CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761148Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA Number: 761148
Assessment Number: 2
Assessment Date: August 5, 2022

Drug Name/Dosage Form	Rolvedon™ (eflapegrastim-xnst)/Injection, solution in single-dose, prefilled syringe
Strength/Potency	13.2 mg/0.6 mL (22 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia
Applicant/Sponsor	Spectrum Pharmaceuticals, Inc.

Product Overview:

Eflapegrastim-xnst (SPI-2012) is a granulocyte colony-stimulating factor (G-CSF) produced by covalent coupling of a human G-CSF analog and an Fc fragment of human immunoglobulin G4 (IgG4), both produced recombinantly in *Escherichia coli*, via a single 3.4 kDa polyethylene glycol (PEG) linker. Eflapegrastim-xnst binds to the G-CSF receptor (CD114) on myeloid progenitor cells and neutrophils and stimulates their differentiation, proliferation, migration, and survival, leading to an increased number of mature neutrophils in the blood. The human IgG4 Fc fragment in eflapegrastim-xnst increases the circulating half-life of G-CSF without inducing Fc-mediated effector functions.

The eflapegrastim-xnst drug product, Rolvedon, is supplied as a sterile, preservative-free, clear, colorless solution in a single-dose prefilled syringe. Each 0.6 mL single-dose prefilled syringe contains 13.2 mg eflapegrastim-xnst, citric acid monohydrate (2.52 mg), mannitol (30 mg), polysorbate 80 (0.72 mg), and sodium chloride (5.26 mg) in Water for Injection at pH of approximately 5.5.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance, Drug Product, Immunogenicity	Zhong Zhao	CDER/OPQ/OBP/DBRRIII
Labeling	Jennifer Kim	CDER/OPQ/OBP
Facility	Michael Shanks	CDER/OPQ/OPMA/DBM/BMB2
Microbiology	Reyes Candau-Chacon	CDER/OPQ/OPMA/DBM/BMB2
Team Lead	Massod Rahimi (OBP product quality) Madushini Dharmasena (facility and microbiology)	CDER/OPQ/OBP/DBRRIII CDR/OPQ/OPMA/DBM/BMB2
OPQ RBPM	Melinda Bauerlien	CDER/OPQ/OPRO/DRBPMI/RBPMB2
Application Team Lead	Massod Rahimi	CDER/OPQ/OBP/DBRRIII
Tertiary Assessor	Maria Gutierrez Lugo	CDER/OPQ/OBP/DBRRIII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	May Zuwannin	CDER/OND/ORO/DROCHEN
Cross-disciplinary Team Lead	Tanya Wroblewki	CDER/OND/OCHEN/DNH
Medical Officer	Hyon-Zyu Lee	CDER/OND/OCHEN/DNH
Pharmacology/Toxicology	Anthony Parola	CDER/OND/OCHEN/DPTCHEN

Clinical Pharmacology	Anusha Ande	CDER/OTS/OCP/DCEP
Statistics	Yeh-Fong Chen	CDER/OTS/OB/DBIX

1. Names:

   a. Proprietary Name: Rolvedon
   b. Trade Name: Rolvedon
   c. Non-Proprietary Name/USAN: eflapegrastim-xnst/eflapegrastim
   d. CAS Name/Registry Number: 1384099-30-2
   e. Common Name: SPI-2012
   f. INN Name: eflapegrastim
   g. OBP systematic name: CONJ: MAB FRAG HUMAN (IGG4 FC); RPROT P09919 (GCSF3_HUMAN); PEG [SPI2102]

2. Pharmacologic category: Leukocyte growth factor

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761148 SD 65/SN 0064 (Complete Response submission)	03/11/2022
STN 761148 SD 66/SN 0065 (Response to 03/29/2022 IR)	03/31/2022
STN 761148 SD 69/SN 0068 (Response to 06/07/2022 IR)	06/21/2022
STN 761148 SD 71/SN 0070 (Response to 06/28/2021 IR)	06/29/2022
STN 761148 SD 74/SN 0073 (Response to 07/25/2021 IR)	08/01/2022

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 Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs: For details on DMFs referenced in this BLA, refer to the original OPQ Executive Summary memo in DARRTS dated October 24, 2020.

   B. Other documents: Refer to the original OPQ Executive Summary memo in DARRTS dated October 24, 2020.

3. Consults: No consults were requested in this assessment cycle.

4. Environmental Assessment of Claim of Categorical Exclusion:
   In the original BLA submission, the Applicant claimed a categorical exclusion per 21 CFR 25.31 (c) from the environmental assessment requirements of 21 CFR 25.20. Categorical exclusion is appropriate for this product.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**
The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761148 for Rolvedon manufactured by Spectrum Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Rolvedon is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Draft Language:

- Manufacturing location:
  - GCSF intermediate: (b) (4)
  - (b) (4) intermediate: (b) (4)
  - Drug substance: (b) (4)
  - Drug product:
    - (b) (4) (drug product manufacturing)
    - (b) (4) [drug product labeling, assembly (prefilled syringe with needle guard), packaging, serialization, and storage]
- Fill size and dosage form: 13.2 mg/0.6 mL solution in a single-dose, prefilled syringe
- Dating period:
  - GCSF intermediate (b) (4) months when stored at (b) (4)
  - (b) (4) intermediate: (b) (4) months when stored at (b) (4)
  - Drug substance: (b) (4) months when stored at (b) (4)
  - Drug product: 24 months when stored at 2 – 8°C

C. Benefit/Risk Considerations:

Rolvedon (eflapegrastim-xnst) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. The efficacy of Rolvedon was demonstrated in two similarly designed, randomized, open-label, noninferiority, clinical studies that compared eflapegrastim with pegfilgrastim in patients with early-stage breast cancer receiving docetaxel and cyclophosphamide. In both studies, treatment of eflapegrastim was non-inferior to pegfilgrastim therapy. The major safety concerns for Rolvedon are consistent with those for other products in this class.

The overall Rolvedon control strategy incorporates control (b) (4) The BLA is recommended for approval from a product quality, microbiology, facilities, immunogenicity assays, device constituent performance, and quality labeling perspectives. The deficiencies observed during the inspection of the (b) (4) manufacturing facilities in the previous assessment cycle were resolved during the current assessment cycle.

The technical assessments for product quality (by OBP) and microbiology and facility (by OPMA) for the current assessment cycle are located as separate documents in Panorama.

D. Recommendation on Post-Marketing Commitments:

To qualify the bioburden test method with two additional drug product batches and submit the qualification report by April 2023.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management
Refer to the original OPQ Executive Summary memo in DARRTS dated October 24, 2020.

B. Drug Substance [GCSF Intermediate, (b) (4) Intermediate, and Eflapegrastim] Quality Summary
Refer to the original OPQ Executive Summary memo in DARRTS dated October 24, 2020.

C. Drug Product [Rolvedon] Quality Summary:
Refer to the original OPQ Executive Summary memo in DARRTS dated October 24, 2020.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations: Prior to use, Rolvedon should be removed from the refrigerator (keeping the prefilled syringe inside the carton) for a minimum of 30 minutes to allow the product to reach room temperature. Any prefilled syringe left at room temperature for greater than 12 hours should be discarded. Rolvedon should not be shaken. If Rolvedon is accidentally frozen, it should not be used. The tray from the box should be removed and the prefilled syringe should be carefully removed from the tray. If the prefilled syringe is dropped onto a hard surface, it should not be used, and a new syringe should be used for injection. Rolvedon should not be administered if discoloration or particulates are observed.

F. Establishment Information:

Overall Recommendation: Approve					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
GCSF intermediate, (b) (4) intermediate, and drug substance manufacturing, labelling, packaging, storage, and release and stability testing for the following: appearance, pH, protein	(b) (4)		Re-inspection needed due to significant GMP deficiencies identified during the pre-license inspection conducted in the previous assessment cycle (inspection	N/A	Approve – based on inspection

concentration, endotoxin, identity/impurities by CE-SDS, RP-HPLC, SE-HPLC, IE-HPLC, specific bioactivity, relative potency, and (b) (4)	(b) (4)	outcome: OAI, withhold approval)		
(b) (4) and in process testing, drug product (b) (4), drug product release and stability testing for the following: appearance, pH, protein concentration, identity/impurities by CE-SDS, RP HPLC, SE-HPLC and IE-HPLC		Re-inspection needed due to significant GMP deficiencies identified during the pre-license inspection conducted in the previous assessment cycle (inspection outcome: OAI, withhold approval)	N/A	Approve – based on inspection
Drug product labeling, assembly (prefilled syringe with needle guard), packaging, serialization and storage		N/A	N/A	Approve – based on previous history
Drug product release and stability testing: particulate matter and sterility		N/A	N/A	Approve – based on previous history
Drug product release and stability testing: break loose force, glide force test, deliverable volume, and activation force		N/A	N/A	Approve – based on previous history
Drug product finished goods storage and distribution		N/A	N/A	No evaluation necessary

(b) (4) storage	(b) (4)	N/A	N/A	Approve – based on previous history
Drug product container closure integrity release and stability testing		N/A	N/A	Approve – based on previous history
Master cell banks (b) (4) intermediate and GCSF intermediate) manufacturing		N/A	N/A	No evaluation necessary
Master and working cell banks (b) (4) intermediate and GCSF intermediate) testing		N/A	N/A	No evaluation necessary
Working cell banks (b) (4) intermediate and GCSF intermediate) manufacturing		N/A	N/A	No evaluation necessary

G. Facilities:

A re-inspection was deemed necessary for the drug substance manufacturing site, (b) (4) and drug product manufacturing site, (b) (4) because significant CGMP deficiencies were identified for the drug substance and drug product operations during the pre-license inspections conducted in support of the BLA in the previous assessment cycle. In the current assessment cycle, (b) (4) was found approvable based on the resolution of CGMP deficiencies covered by the re-inspection of the facility by the Office of Regulatory Affairs (ORA) for other applications. A re-inspection was conducted at (b) (4) from (b) (4) which resulted in a two-item FDA Form 483. The OPMA compliance review of the firm's response to the issued FDA Form 483 was found adequate and OPMA concurred with field recommendation of acceptable and approve for BLA 761148.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

- Cell bank storage stability
- Validation of (b) (4)
- Validation of (b) (4)
- Stability of reference standards

- (b) (4)
- Post-approval DS stability protocol

ii. Outstanding assessment issues/residual risk: None.

iii. Future inspection points to consider: None.

b. Drug Product

i. Protocols approved:
- Post-approval DP stability protocol

ii. Outstanding assessment issues/residual risk: None.

iii. Future inspection points to consider: None.

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

/s/

MASSOD RAHIMI
08/05/2022 02:49:50 PM

MARIA T GUTIERREZ LUGO
08/05/2022 04:26:45 PM

Recommendation: Pending

BLA STN 761148
Review Number: 1
Review Date: June 24, 2020

Drug Name/Dosage Form	ROLONTIS (eflapegrastim-xnst)/injection
Strength/Potency	13.2 mg eflapegrastim /0.6 mL solution in a single-dose pre-filled syringe
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs
Applicant/Sponsor	Spectrum Pharmaceuticals, Inc.

Product Overview

Eflapegrastim (Rolontis®, SPI-002, HM10460A) is a long-acting granulocyte-colony stimulating factor (G-CSF) and is produced by covalent coupling of a human G-CSF analog (HM10411) and human immunoglobulin G4 (IgG4) Fc fragment (HM001), via a 3.4 kDa polyethylene glycol (PEG) linker.

G-CSF is a hematopoietic growth factor that regulates the production of neutrophils within the bone marrow. The Mechanism of Action (MOA) of eflapegrastim is to stimulate neutrophil production by binding to the cell surface G-CSF receptors on hematopoietic cells in the bone marrow and stimulates their proliferation and differentiation leading to an increased number of mature neutrophils in the blood. The human IgG4 Fc fragment in eflapegrastim increases the circulating half-life of G-CSF without inducing Fc-mediated effector functions.

GCSF-intermediate, Fc intermediate, and eflapegrastim drug substance are manufactured at (b) (4) Both GCSF- and Fc (b) (4) intermediates are derived from recombinant Escherichia coli (*E. coli*). For the production of each (b) (4) (b) (4) For eflapegrastim DS, the data provided in the BLA submission support an expiration dating period of (b) (4) months when stored at (b) (4)

Eflapegrastim drug product (DP) is manufactured at [redacted] Eflapegrastim DP manufacturing involves [redacted] inspection, and labeling and packaging. The primary container closure for eflapegrastim DP includes a single-use, [redacted] 1-mL Type [redacted] clear, colorless glass syringe, with 29G stainless steel stacked needle and a [redacted] needle shield, [redacted] Gray [redacted] rubber plunger, and an [redacted] plunger rod made of [redacted] Eflapegrastim DP is supplied at 13.2 mg eflapegrastim /0.6 mL solution in a single-dose pre-filled syringe. Eflapegrastim DP is formulated at 13.2 mg/0.6 mL in 2.52 mg citric acid monohydrate, 5.26 mg sodium chloride, 30 [redacted] mg mannitol, and 0.72 mg polysorbate 80, pH 5.5. For eflapegrastim DP, the data provided in the BLA submission support an expiration dating period of [redacted] months when stored at 5 ± 3˚C.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Zhong Zhao	DBRR III/OBP/OPQ
Drug Product	Zhong Zhao	DBRR III/OBP/OPQ
Immunogenicity	Zhong Zhao	DBRR III/OBP/OPQ
Labeling	Scott Dallas and James Barlow	OBP/OPQ
Facility	Michael Shanks	DBM/OPMA/OPQ
Microbiology (DS)	Reyes Candau-Chacon	DBM/OPMA/OPQ
Microbiology (DP)	Madushini Dharmasena	DBM/OPMA/OPQ
Business Process Manager	Melinda Bauerlien	RBPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Patricia Hughes	DBM/OPMA/OPQ
Microbiology Team Lead (DP)	Reyes Candau-Chacon	DBM/OPMA/OPQ
Microbiology Tertiary Reviewer	Patricia Hughes	DBM/OPMA/OPQ
Facilities Team Lead	Peter Qiu	DBM/OPMA/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Elizabeth Godwin	DROCHEN/ORO/OND
Cross-disciplinary Team Lead	Kathy Robie-Suh	DNH/OCHEN/OND
Medical Officer	Hyon-Zu Lee	DNH/OCHEN/OND
Pharm/Tox	Huiqing Hao	DPTCHEN/OCHEN/OND
Clinical Pharmacology	Anusha Ande	DCEP/OCP/OTS
Statistics	Kate Dwyer	DBIX/OB/OTS

1. Names:

a. Proprietary Name: Rolontis
b. Trade Name: Rolontis
c. Non-Proprietary Name/USAN: eflapegrastim
d. CAS Name: 1384099-30-2
e. Common Name: eflapegrastim
f. INN Name: eflapegrastim
g. Compendial Name: N/A
h. OBP systematic name: CONJ: MAB FRAG HUMAN (IGG4 FC); RPROT P09919 (GCSF3_HUMAN); PEG [SPI2102]
i. Other names: SPI-002, HM10460A

Submissions Reviewed

Submission(s) Reviewed	Document Date
Original BLA	10/24/2019
Response to IR 1 (OPMA)	12/10/2019
CMC amendment	12/17/2019
Response to IR 2 (OPMA)	12/19/2019
Response to IR 3 (OPMA)	02/03/2020
Response to IR 4 (OBP)	02/06/2020
Response to IR 5 (OPMA)	02/20/2020
Response to IR 6 (OPMA)	03/12/2020
Response to IR 7 (OBP)	03/16/2020
Response to IR 8 (OPMA)	03/25/2020
Response to IR 9 (OPMA)	04/13/2020
CMC amendment	04/17/2020
Response to IR 10 (OBP)	04/22/2020
Response to IR 11 (OPMA)	05/11/2020
Response to IR 12 (OPMA)	05/19/2020
Response to IR 13 (OBP & OPMA)	06/01/2020
Response to IR 14 (OPMA)	06/10/2020
Response to IR 15 (OPMA)	06/17/2020
Response to IR 16 (OBP & OPMA)	06/29/2020

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments

(b) (4)	V	(b) (4)	3	N/A	Not reviewed. Sufficient information related to compatibility with the product is provided in the BLA.
	III		3	N/A	
	III		3	N/A	
	V		3	N/A	
	V		3	N/A	
	III		3	N/A	

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")

B. Other documents: The Sponsor provided a Letter of Authorization from (b) (4) to allow Spectrum to cross-reference 510(k) (b) (4) for information on (b) (4) We defer to CDRH for evaluating the adequacy of information provided in 510(k) (b) (4)

3. Consults: None requested by OBP. (OND Requested CDRH ODE and OC consults)

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Pending.

Currently, there are no product quality deficiencies precluding approval of this BLA. However, a final recommendation regarding product quality is currently pending and will be made in an addendum to this report after satisfactory resolution of the following outstanding items:

1. A pre-license inspection of [redacted] (b) (4) drug substance manufacturing facility [redacted] (b) (4) is required to verify that the firm's manufacturing operations are in compliance with cGMPs and that the product quality data submitted to the eflapegrastim BLA is accurate, reliable, and complete. This facility has never been inspected by the FDA before.

2. Sponsor responses to all outstanding information requests.

3. Updates to the BLA reflecting all changes made in response to FDA product quality information requests.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: [redacted] (b) (4)
- Drug Product:
  - [redacted] (b) (4) (drug product manufacturing, release, and stability testing)
  - [redacted] (b) (4) (drug product labeling, assembly (pre-filled syringe with needle guard), packaging, serialization, and storage)

- Fill size and dosage form – 13.2 mg/0.6 mL solution in a single-dose pre-filled syringe

- Dating period:
  - Drug Product [redacted] (b) (4) months; 2-8 °C
  - Drug Substance: [redacted] (b) (4) months; [redacted] (b) (4)

- Exempt from lot release

- Rolontis® is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Rolontis (eflapegrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia.

A review of benefit-risk assessment will be documented in the addendum to this report once all outstanding information has been reviewed.

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

(b) (4)

Other potential post marketing commitments/requirements will be documented in the addendum to this report once all outstanding information has been reviewed.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to GCSF intermediate, Fc (b) (4) intermediate, eflapegrastim drug substance and drug product.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA type	CQA	Risk	Origin	Control Strategy
Size Variants (product related impurity)	Soluble aggregates (HMW species)	Potency, PK, immunogenicity,	Production and purification processes, on stability	(b) (4)
	Fragments (LMW species)	Potency, PK, immunogenicity	Production and purification processes, on stability	

Post Translational Modifications	(b) (4)	No effect to potency	Production processes	(b) (4)
	Peptide bond breaks	Potency, safety, immunogenicity	Production processes	
	Oxidized at (b) (4)	Potency, PK,	Production and purification processes	
Structural Variants	(b) (4)	Potency, PK, immunogenicity,	Production and purification processes, on stability	
	(b) (4)	Potency	Characterized in the DS	
	Primary structure	Potency, PK, immunogenicity, safety	Cell line, production, and conjugation processes	
	Secondary structure	Potency, PK, immunogenicity, safety	Production, and conjugation processes	
	Tertiary structure	Potency, PK, immunogenicity, safety	Production, and conjugation processes	
Identity	Primary sequence	Safety, potency	Intrinsic to the molecule	

Potency	(b) (4)	Biological activity	Intrinsic to the molecule. Production and purification processes and on stability	(b) (4)
Charge Heterogeneity	Acidic, main, and basic species	Potency, immunogenicity	(b) (4) processes	

B. Drug Substance [eflapegrastim] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for GCSF intermediate, Fc (b) (4) intermediate, and drug substance CQAs that are derived from the intermediate and drug substance manufacturing processes and general drug substance attributes.

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

CQA type	CQA	Risk	Origin	Control Strategy
Process-related impurities	Host Cell DNA	Safety, immunogenicity	Cell culture and harvest	(b) (4)
	Host Cell Proteins	Immunogenicity, safety, biological activity (degradation or modification of the product)	Cell culture and harvest	
	(b) (4)	Immunogenicity	Process related impurity (b) (4)	
	(b) (4)	Toxic	Process related impurity (b) (4)	
	(b) (4)	Reduced formulation control	(b) (4)	
	(b) (4)	Toxic, mutagen	(b) (4)	
	Leachables	Safety (Toxicity, mutagen)	Product-contact equipment and materials throughout the manufacturing process. (b) (4)	
	Endotoxin	Safety, contamination	Harvest materials, manufacturing materials, and manufacturing process	

	Bioburden	Safety, purity, efficacy (degradation or modification of the product)	Raw materials and manufacturing process	(b) (4)
DS Composition	Appearance (color, clarity/ opalescence)	Potency, safety	Product and formulation	
	Protein concentration	Inaccurate dosing impacting PK, efficacy and safety	Manufacturing process (b) (4)	
	pH	Bioactivity, product stability	Formulation (b) (4)	
	(b) (4)			
Structural Variants	(b) (4)	Potency, PK, immunogenicity, safety	Production processes in (b) (4)	

- Description:
  Eflapegrastim (SPI-2012, HM10460A) is a conjugated protein comprised of a recombinant human GCSF analog and a human IgG4Fc fragment. The GCSF intermediate and human IgG4 Fc fragment (b) (4) intermediate) are linked at their N-terminus to the N-terminus via a 3.4 kDa polyethylene glycol (PEG).

  The GCSF intermediate is (b) (4)

  Since GCSF intermediate is produced from *E. coli* cells (b) (4)

  The Fc (b) (4) intermediate (b) (4) is the Fc region of IgG4 (b) (4)

Eflapegrastim DS is manufactured by [redacted] (b) (4)

- Mechanism of Action (MoA):
  Eflapegrastim binds to the cell surface G-CSF receptors on hematopoietic cells in the bone marrow and stimulates their proliferation and differentiation, resulting in an increased number of mature neutrophils in circulation, which is a relevant pharmacodynamic marker for neutropenia, and enhanced neutrophil function.

- Potency Assay:
  Potency of eflapegrastim is determined by measuring its ability to stimulate proliferation of NFS-60 cells compared to a reference standard. [redacted] (b) (4) The cells are incubated with a tetrazolium dye (MTS) and phenazine ethosulfate (PES; serves as an electron acceptor) solution (Celltiter 96® AQueous one solution from Promega). NADPH or NADH, produced by dehydrogenase enzymes in metabolically active cells, reduces MTS to a purple formazan compound. The quantity of formazan produced is measured by absorbance at 490 nm and is proportional to the number of viable cells present. PLA software is used to assess parallelism and determine potency relative an in-house reference standard.

- Reference Materials:
  The eflapegrastim program currently uses primary reference material batch [redacted] (b) (4) in the QC release and stability testing of both DS and DP. The primary reference material [redacted] (b) (4) was developed from drug substance batch [redacted] (b) (4), which was used as the study drug for the pivotal Phase III clinical studies SPI-GCF-301 and SPI-GCF-302 and manufactured using DS process [redacted] (b) (4), which is comparable to commercial DS process [redacted] (b) (4). Clinical studies SPI-GCF-301 and SPI-GCF-302 are the pivotal trials to support efficacy and safety of eflapegrastim for the proposed indication.
  The Sponsor commits to implement a two-tier reference material system, comprised of primary and working reference materials, which will be consistent with ICH Q6B.

- Critical starting materials or intermediates:
  The GCSF intermediate and Fc [redacted] (b) (4) intermediate are of biologic origin and are produced from [redacted] (b) (4) E. Coli [redacted] (b) (4). A two-tiered cell banking system, comprising of Master Cell bank (MCB) and Working Cell Bank (WCB), is in place for both GCSF intermediate and Fc [redacted] (b) (4) intermediate. Use of the respective WCBs for commercial purposes is acceptable.

- Manufacturing process summary:
  [redacted] (b) (4)

(b) (4)

- Container closure:
  The eflapegrastim DS is stored (b) (4)
  (b) (4)

- Dating period and storage conditions:
  The data support an expiration dating period of (b) (4) months when stored at (b) (4)

C. Drug Product [Rolontis] 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 Knowledge Management

CQA type	CQA	Risk	Origin	Control Strategy
Particles	Visible and Subvisible Particles	Immunogenicity, safety, potency	Manufacturing process, CCS and product on stability	(b) (4)
Safety	Sterility	Safety (infection), efficacy (degradation or modification of the product)	Contamination may be introduced throughout the DP manufacturing process, container closure failure	
	Endotoxin	Safety, purity	Raw materials and manufacturing process	

	Bioburden	Safety, purity, efficacy (degradation or modification of the product)	Raw materials and manufacturing process
DP Composition and Strength	Protein Concentration and Deliverable Volume	Inaccurate dosing impacting PK, efficacy and safety	DP manufacturing process (b) (4)
	pH	Impacting stability	DP manufacturing process (b) (4)
	(b) (4)	Particle formation, product stability (potency, PK, immunogenicity, safety)	Raw material control, Manufacturing process (b) (4)
	Appearance (color, clarity, opalescence)	Potency, safety	Manufacturing process, product and formulation
	Dose Uniformity	Inaccurate dosing related potency and safety	Manufacturing process,
Purity/ impurity	Leachables	safety	product contact equipment, container closure and consumables
Container closure system	PFS appearance	Safety and efficacy	Raw materials and manufacturing process
	PFS functional performance	Safety and efficacy	Raw materials and manufacturing process
	Sterility/Container Closure Integrity	Safety (loss of sterility), efficacy (change in product strength due to evaporation or leakage)	Container closure breaches during manufacture and storage

(b) (4)

- Potency and Strength:
  Eflapegrastim is supplied at 13.2 mg/0.6 mL in a pre-filled syringe. Potency is defined as the percent activity relative to the current eflapegrastim reference standard. The potency assay is the same as described in the DS section of this review memo.

- Summary of Product Design:
  Eflapegrastim is supplied as a sterile, clear, colorless, preservative-free solution in a single-dose pre-filled syringe for subcutaneous injection. Eflapegrastim DP is formulated at 13.2 mg/0.6 mL in 2.52 mg citric acid monohydrate, 5.26 mg sodium chloride, 30 (b) (4) mg mannitol, and 0.72 mg polysorbate 80, pH 5.5. The deliverable volume (b) (4)

- List of Excipients:
  Excipients include citric acid monohydrate, sodium chloride, mannitol, and polysorbate 80. Sodium hydroxide may be used to adjust the final pH.

- Reference Materials:
  (b) (4)

- Manufacturing process summary:
  (b) (4)

- Container closure:
  The primary container closure for eflapegrastim DP consists of a single-(b) (4) 1-mL Type (b) (4) clear, colorless glass syringe with 29G stainless steel stacked needle and a (b) (4) needle shield (b) (4) Gray (b) (4) rubber plunger (b) (4) and (b) (4) plunger rod made of (b) (4)

- Dating period and storage conditions:
  The dating period for eflapegrastim DP is (b) (4) months when stored at 2˚C to 8˚C, protected from light.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F).
- Protect from light until use.
- Do not shake.
- Do not freeze.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
Drug Substance Storage Warehousing	(b) (4)		No assessment required	N/A	No Evaluation Necessary
GCSF intermediate, (b) (4) intermediate, and Drug Substance manufacturing, labelling, packaging, storage, and release and stability testing			PLI Required	Pending	Pending PLI
Master cell banks manufacturing			No assessment required	N/A	No Evaluation Necessary
Master and working cell banks testing			No assessment required	N/A	No Evaluation Necessary
Working cell banks manufacturing			No assessment required	N/A	No Evaluation Necessary
DRUG PRODUCT					
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**

Drug Product manufacturing and testing	(b) (4)	PLI required	3-item FDA Form 483, recommend approval	Approve, based on inspection
Drug Product labeling, assembly, packaging, serialization and storage (PFS with needle guard)		Facility has acceptable profile/history	N/A	Approve, Based on Profile
Drug Product Container closure integrity release and stability testing		Facility has acceptable profile/history	N/A	Approve, Based on Profile
Drug Product release and stability testing		Facility has acceptable profile/history	N/A	Approve, Based on Profile
Release and stability testing		Facility has acceptable profile/history	N/A	Approve, Based on Profile
Finished goods storage and distribution		No assessment required	N/A	No Evaluation Necessary
Release and stability testing		No inspection history, PLI requested	Pending	Pending PLI

G. Facilities:

(b) (4) responsible for GCSF and (b) (4) and Drug Substance manufacturing is currently pending a requested pre-license inspection and no recommendation has been made for this facility (b) (4) had a pre-license inspection (b) (4) At the conclusion of the inspection a 3-item FDA Form 483 was issued with an approval recommendation. Following the compliance review of the firm's response a recommendation of approve for BLA 761148 was made. All other facilities that required evaluation were found adequate and had approve recommendations made.

Presently, neither an approve or withhold recommendation can be made due to the pending pre-license inspection of the drug substance manufacturer, (b) (4)

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H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols :
   1. Validation of (b) (4)

2. Validation of [redacted] (b) (4)
3. Post-approval DS stability protocol

ii. Outstanding review issues/residual risk: See "Recommendation" section for outstanding review issues.

iii. Future inspection points to consider: A pre-license inspection of the [redacted] (b) (4), the manufacturing facility for GCSF intermediate, [redacted] (b) (4) and eflapegrastim drug substance, is required before the application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to COVID-19 related U.S. Government and Agency-wide restrictions on foreign travel, we will be unable to conduct an inspection of the [redacted] (b) (4) until the restriction is lifted.

b. Drug Product

i. Protocols:
   1. Post-approval DP stability protocol

ii. Outstanding review issues/residual risk: See "Recommendation" section for outstanding review issues. The following information will be reviewed as addenda to the microbiology DP review memo:
   1. CCI testing of the PFS after assembly from 2 additional lots of DP and 2 additional shipping runs. Report will be submitted by 31 June 2020.
   2. Sterility method qualification with 2 additional lots. Report will be submitted by August 2020.
   3. Plunger movement study using the worst-case plunger position. Study report will be submitted by July 2020.

   Additional Information Requests (IR) will be sent to the Sponsor to address pending review issues and an assessment of Sponsor's IR response will be documented in the addendum to this report once all outstanding information has been reviewed.

iii. Future inspection points to consider: See 483 observations in the establishment information section and Facilities review by OPMA assessor.

Ramesh Potla

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Susan Kirshner

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/s/

RAMESH B POTLA
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