicant tested MSB11455 and US-licensed Neulasta using multiple orthogonal methods to adequately evaluate the necessary quality attributes of the products.

The expiry dates of the US-licensed Neulasta lots ranged from June 2015 to June 2020, which spans the shelf-life of US-licensed Neulasta and were adequate to capture potential reference product differences over time. The Applicant also performed comparative forced degradation studies under mechanical, pH, light, thermal and oxidative stress conditions. The comparative forced degradation studies support that MSB11455 and US-licensed Neulasta have a similar degradation profile.

Two types of bioactivity assays reflecting the mechanism of action of US-licensed Neulasta and MSB11455 were conducted. In vitro potency was determined using a murine myelogenous leukemia cell line (M-NFS-60 cell line) to evaluate the receptor-activated hematopoietic cell proliferation induced by the products. The Applicant chose to evaluate results from the in vitro cell-based assay for both relative activity and specific activity with an equivalence test as well as a QR approach because of the high risk level for this critical quality attribute. A surface plasmon resonance (SPR) assay with a Biacore instrument to measure G-CSF receptor binding affinity was conducted. The comparison of G-CSF receptor binding affinity (equilibrium dissociation constant-KD) by a QR approach as well as the association constant (Ka) and dissociation constant (Kd) by a RD approach support a determination that the higher order structure required for binding to the receptor and response binding kinetics are similar between MSB11455 and US-licensed Neulasta. The two bioactivity assays support the proposed mechanism of action of MSB11455.

Our assessment of the MSB11455 and US-licensed Neulasta data supports a demonstration that MSB11455 is highly similar to US-licensed Neulasta, notwithstanding minor differences in clinically inactive components. MSB11455 has the same strength, dosage form, and route of administration as US-licensed Neulasta. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of MSB11455 and US-licensed Neulasta to support a demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. Observed differences do not preclude a demonstration that MSB11455 is highly Similar to US-licensed Neulasta.

b. Results of Comparative Analytical Assessment

The results of the analytical comparisons that support a demonstration that MSB11455 is highly similar to US-licensed Neulasta are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
Primary Structure	Amino acid sequence	Yes
	Comparison of levels of post translational modifications (oxidation at Met122, Met127, Met138; total oxidation; deamidation at Gln26; succinimide at Asp28)	Yes
	mPEG attachment site	Yes
	Extinction coefficient	Yes
	Molecular weight	Yes*
	Polydispersity of molecular weights distribution	Yes
Higher Order Structure	Disulfide bonds and free sulfhydryl groups	Yes
	Secondary structure (fluorescence spectroscopy, Far-UV CD & 2D NMR spectra)	Yes
	Tertiary structure (near UV CD & 2D NMR spectra)	Yes
	Thermal stability (DSC)	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed		Supports a Demonstration of Highly Similar
Product-Related Substance and Impurities	Size variants and impurities	Monomer/purity (SE-HPLC, AUC, SEC-MALLS and reduced CGE-SDS)	Yes*
		High molecular weight (HMW) species (e.g., aggregates, dimer & Di-Peg/HMW) (SE-HPLC, AUC and SEC-MALLS)	Yes*
		Low molecular weight (LMW) species (e.g., fragments, free G-CSF and free mPEG) (SE-HPLC, AUC, SEC-MALLS, reduced CGE-SDS, SDS-PAGE and RP-HPLC)	Yes
	Charge variants	Acidic variants (icIEF and SCX-HPLC)	Yes
		Main species (icIEF and SCX-HPLC)	Yes*
		Basic variants (icIEF and SCX-HPLC)	Yes
	Hydrophobic variants	Pre-peak groups (RP-HPLC) (M-1, M-2 and M-3)	Yes*
		Main species (RP-HPLC)	Yes*
		Post peak groups (RP-HPLC) (M+1, M+2 and M+3)	Yes*
Bioactivity	G-CSF receptor binding (SPR)	Binding affinity KD	Yes
		Binding kinetics Ka	Yes
		Binding kinetics Kd	Yes
	M-NFS-60 cell proliferation	Relative potency	Yes
		Specific activity	Yes
Drug Product Attributes	Protein concentration		Yes

"Yes*": Differences were noted, but do not preclude a determination of highly similar and will be explained further below.

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

Not applicable.

Data generated from studies using EU-approved Neulasta were not used to support a demonstration of biosimilarity. Therefore, the analytical testing results from 24 lots of EU-approved Neulasta submitted in the BLA in section 3.2.R Regional Information were not assessed, as there was no need to establish an adequate scientific bridge.

d. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all quality attributes with the following exceptions between MSB11455 and US-licensed Neulasta:

- Molecular weight: the molecular weight (MW) measured by MALDI-TOF analysis is from 39767.8 to 40950.0 Da for MSB11455 and is from 39999.9 to 40264.7 Da for US-licensed Neulasta, respectively. The data showed that the MW of mPEG used to manufacture MSB11455 drug substance is in a good alignment with the mass of MSB11455 indicating that the MW differences are due to the different sizes of mPEG used during manufacture. LC-MS/MS results suggest that the mPEG used for US-licensed Neulasta is centered at an average MW of ~20.9 kDa, whereas the mPEG used for these MSB11455 lots is centered at an average MW of ~21.7 kDa. However, the polydispersity index determined by LC-MS used as a measure of MW distribution of mPEG is similar between MSB11455 (1.0003) and US-licensed Neulasta (1.0003-1.0004) suggesting the similar mPEG quality and MW distribution. In addition, the size of the mPEG used in the manufacture of MSB11455 is controlled in the specification with the

acceptance criterion as (b) (4) kDa. The highly flexible mPEG molecule is predicted to form a thick, flexible layer across the surface of the protein and thereby increase the hydrodynamic radius of pegylated protein which impacts its in vivo residence time, the half-life and bioactivity. The hydrodynamic radius (by SEC-MALLS) ranges of all tested MSB11455 lots (5.3 nm - 6.1 nm) are within the hydrodynamic radius ranges of US-licensed Neulasta (5.3 nm - 8.9 nm) lots. The bioactivity ranges of all tested MSB11455 lots are within the bioactivity QR of US-licensed Neulasta. These data suggest that the differences in MW between MSB11455 and US-licensed Neulasta have a minimal impact on the PK and bioactivity. We consulted with the clinical pharmacology reviewers, who reviewed this PK/PD similarity study EMR200621-001 and found the results corroborate with the analytical finding, and the data suggested that the minor difference in MW would not differentially impact the PK/PD profiles. Therefore, the differences in MW between MSB11455 and US-Neulasta do not preclude a demonstration of highly similar.

- Size variants and impurities: all size variants and impurities detected by SE-HPLC, AUC, SEC-MALLS, and reduced SDS-PAGE in MSB11455 lots are also observed in US-licensed Neulasta with similar level with exception of % Di-Peg/HMW and % monomer determined by SE-HPLC. % Di-Peg/HMW (~62.7 kDa) measured by SE-HPLC in MSB11455 (0.48-1.67%) is outside the QR of US-licensed Neulasta (0.85-1.58%). The differences in % Di-Peg/HMW might theoretically impact the PK and bioactivity. Due to the differences in the % Di-Peg/HMW determined by SE-HPLC, the %monomer (~39 kDa) in MSB11455 (97.89-99.30%) is slightly outside the QR of US-licensed Neulasta (97.91-98.86%) although the aggregates including dimer and other HMW determined by SE-HPLC are similar. However, based on the bioactivity data, the bioactivity is similar between MSB11455 and US-licensed Neulasta despite the small differences in levels of % Di-Peg/HMW. Overall the slight differences in % Di-Peg/HMW do not impact the bioactivity as evidenced by results showing similar bioactivity between MSB11455 and US-licensed Neulasta. Furthermore, the small difference in the maximum levels of % Di-Peg/HMW for MSB11455 of 0.2% compared to US-licensed Neulasta is not expected to impact PK. We consulted with the clinical pharmacology reviewers, and the PK data are consistent with the conclusion that similar PK and PD profiles were obtained from MSB11455 and US-licensed Neulasta lots used in the PK/PD similarity study EMR200621-001 (refer to the Biosimilar Multi-Disciplinary Evaluation and Review (BMER) for details) despite the % Di-Peg/HMW contents from the MSB11455 (1.09 %) and US-licensed Neulasta (1.5 %) lots being slightly different. Therefore, the small differences in % Di-Peg/HMW and %monomer do not preclude a demonstration of highly similar.

- Charge variants: the charge variants evaluated by icIEF were further assessed by SCX-HPLC. The acidic groups of Cluster 1, Cluster 2 and Cluster 3 by icIEF contain positional isomers of mono-pegylated protein (Lys 35 or Lys 41) and forms with deamidation at Gln68 or Gln174, and Cluster 2 also contains dimer and dipegylated (Met 1 and Lys 35 or Lys 41) forms. The major isoform (Cluster 4 and Cluster 5) by icIEF were identified by SCX-HPLC as native mono-pegylated MSB11455 (correlated to Cluster 4) and basic isoforms with oxidation at Met122, Met127 or Met138 (correlated to Cluster 5).

  For native mono-pegylated pegfilgrastim (Cluster 4), 85% of MSB11455 lots were within the QR of US-licensed Neulasta (52.82 – 65.36%). One lot of MSB11455, BA052548P had the level of Cluster 4 (65.78%) above, but very close to, the upper QR of US-licensed Neulasta (65.36 %) lots. One lot of MSB11455, BA051607P, had the level of Cluster 4 (52.73%) below, but very close to, the lower QR of US-licensed Neulasta (52.82%). However, MSB11455 and US-licensed

Neulasta lots contain similar levels of Cluster 1, Cluster 2, Cluster 3 and Cluster 5 (more than 90% of MSB11455 lots within the QR of US-licensed Neulasta). In addition, the bioactivity is similar between MSB11455 and US-licensed Neulasta. Therefore, the slightly higher level of Cluster 4 observed in BA052548P and slightly lower level of Cluster 4 observed in BA051607P are highly unlikely to be clinically significant and do not preclude a demonstration of highly similar.

- Hydrophobic variants: RP-HPLC is used to separate variants based on their capacity to create hydrophobic interaction. Peak characterization studies suggest that main peak corresponds to the molecule intact form; all pre-peaks (M-3, M-2 and M-1) have positional isomers of mono-pegylated species where M-1 also contains variants with oxidation at Met138, but M-2 and M-3 contain variants with oxidation at Met122 and Met127; post peaks M+1 and M+2 contain di-pegylated forms (Met1 and Lys35 or Lys41) and/or positional isomers of mono-pegylated forms (Lys35 or Lys41) where M+1 also contains variants with deamidation at Gln68 and Gln174 as well reduced variants, but M+2 contains variants with deamidation at Gln108 and species related to G-CSF as well as pegylation variants, and post peak M+3 contains dimer.

  The differences were observed for main species, M-1 peak, overall total oxidation levels, M+2 peak and overall total deamidation levels between MSB11455 and US-licensed Neulasta. Specifically, for main species 77% of MSB11455 lots (min-max: 95.16-97.37%) is within the QR of US-licensed Neulasta (94.43 – 97.24%); for M-1 54% of MSB11455 lots (min-max: 0.98-1.28%) is within the QR of US-licensed Neulasta (0.56 - 1.07%); for total oxidation 77% of MSB11455 lots (min-max: 1.27 - 1.62%) is within the QR of US-licensed Neulasta (0.82 - 1.48%); for M+2 54% of MSB11455 lots (min-max: 0.13 - 1.65%) is within the QR of US-licensed Neulasta (0.16 - 1.24%); for total deamidation 54% of MSB11455 lots (min-max: 1.24 - 3.53%) is within the QR of US-licensed Neulasta (1.66 - 4.36%). The difference for M-1 is mainly due to the Met138 oxidation. However, the small differences in total oxidation have minimal impact on potency based on the characterization data where up to 12.25% total oxidation by RP-HPLC does not impact binding affinity to G-CSF-R or G-CSF-mediated cell proliferation. In addition, similar levels of Met122, Met127, Met138 and total oxidation were observed between MSB11455 and US-licensed Neulasta by peptide mapping LC-ESI-MS/MS. The difference for M+2 is mainly due to the Gln108 deamidation. But the levels of total deamidated forms in MSB11455 lots are the same or lower than those present in US-licensed Neulasta, and lower levels would not be expected to have an adverse impact on clinical efficacy or safety. The differences for main species are due to the differences for M-1 peak, overall total oxidation levels, M+2 peak and overall total deamidation levels. Overall the differences in hydrophobic variants do not impact the bioactivity because the bioactivity is similar between MSB11455 and US-licensed Neulasta. Therefore, these differences in hydrophobic impurities do not preclude a demonstration of highly similar.

  In summary, based on the above, there are no residual uncertainties regarding the comparative analytical assessment that would preclude a demonstration that MSB11455 is highly similar to US-licensed Neulasta.

B. Same Strength(s)

MSB11455 has the same dosage form and route of administration as US-licensed Neulasta. Fresenius Kabi USA, LLC (Fresenius Kabi) is seeking approval of 6.0 mg/0.6 mL MSB11455 in a prefilled syringe.

US-licensed Neulasta is available at this strength as 6.0 mg/0.6 mL in a prefilled syringe. Fresenius Kabi is seeking approval of MSB11455 for the same strength as US-licensed Neulasta. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. (b) (4) The proposed presentation of MSB11455 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Neulasta (6 mg/0.6 mL). The strength of MSB11455 prefilled syringe is the same as that of US-licensed Neulasta.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for MSB11455

Table 1: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
In vitro cell-based bioassay (potency)	Efficacy	Intrinsic to the molecule, impacted by exposure to heat, oxidation reagent stress and light stress	(b) (4)	(b) (4)
Receptor binding	Efficacy	Intrinsic to the molecule		Binding kinetics are characterized by binding affinity (equilibrium dissociation constant-KD), the association constant (Ka) and dissociation constant (Kd)
Identity	Efficacy and Safety	Intrinsic to the molecule		N/A

(b) (4)

HMW species (Product related impurity)	PK and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, low pH, mechanical stress, oxidation reagent stress, and light stress
LMW species/Fragments (Product related impurity)	Efficacy, PK and Safety (Immunogenicity)	Manufacturing process, and exposure to low pH, heat, mechanical stress, and light stress
Hydrophobic variants including oxidized, deamidated and reduced impurities as well as positional mono-pegylated isomers)	Efficacy and safety (Immunogenicity)	Manufacturing process and exposure to heat, oxidation reagent stress and light stress
Charge variants including oxidized impurity, Di-Peg/HMW and positional mono-pegylated isomers	Efficacy and PK	Manufacturing process and exposure to heat, oxidation reagent stress and light stress

B. Drug Substance (MSB11455) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process	(b) (4)	Assessed by CDER/OPQ/OPMA team (b) (4)
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process		Assessed by CDER/OPQ/OPMA team
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Appearance (General)	Stability	Formulation components and stability		N/A
Degree of coloration (General)	Stability	Formulation components and stability		N/A
Clarity and degree of opalescence (General)	Stability	Formulation components and stability		N/A
(b) (4)	Stability	Formulation component and stability		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line, bioreactor and harvest, cell viability and % viable cell density		(b) (4)

				(b) (4)
Host cell protein (Process related impurity)	Safety (Immunogenicity) and Purity	Production cell line, bioreactor and harvest cell viability and % viable cell density	(b) (4)	
(b) (4)	Safety and Purity	(b) (4)		Assessed also by CDER/OPQ/ONDP team
Residual (b) (4) (Process related impurity)	Safety and Purity			Assessed also by CDER/OPQ/ONDP team
(b) (4) (Process related impurity)	Safety and Purity	Cell banks, raw materials		(b) (4)
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and (b) (4) DS container closure system (CCS)		PMCs to complete a real time leachables study using the final CCS for (b) (4) DS through the shelf-life
Culture medium additives, buffer components and other added materials (b) (4)	Safety and Purity	(b) (4)		Levels are below toxicological concern based on the risk assessment for non-animal derived materials

			(b) (4)	

- Description:
  G-CSF intermediate, a non-glycosylated recombinant methionyl human granulocyte colony stimulating factor, is produced in E. coli. The G-CSF intermediate is composed of 175 amino acids which is identical to natural G-CSF, except for an additional methionine residue at the N-terminus. G-CSF intermediate is an antiparallel, four α-helix bundle arranged in an up-up and down-down topology with a left-handed twist. To produce MSB11455, a 20 kDa mPEG-PAL molecule is covalently bound to the N-terminal methionyl residue of G-CSF intermediate. MSB11455 possesses two disulfide bonds between cysteine residues Cys37 and Cys43, and between Cys65 and Cys75, maintaining the biologically active conformation of G-CSF. The average molecular weight of MSB11455 is approximately 39 kDa. MSB11455 is a proposed biosimilar to US-licensed Neulasta.

- Mechanism of Action (MoA):
  G-CSF binds to G-CSF receptors, which stimulates proliferation, differentiation, commitment, and target cell functional activation. Endogenous G-CSF is known to stimulate proliferation of mitotic cells, to reduce the maturation time of non-mitotic cells in the bone marrow, and to prolong the life span and enhance the function of mature neutrophils. Pegylated G-CSF has the same MOA as G-CSF.

- Potency Assays:
  A cell-based bioassay is used to determine the potency of G-CSF intermediate or MDB11455 DS based on its ability to stimulate the G-CSF dependent proliferation of G-CSF-adapted M-NFS-60 murine myelogenous leukemia cells. Specifically, after incubation of M-NFS-60 cells with 30 ng/mL G-CSF intermediate or MDB11455 DS, a cell-permeable resazurin-based dye, that is reduced to fluorescent resorufin in viable cells, is added. The resulting fluorescence is then read at an excitation wavelength of 560 nm and an emission wavelength of 590 nm. The fluorescence measured is proportional to cell proliferation. The potency of G-CSF intermediate or MSB11455 DS test samples is determined in comparison to the EC50 of the relevant G-CSF intermediate reference standard or MSB11455 DS reference standard, respectively.

- Reference Materials:
  - (b) (4)

(b) (4)

- For MSB11455 DS: A two-tiered reference material system is in place. The current primary reference standard - (b) (4) and working reference standard - (b) (4) The Applicant has provided sufficient data to bridge the current primary reference standard with the clinical reference standard used in the clinical studies and the reference standards used in the comparative analytical assessment. Therefore, the current primary and working reference standards are representative of the clinical and manufacturing experiences as well as materials used to support a demonstration of analytical similarity with US-licensed Neulasta. A protocol is provided for the qualification of future primary and working reference standards. The protocol contains adequate testing and acceptance criteria. The procedures (i.e., requalification) to monitor the potential changes and stability of the primary and working reference standards are appropriate.

- Critical Starting Materials or Intermediates:

(b) (4)

- Manufacturing Process Summary:

(b) (4)

(b) (4)

- Container Closure System:

(b) (4)

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

  The dating period for the (b) (4) is (b) (4) months when stored at (b) (4) °C.

C. Drug Product (MSB11455) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process	(b) (4)	Assessed by CDER/OPQ/OPMA team
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		Assessed by CDER/OPQ/OPMA team
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DP		N/A
Appearance (General)	Stability	Formulation components and stability		N/A
Degree of coloration (General)	Stability	Formulation components and stability		N/A
Clarity and degree of opalescence (General)	Stability	Formulation components and stability		N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Extractable volume (General)	Efficacy/Dosing	Fill process		N/A
Polysorbate 20 Concentration	Stability	Formulation component and stability		N/A
(b) (4)	Safety and Purity	(b) (4)		Assessed also by CDER/OPQ/ONDP team
Break loose and gliding force	Efficacy and Safety	Device performance		Assessed also by CDRH team
(b) (4)	Safety	CCS		(b) (4)

				(b) (4)
(b) (4)	Safety	CCS	(b) (4)	
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	Only evaluated a real time elemental leachables study for DP at 3 months under long-term storage condition at 2-8°C	PMC to complete a real time leachables study using the final CCS for DP through the shelf-life

- Potency and Strength:
  MSB11455 is supplied in a pre-filled syringe (PFS) at a strength of 6 mg/0.6 mL. MSB11455 was developed to have the same strength as US-licensed Neulasta. Potency is defined as the percent activity relative to the current MSB11455 primary reference standard. The potency assays are the same as described in the DS section of this memo.

- Summary of Product Design:
  MSB11455 is supplied as a sterile, single-dose, clear, colorless, preservative-free solution for subcutaneous injection in one strength. MSB11455 was developed as a biosimilar to US-licensed Neulasta and targets the quality profile of US-licensed Neulasta.

- List of Excipients:
  Each mL of solution contains 50.0 mg (b) (4) sorbitol, (b) (4) 0.03 mg polysorbate 20 and water for injection, pH 4.0.

- Reference Materials:
  The same reference standards are used for (b) (4) and DP.

- Manufacturing Process Summary:
  (b) (4)

- Container Closure System:
  The MSB11455 DP primary container closure system is a single-dose PFS consisting of a 1 mL [(b) (4)] glass syringe closed with a [(b) (4)] plunger stopper and combined with a 27 Gauge, [(b) (4)] steel needle protected by a rigid needle shield. The needle shield [(b) (4)] contains [(b) (4)] of Dry natural rubber which has been reflected in the final prescribing information.

- Dating Period and Storage Conditions:
  The dating period for the DP is 24 months when stored at 2-8°C (pending on final stability updates committed to be submitted in February 2021)

- List of Co-Package Components (if applicable): None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C in the original carton
- Protect from light
- Do not shake
- Do not freeze
- Discard syringe if frozen
- Discard syringes stored at room temperature for more than 72 hours

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS intermediate manufacturing and QC testing (except potency), cell bank preparation and storage	[redacted]	(b) (4)	Pending PLI	N/A	Deferred – Travel Restrictions - COVID
DS manufacturing, in-process control, and QC testing [(b) (4)]			Pending PLI	N/A	Deferred – Travel Restrictions - COVID
DS intermediate and DS QC and stability testing			Pending PLI	N/A	Deferred – Travel Restrictions - COVID
Cell bank testing and storage			No Evaluation Necessary	N/A	N/A

	(b) (4)				
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture and device assembly	(b) (4)		The inspection of the DP facility has been waived based on inspection history	N/A	Approved
DP QC and stability testing			Inspection is needed before approval	N/A	Deferred – Travel Restrictions - COVID
Labeling and secondary packaging			No evaluation necessary	N/A	N/A
			No evaluation necessary	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for MSB11455 DP manufacture. The proposed manufacturing for this facility is acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

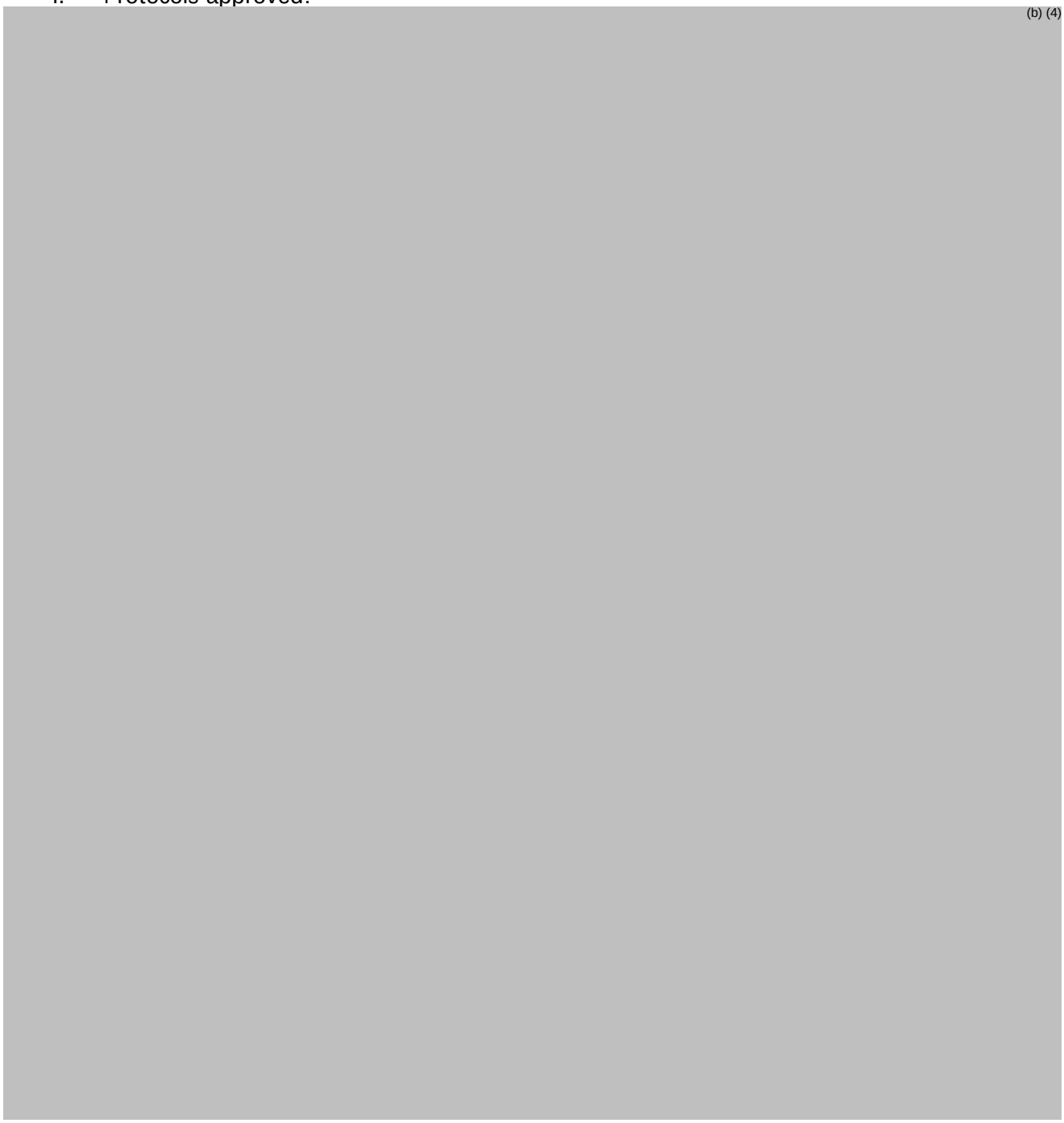
Inspections of the G-CSF intermediate manufacturing facility (b) (4) MSB11455 DS manufacturing facility (b) (4) as well as quality control testing and comparative analytical assessment site (b) (4) are required before the application can be approved. Due to restrictions on travel, OPQ may be unable to conduct inspections of these facilities prior to the User Fee Date.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

(b) (4)



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

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category

3.2.P.8.2	Annual stability protocol for MCB11455 DP with shelf-life extension	At 5 ± 3°C at least one bath per year at initial, 3, 6, 12, 18, 24, 30, 36 months, according to the tests and AC listed in 3.2.P.5.1 Specification.	Stability updates will be provided annually as part of the Annual Report

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

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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

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/s/

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