CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication

Recommendation: Approval

BLA Number: 761166
Office of Pharmaceutical Quality
Application Technical Lead Assessment Number: 2

Assessment Date: October 29, 2021

Addendum: The Executive Summary memorandum finalized in Panorama on February 26, 2021 still applies and is valid. This addendum is to update the OPQ recommendation from Pending to Approval following the pre-license inspection of the drug substance manufacturing and testing facility.

Drug Name/Dosage Form	Besremi, Injection
Strength/Potency	500 mcg/1.0 mL prefilled syringe
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Treatment of polycythemia vera in adults without symptomatic splenomegaly
Applicant/Sponsor	PharmaEssentia Corporation

Product Overview:

Besremi is long-acting recombinant interferon alfa-2b analog conjugated to a two-arm branched methoxypolyethylene glycol (mPEG) moiety attached at the N-terminal proline residue. The mechanism of action is mediated through binding of the interferon alfa-2b portion of the molecule to interferon alpha receptors (IFNAR) on the cell surface, which in turn induces complex intracellular signaling pathways and activation of kinases. The drug substance is produced by recombinant DNA technology in cultures of *Escherichia coli* cells (b) (4) The final drug product is a clear and colorless to slightly yes solution for injection, provided in a pre-filled syringe. Besremi drug product is formulated in 8.0 mg sodium chloride, 1.58 mg sodium acetate, 0.05 mg acetic acid, 10 mg benzyl alcohol, 0.05 mg polysorbate 80, and water for injection (WFI) up to 1.0 mL at pH 6.0.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Phillip Angart	OPQ/OBP/DBRRII
Drug Product	Phillip Angart	OPQ/OBP/DBRRII
Immunogenicity Assays	Phillip Angart	OPQ/OBP/DBRRII

Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facility	Richard Ledwidge; Candace Gomez-Broughton (TL)[1]	OPQ/OPMA/DBM
Microbiology Drug Substance	Richard Ledwidge; Candace Gomez-Broughton (TL)	OPQ/OPMA/DBM
Microbiology Drug Product	Maria Gema Martin Manso; Candace Gomez-Broughton (TL)	OPQ/OPMA/DBM
Small Molecule	Zhengfu Wang; Su (Suong) Tran (TL)	OPQ/ONDP/DNDAPI
Team Lead	Anjali Shukla	OPQ/OBP/DBRRII
Application Technical Lead	Anjali Shukla	OPQ/OBP/DBRRII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Alice Kacuba, Carleveva Thompson	OND/ORO/DRO-CHEN
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Patricia O'Neal	OND/OCHEN/DNH
Pharmacology/Toxicology	Jeffery Quinn/Todd Bourcier (TL)	OND/OCHEN/DPT-CHEN
Clinical Pharmacology	Li Wang/Sudharshan Hariharan (TL)	OTS/OCP/DCEP
Statistics	Lola Luo/Yeh-Fong Chen (TL)	OTS/OB/DBIX
Pharmacometrics	Eliford Kitabi/Justin Earp	OTS/OCP/DPM

1. Names:

a. Proprietary Name:	Besremi
b. Trade Name:	Besremi
c. Non-Proprietary Name/USAN:	ropeginterferon alfa-2b-njft
d. CAS Name:	1335098-50-4
e. Common Name:	ropeginterferon alfa-2b-njft
f. INN Name:	Ropeginterferon alfa-2b
g. Compendial Name:	Not established
h. OBP systematic name:	RPROTFRAG P01563 (IFNA2_HUMAN) INTERFERON ALPHA-2 [P1101]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761166/48 (OPMA, OBP)	May 13, 2021
STN 761166/51 (OPMA, OBP)	October 05, 2021

[1] Team Lead

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761166 for Besremi manufactured by PharmaEssentia Corporation. The data submitted in this application are adequate to support the conclusion that the manufacture of Besremi 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.

The OPQ Executive Summary finalized in Panorama on February 26, 2021 noted that the recommendation on approvability of STN 761166 for Besremi manufactured by PharmaEssentia was pending final determinations of compliance status of the PharmaEssentia Corporation (PEC) Taichung Plant drug substance manufacturing and testing facility and PharmaEssentia Corporation Taipei (b) (4) manufacturing and testing facility. The Complete Response (CR) Letter forwarded to the Sponsor on March 12, 2021 indicated that inspections of PharmaEssentia Corporation, FEI 2000012832, Taichung, Taiwan and PharmaEssentia Corporation, FEI 3005182038, Taipei, Taiwan are required before this application can be approved. Upon resubmission of BLA 761166 on May 13, 2021, it was determined that inspection of the PEC Taichung facility was still required. Inspection of the PEC Taipei facility that manufactures the (b) (4) was waived (Refer to the Facilities memorandum finalized in Panorama on October 29, 2021). A pre-license inspection of the PEC Taichung facility was conducted September 20-28, 2021, which resulted in issuance of a 5-item FDA Form 483. The compliance status of the PEC Taichung facility was determined to be 'Approve'.

In response to the Agency's information request (IR) based on observations made during the pre-license inspection of the PEC Taichung facility, three testing sites were added to the BLA (IR response received October 5, 2021). These testing sites were used to support the Process Performance Qualification (PPQ) in the BLA but will not be used for quality control testing of commercial BESREMI (ropeginterferon alfa-2b-njft) intermediate, drug substance, or drug product samples. The method transfer and qualification information from these testing sites was deemed acceptable. The inspections of these testing sites were waived. For additional details, refer to the Facilities memorandum finalized in Panorama on October 29, 2021 and the Office of Biotechnology Products (OBP) memorandum finalized in Panorama on October 5, 2021.

Additional product quality issues that were not approvability issues listed on the March 12, 2021 CR Letter were addressed by the Applicant in this resubmission. The response was deemed to be satisfactory by the Office of Pharmaceutical Manufacturing Assessment (OPMA). For additional details, refer to the drug product microbiology technical assessment memorandum finalized in Panorama on October 29, 2021.

B. Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - (b) (4)
      PharmaEssentia Corporation (PEC)
      13F and 19F, No. 3, Park St.
      Nangang Dist., Taipei 115, Taiwan
    - Ropeginteferon alfa-2b-njft drug substance:
      PharmaEssentia Corporation (PEC) Taichung Plant.
      3F, No. 28, Keya West Road
      Daya District, Taichung 428, Taiwan
  - Drug Product:
    (b) (4)
- Fill size and dosage form: 500 mcg in 1.0 mL solution in a prefilled syringe
- Dating period:
  - Drug Product: 24 months: 5 ± 3 °C
  - Drug Substance (b) (4) months: (b) (4) °C
    (b) (4)
  - For packaged products: "Not packaged"
  - Stability Option:
    - For stability protocols:
      - We have approved the stability protocol 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
  - Yes
  - Rationale, if exempted: specified product
    Note: Besremi is exempted from lot release per FR 95-29960.

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

None

II. Summary of Quality Assessments:

A. Establishment Information:

Overall Recommendation: Pending				
DRUG SUBSTANCE				
Functions	**Site Information**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
• Manufacture of (b) (4) Ropeginterferon alfa-2b-njft DS • Manufacture of (b) (4) • Testing (in-process, release, and stability) of DI and DS • Release of (b) (4) • Storage of (b) (4) (b) (4) (b) (4) DS • Storage of cell banks (MCB and WCB)	PharmaEssentia Corporation (PEC) Taichung Plant 3F, No. 28, Keya West Rd, Daya District, Taichung 428, Taiwan DUNS: 658873411 FEI: 2000012832	Pre-license inspection required	A pre-license inspection was conducted from September 20 to September 28, 2021. A 5-item FDA Form 483 was issued. The inspection was classified as Voluntary Action Indicated (VAI).	Approve
• Manufacture of (b) (4) • Testing (in-process, release, and stability) of (b) (4) • Storage of (b) (4)	PharmaEssentia Corporation (PEC) 13F and 19F, No. 3, Park St., Nangang Dist., Taipei 115, Taiwan DUNS: 658647354 FEI: 3005182038	Pre-license inspection waived	Not inspected for this application	Approve
• Production and characterization	(b) (4)	Facility has acceptable	Not inspected for this application	No evaluation necessary

of cell banks (MCB and WCB) • Storage of cell banks (MCB and WCB)	(b) (4)	compliance history		
• Potency testing for drug intermediate (DI) and DS, (b) (4) (b) (4)		Pre-license inspection waived	Not inspected for this application	No evaluation necessary
(b) (4)		Pre-license inspection waived	Not inspected for this application	No evaluation necessary
		Pre-license inspection waived	Not inspected for this application	No evaluation necessary
DRUG PRODUCT				
Function	**Site Information**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
• Manufacture of DP • Testing (in-process) of DP • Labeling, packaging, and storage of DP	(b) (4)	Pre-license inspection required	A pre-license inspection was conducted from (b) (4) A one item Form 483 was issued. The inspection was classified VAI.	Approve
• Testing (release and stability) of DP • Release of finish DP to market	PharmaEssentia Corporation (PEC) Taichung Plant 3F, No. 28, Keya West Rd, Daya District, Taichung 428, Taiwan DUNS: 658873411 FEI: 2000012832	Pre-license inspection required	A pre-license inspection was conducted from September 20 to September 28, 2021. A 5-item FDA Form 483 was issued. The	Approve

			inspection was classified VAI.	
• Testing (in-process bioburden)	(b) (4)	Facility has acceptable compliance history	Not inspected for this application	Approve
• Potency testing (b) (4)		Pre-license inspection waived	Not inspected for this application	No evaluation necessary

*Site not used for testing of commercial BESREMI (ropeginterferon alfa-2b-njft) intermediate, drug substance, or drug product samples in the license.

B. Facilities:

A pre-license inspection of the PEC Taichung Plant was conducted from September 20-28, 2021 to support approval of this BLA. A 5-item FDA Form 483 was issued. The inspection was classified VAI. A pre-license inspection of the (b) (4) A one item FDA Form 483 was issued. The inspection was classified VAI. All other proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status, or inspection waivers. For details, refer to the Facilities memorandum finalized in Panorama on October 29, 2021

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 10/29/2021 04:08:26PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 10/29/2021 04:10:11PM
GUID: 54bfb193000693c35f4278034f85d77a

First Approval for Indication

Recommendation: Pending

BLA Number: 761166
Office of Pharmaceutical Quality
Application Technical Lead Assessment Number: 1

Assessment Date: February 26, 2021

Drug Name/Dosage Form	Besremi, Injection
Strength/Potency	500 mcg/1.0 mL prefilled syringe
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Treatment of polycythemia vera in adults without symptomatic splenomegaly
Applicant/Sponsor	PharmaEssentia Corporation

Product Overview:

Besremi is long-acting recombinant interferon alfa-2b analog conjugated to a two-arm branched methoxypolyethylene glycol (mPEG) moiety attached at the N-terminal proline residue. The mechanism of action is mediated through binding of the interferon alfa-2b portion of the molecule to interferon alpha receptors (IFNAR) on the cell surface, which in turn induces complex intracellular signaling pathways and activation of kinases. The drug substance is produced by recombinant DNA technology in cultures of *Escherichia coli* cells followed (b) (4). The final drug product is a clear and colorless to slightly yes solution for injection, provided in a pre-filled syringe. Besremi drug product is formulated in 8.0 mg sodium chloride, 1.58 mg sodium acetate, 0.05 mg acetic acid, 10 mg benzyl alcohol, 0.05 mg polysorbate 80, and water for injection (WFI) up to 1.0 mL at pH 6.0.

Quality Assessment Team:

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Drug Product	Phillip Angart	OPQ/OBP/DBRRII
Immunogenicity Assays	Phillip Angart	OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facility	Richard Ledwidge; Peter Qiu (TL)[1]	OPQ/OPMA/DBM

[1] Team Lead

Microbiology Drug Substance	Richard Ledwidge; Candace Gomez-Broughton (TL)	OPQ/OPMA/DBM
Microbiology Drug Product	Maria Gema Martin Manso; Candace Gomez-Broughton (TL)	OPQ/OPMA/DBM
Small Molecule	Zhengfu Wang; Su (Suong) Tran (TL)	OPQ/ONDP/DNDAPI
Team Lead	Patrick Lynch	OPQ/OBP/DBRRII
Application Team Lead	Patrick Lynch	OPQ/OBP/DBRRII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Alice Kacuba, Carleveva Thompson	OND/ORO/DRO-CHEN
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Patricia O'Neal	OND/OCHEN/DNH
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Clinical Pharmacology	Li Wang/Sudharshan Hariharan (TL)	OTS/OCP/DCEP
Statistics	Lola Luo/Yeh-Fong Chen (TL)	OTS/OB/DBIX
Pharmacometrics	Eliford Kitabi/Justin Earp	OTS/OCP/DPM

1. Names:

a. Proprietary Name: Besremi
b. Trade Name: Besremi
c. Non-Proprietary Name/USAN: ropeginterferon alfa-2b-njft
d. CAS Name: 1335098-50-4
e. Common Name: ropeginterferon alfa-2b-njft
f. INN Name: Ropeginterferon alfa-2b
g. Compendial Name: Not established
h. OBP systematic name: RPROTFRAG P01563 (IFNA2_HUMAN) INTERFERON ALPHA-2 [P1101]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761166/1, Original Submission	March 13, 2020
STN 761166/3 (OPMA)	April 27, 2020
STN 761166/6 (OPMA)	May 18, 2020
STN 761166/7 (ONDP)	June 5, 2020
STN 761166/9 (OPMA)	June 15, 2020
STN 761166/10 (OPMA)	June 24, 2020
STN 761166/11 (OPMA)	June 30, 2020

STN 761166/13 (ONDP)	July 7, 2020
STN 761166/15 (OBP)	July 16, 2020
STN 761166/17 (OBP)	August 14, 2020
STN 761166/19 (OBP)	September 2, 2020
STN 761166/20 (OBP)	September 4, 2020
STN 761166/22 (OPMA)	October 1, 2020
STN 761166/23 (OBP)	October 1, 2020
STN 761166/24 (OBP)	October 2, 2020
STN 761166/25 (OBP)	October 23, 2020
STN 761166/27 (OBP, OPMA, CDRH)	November 6, 2020
STN 761166/28 (OBP, CDRH)	November 30, 2020
STN 761166/29 (OBP, OPMA, CDRH)	December 14, 2020
STN 761166/30 (OPMA)	December 18, 2020
STN 761166/32 (OBP, OPMA)	December 23, 2020
STN 761166/34 (OBP)	January 4, 2021
STN 761166/37 (OPMA)	January 19, 2021
STN 761166/40 (OPMA)	February 1, 2021
STN 761166/42 (OPMA)	February 12, 2021

Quality Assessment 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]
(b) (4)	III	(b) (4)		2	Adequate
	III			3	N/A

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

2. Action codes for Status column: 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 assessed.

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

Document	Application Number	Description
IND Application	119047	IND for development of ropeginterferon alfa-2b-njft

3. Consults:

   A consult to CDRH for assessment of the prefilled syringe was requested by OND.

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH	OPEQ/OHTIII/DHTIIIC	Prefilled syringe	Pending	Rumi Young

4. Environmental Assessment of Claim of Categorical Exclusion:

   A categorical exclusion from submitting an Environmental Assessment of ropeginterferon alfa-2b-njft is requested per 21 CFR 25, section 25.31. Ropeginterferon alfa-2b-njft is considered naturally occurring in the environment. No extraordinary conditions exist.

The request for categorical exclusion is granted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of STN 761166 for Besremi manufactured by PharmaEssentia is pending final determinations of compliance status of the PhamaEssentia Corporation (PEC) Taichung Plant drug substance manufacturing and testing facility and PharmaEssentia (PEC) (b) (4) manufacturing and testing facility. FDA assessment of the ability of these facilities to conduct manufacturing operations in compliance with CGMP is required to support approval of the application. Pre-license inspections are delayed due to travel restrictions related to the Coronavirus Disease 2019 (COVID-19) public health emergency. From the product quality and product quality microbiology and sterility assurance perspectives, OPQ, CDER, does not note any product quality deficiencies that would preclude approval of STN 761166 for Besremi manufactured by PharmaEssentia at this time. This memo will be amended with the outcome of the facility assessment in the future. Remaining product quality issues that are not approvability issues are listed in the summary of additional comments below. These comments are recommended for inclusion in the letter to the Sponsor.

B. Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - (b) (4)
      PharmaEssentia Corporation (PEC)
      13F and 19F, No. 3, Park St.
      Nangang Dist., Taipei 115, Taiwan
    - Ropeginteferon alfa-2b-njft drug substance:
      PharmaEssentia Corporation (PEC) Taichung Plant.
      3F, No. 28, Keya West Road
      Daya District, Taichung 428, Taiwan
  - Drug Product:
    (b) (4)
- Fill size and dosage form: 500 mcg in 1.0 mL solution in a prefilled syringe
- Dating period:
  - Drug Product: 24 months: 5 ± 3 °C
  - Drug Substance: (b) (4) months: (b) (4) °C
    (b) (4)

- For packaged products: "Not packaged"
- Stability Option:
  - For stability protocols:
    - We have approved the stability protocol 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
  - Yes
  - Rationale, if exempted: specified product

    Note: Besremi is exempted from lot release per FR 95-29960.

C. Summary of Additional Comments to be Provided to the Sponsor (provided by OPMA):

1. Inspections of PharmaEssentia Corporation, FEI: 2000012832, Taichung, Taiwan and PharmaEssentia Corporation, FEI: 3005182038, Taipei, Taiwan facilities are required before this application can be approved. FDA must assess the ability of each facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct any inspections during the current review cycle for your application. The application cannot be approved until the required FDA inspections are conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

2. Two batches of drug product were used to determine the suitability of the in-process bioburden test method conducted by (b) (4). However, three batches should be used for testing method suitability in the bacteriostasis/fungistasis assay. Therefore, provide in-process bioburden test method suitability results from one additional batch of ropeginterferon alfa-2b solution for injection, 500 mcg/mL tested at (b) (4).

3. One batch of drug product was used to determine the suitability of the sterility test method conducted by PharmaEssentia Corporation. However, three batches should be used for testing method suitability in the bacteriostasis/fungistasis assay. Therefore, provide sterility test method suitability results from two additional batches of ropeginterferon alfa-2b solution for injection, 500 mcg/mL tested at PharmaEssentia Corporation.

D. Benefit/Risk Considerations:

Besremi is indicated for treatment of polycythemia vera in adults without symptomatic splenomegaly. Polycythemia vera is a myeloproliferative disorder characterized by increase in red blood cell mass with a risk of thrombotic and hemorrhagic complications and long-term evolution to myelofibrosis and acute leukemia. Addition (b) (4)

The manufacturing processes for Besremi are well controlled and consistently produce product that is pure and potent. The drug substance process is (b) (4) The overall control strategy for drug substance and drug product is comprehensive for control (b) (4) (b) (4)

OPQ recommendations regarding CGMP compliance for the commercial manufacture of (b) (4) and Besremi drug substance at PharmaEssentia Corporation in Taichung, Taiwan, (b) (4) at PharmaEssentia Corporation in Taipei, Taiwan, and drug product at (b) (4) are pending completion of pre-license inspection activities. This OPQ Executive Summary memo will be amended with the final compliance recommendations upon resolution of travel restrictions related to the COVID-19 public health emergency. The immunogenicity assays used to evaluate anti-drug antibodies in clinical samples provided in support of this BLA are adequately validated and suitable for their intended purpose. Additional data and information to support the overall quality assessment are in the OPQ primary technical reviews for product quality, (b) (4) microbiology, and facilities. OPQ primary technical reviews are located in Panorama.

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 drug substance and drug product.

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

CQA (type)	Risk	Origin	Control Strategy	Other
(b) (4) Assay (Potency)	Efficacy	Intrinsic to the molecule Minimal or minor change is expected when stored under recommended storage conditions Increases upon exposure to room	(b) (4)	(b) (4) Potency is a stability-indicating attribute

		temperatures at 25ºC, low or high pH, light Decrease upon exposure to heat		
Identity (Identity)	Efficacy, Safety	Intrinsic to the molecule	(b) (4)	N/A
(b) (4) (Product-related impurity)	Efficacy, Pharmacokinetics, Immunogenicity (b) (4) (b) (4)	Manufacturing process, stability		N/A
(b) (4) (Product-related impurity)	Safety	Manufacturing process		N/A
(b) (4) (Product-related impurity)	Efficacy, Pharmacokinetics, Safety, Immunogenicity (b) (4)	Manufacturing process, stability Increases upon exposure to heat, low or high pH, light		(b) (4) is stability indicating (b) (4) is a stability-indicating attribute
High Molecular Weight Species (HMWS) (Product-related impurity) (b) (4)	Efficacy, Pharmacokinetics, Safety, Immunogenicity HMWS reduce potency, (b) (4)	Manufacturing process, stability Increases upon exposure to light		N/A

(b) (4)	(b) (4)			
High Molecular Weight Aggregates (HMWA) (Product-related impurity)	Efficacy, Pharmacokinetics, Safety, Immunogenicity	Manufacturing process, stability Increases upon exposure to heat, low or high pH, light	(b) (4)	(b) (4) is stability indicating HMWA is a stability-indicating attribute
(b) (4) (Product-related impurity)	Efficacy, Pharmacokinetics, Safety, Immunogenicity (b) (4)	Manufacturing process		N/A
(b) (4) (Product-related substance)	Pharmacokinetics, Safety, Immunogenicity	Manufacturing process, stability Increase upon exposure to heat, low or high pH, light		(b) (4)
(b) (4) (Product-related impurity)	Efficacy, Pharmacokinetics, Safety, Immunogenicity	(b) (4)		
(b) (4) (Product-related substance)	Immunogenicity	Manufacturing process, stability Increase upon exposure to light		

			(b) (4)	
Protein content (General)	Efficacy	Manufacturing process Recovery of protein decreases upon exposure to heat, low or high pH		N/A
pH (General)	Stability	Manufacturing process, formulation		N/A

B. Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management
Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (General)	Safety	Manufacturing process	(b) (4)	N/A
Host Cell Proteins (Process-related impurity)	Safety, Immunogenicity	Production cell line		N/A
Host Cell DNA (Process-related impurity)	Low hypothetical safety or immunogenicity risk	Production cell line		N/A
(b) (4)	Safety	(b) (4)		N/A

(Process-related impurity)		(b) (4)	(b) (4)	
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
(b) (4) (Process-related impurity)	Low potential impact on safety	(b) (4)		N/A
Leachable Components (Process-related impurities)	Safety and efficacy Leached components may	Manufacturing components and DS container closure system (CCS)		N/A

	impact product stability		(b) (4)	
Bioburden (Contaminant)	Safety, purity, efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and throughout the manufacturing process		N/A
Endotoxin (Contaminant)	Safety, purity	Raw materials and throughout manufacturing process		N/A

- **Description:**
  Ropeginterferon alfa-2b-njft is a conjugate of recombinant proline-interferon alfa-2b derivative produced in *Eschericia coli* cells, with a two-arm 40 kDa methoxypolyethylene glycol (mPEG) moiety attached to the N-terminal proline amino acid by (b) (4) . (b) (4) Conjugation to mPEG functions to increase the *in vivo* half-life of the molecule. Ropeginterferon alfa-2b-njft has a molecular weight of approximately 60 kDa and an isoelectric point of 6.0 ± 0.1.

- **Mechanism of Action (MoA):**
  The proposed mechanism of action is mediated through binding of the interferon alfa-2b portion of the molecule to interferon alpha receptors on the cell surface, which in turn induces complex intracellular signaling pathways such as JAK/STAT. The molecular mechanism by which ropeginterferon alfa-2b-njft mediates therapeutic effect in Polycythemia vera (PV) patients remains poorly understood. It is hypothesized that interferons abrogate proliferation and promote depletion of aberrant hematopoietic stem cells that contain a somatic mutation in Janus 2 kinase (*JAK2V617F*), which is thought to drive the disease in PV patients.

- **Potency Assay:**

Potency is measured in an anti-viral cytopathic effect (CPE) bioassay that quantitates the ability of ropeginterferon alfa-2b-njft to protect human lung carcinoma A549 cells from cytotoxicity caused by infection of encephalomyocarditis virus (ECMV). This assay is considered relevant to the proposed mode of action because protection from cytotoxicity is dependent on activation of JAK/STAT pathway through binding of ropeginterferon alfa-2b-njft to type I interferon receptors. Viability of A549 cells exposed to ECMV is measured using an indicator reagent (CellTiter-Glo) that detects metabolic activity. The fluorescence readout is proportional to the number of viable cells. Potency values are determined relative to the reference material.

- **Reference Materials:**
  Two types of in-house reference standards (RS) are used to support manufacture of ropeginterferon alfa-2b-njft: (b) (4) (b) (4) (b) (4) for drug substance and drug product) were manufactured (b) (4) and stored at (b) (4)°C (b) (4)°C. The qualification of these RSs includes calibration of potency against the WHO international standard for interferon alpha 2b, which was used for the calibration of RS potency throughout clinical development.

  The Sponsor is currently implementing a two-tier reference standard program consistent with ICH Q6B recommendations. Protocols for qualification and annual re-qualification of primary and working reference standards are included in the BLA. These protocols include sufficient tests and acceptance criteria to ensure future commercial primary RS and working RS are representative of the clinical study material. The qualification of future RSs includes calibration of potency using the current primary RSs.

- **Critical starting materials or intermediates:**
  A two-tiered cell bank system consisting of a master cell bank (MCB) and working cell bank (WCB) is in place to ensure continued source of product. The host cell production (b) (4)

(b) (4)

[redacted]

- **Manufacturing process summary:**

(b) (4)

[redacted]

Additional information is in the Product Quality and DS Microbiology primary technical reviews.

- **Container closure:**
The DS container closure system is a [redacted] (b) (4) [redacted] (b) (4) Compatibility of the container closure system is supported by DS stability studies carried out in containers of the same material. Extractables study and leachables risk assessment support the use of the container closure system.

- **Dating period and storage conditions:**
The data provided in the BLA support the establishment of a shelf life of (b) (4) months for the ropeginterferon alfa-2b-njft DS [redacted] (b) (4) [redacted]

C. Drug Product 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 (b) (4)	Other
Sterility (Contaminant)	Safety and efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout DP manufacturing process		N/A
Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contamination may be introduced throughout DP manufacturing process and raw materials		N/A
Container Closure Integrity (Sterility assurance)	Safety	Potentially impacted by storage conditions		N/A

Appearance (General)	Safety	Manufacturing process, formulation, impact with CCS	(b) (4)	N/A
Particulate matter (General)	Safety and immunogenicity	Manufacturing process, storage		N/A
Osmolality (General)	Stability, patient comfort	DP formulation		N/A
(b) (4) (General)	Stability	DP formulation		N/A
(b) (4) (General)	Stability	DP formulation		N/A
Extractable volume (General)	Efficacy	Manufacturing process		N/A
Break loose force and glide force (General)	Efficacy, safety	Prefilled syringe device		N/A

- **Potency and Strength:**
  Besremi is supplied at 500 mcg per 1.0 mL strength. The prefilled syringe contains (b) (4) mcg of ropeginterferon alfa-2b-njft in (b) (4) mL volume. Potency is defined as the percent activity relative to reference material. The cell-based assay used to determine potency is the same as described in the DS section of this memo. The DP specification for potency is (b) (4) % on release and (b) (4) % on stability.

- **Summary of Product Design:**
  Besremi is supplied as a sterile solution for subcutaneous injection, which is prefilled in a 1 mL Type (b) (4) glass syringe. Each prefilled syringe is filled with (b) (4) mL of solution to allow for single-dose delivery of up to 1.0 mL of DP. Each 500 mcg prefilled syringe is formulated in 8.0 mg of Sodium Chloride, 1.58 mg of Sodium Acetate, 0.05 mg of Acetic Acid, 10.0 mg of Benzyl Alcohol, and 0.05 mg of Polysorbate 80. The product is designed to deliver a single target dose in 50 mcg intervals in the range of 50 mcg to 500 mcg per dose.

- **List of Excipients:**

Excipients include Acetic Acid (Ph.Eur., USP), Benzyl Alcohol (Ph.Eur., USP, JP, BP), Polysorbate 80 (Ph.Eur., USP, JP, BP), Sodium Acetate (USP), Sodium Chloride (Ph.Eur., USP, JP, BP), Water for Injection (Ph.Eur., USP, JP).

- **Reference Materials:**
  The same reference material is used for testing DS and DP.

- **Manufacturing process summary:**
  (b) (4)

- **Container closure:**
  The primary container closure systems for Besremi consists of a 1 mL clear Type (b) (4) glass syringe barrel, luer tip cap with a (b) (4), luer-lock adapter made of (b) (4), plunger stopper (b) (4) plunger rod made of (b) (4) and backstop made of (b) (4) The luer-lock adapter, plunger rod, and backstop do not come in direct contact with the drug product solution.

- **Dating period and storage conditions:**
  The stability data in the BLA support a shelf life for Besremi of 24 months when stored at the recommended storage condition of 2-8°C and protected from light.

- **List of co-package components:**
  Each finished prefilled syringe is packaged with a separate 30 gauge, ½ inch long, single-use safety needle for hypodermic injection.

D. Novel Approaches/Precedents:
None

E. Any Special Product Quality Labeling Recommendations:
Store Besremi refrigerated at 2-8°C and protected from light. (b) (4). Do not freeze the product. (b) (4).

F. Establishment Information:

Overall Recommendation: Pending				
DRUG SUBSTANCE				
Functions	**Site Information**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**

• Manufacture of (b) (4) Ropeginterferon alfa-2b-njft DS • Manufacture of (b) (4) • Testing (in-process, release, and stability) of DI and DS • Release of (b) (4) • Storage of (b) (4) and DS • Storage of cell banks (MCB and WCB)	PharmaEssentia Corporation (PEC) Taichung Plant 3F, No. 28, Keya West Rd, Daya District, Taichung 428, Taiwan DUNS: 658873411 FEI: 2000012832	Pre-license inspection required	Inspection pending	Recommendation pending outcome of inspection
• Manufacture of (b) (4) • Testing (in-process, release, and stability) of (b) (4) • Storage of (b) (4)	PharmaEssentia Corporation (PEC) 13F and 19F, No. 3, Park St., Nangang Dist., Taipei 115, Taiwan DUNS: 658647354 FEI: NA	Pre-license inspection required	Inspection pending	Recommendation pending outcome of inspection
• Production and characterization of cell banks (MCB and WCB) • Storage of cell banks (MCB and WCB)	(b) (4)	Facility has acceptable compliance history	Not inspected for this application	Approve

DRUG PRODUCT				
Function	**Site Information**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**

• Manufacture of DP • Testing (in-process) of DP • Labeling, packaging, and storage of DP	(b) (4)	Pre-license inspection required	A pre-license inspection was conducted from (b) (4) A one item Form 483 was issued. The inspection was classified VAI. Refer to the Form 483 for additional details.	Approve
• Testing (release and stability) of DP • Release of finish DP to market	PharmaEssentia Corporation (PEC) Taichung Plant 3F, No. 28, Keya West Rd, Daya District, Taichung 428, Taiwan DUNS: 658873411 FEI: 2000012832	Pre-license inspection required	Inspection pending	Recommendation pending outcome of inspection
• Testing (in-process bioburden)	(b) (4)	Facility has acceptable compliance history	Not inspected for this application	Approve

G. Facilities:

Pre-license inspections of PEC Taichung Plant, PEC, and PLI facilities are needed to support approval of this BLA. These inspections were delayed due to travel restrictions related to the coronavirus disease 2019 (COVID-19) pandemic. The inspections remain pending at the time of this review memo, which will be amended in the future with the outcome of the facility inspections.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. Annual stability protocol for drug substance

2. Qualification of future working cell banks
3. Stability protocol for master and working cell banks
4. Qualification for future primary and working reference standards
5. Concurrent qualification of (b) (4)

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

b. Drug Product

i. Protocols approved:
   1. Annual stability protocol for drug product
   2. Stability protocol for extension of drug product shelf-life
ii. Outstanding assessment issues/residual risk: None
iii. Future inspection points to consider: None

Patrick Lynch

Digitally signed by Patrick Lynch
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