CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 26, 2021
To:	Carleveva J. Thompson Regulatory Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	BESREMI (ropeginterferon alfa-2b-njft)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761166
Applicant:	PharmaEssentia Corporation c/o PharmaEssentia US, LLC

1 INTRODUCTION

On May 13, 2021, PharmaEssentia Corporation c/o PharmaEssentia US, LLC re-submitted for the Agency's review an original Biologics Licens Application (BLA) 761166 for BESREMI (ropeginterferon alfa-2b-njft) injection, in response to the Agency's Complete Response Letter dated March 12, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology (DNH) on June 3, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BESREMI (ropeginterferon alfa-2b-njft) injection.

2 MATERIAL REVIEWED

- Draft BESREMI (ropeginterferon alfa-2b-njft) injection MG and IFU received on May 13, 2021, revised on October 4, 2021, and received by DMPP on October 13, 2021.
- Draft BESREMI (ropeginterferon alfa-2b-njft) injection Prescribing Information (PI) received on May 13, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on October 13, 2021 and October 21, 2021.
- Approved PEGINTRON (peginterferon) injection labeling dated January 8, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10 and the IFU using the Arial font, size 11.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

34 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

SHARON R MILLS
10/26/2021 04:49:19 PM

REBECCA A FALTER
10/27/2021 07:59:35 AM

LASHAWN M GRIFFITHS
10/27/2021 08:35:13 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 27, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761166
Product Type: Drug Constituent Name and Strength Device Constituent:	Combination Product Besremi (ropeginterferon alfa-2b-njft[a]) injection, 500 mcg/mL Prefilled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	PharmaEssentia
Submission Date:	5/13/21; 9/13/21; 10/4/21; 10/12/21; 10/26/21
OSE RCM #:	2020-503-1; 2021-1981
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader:	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita White, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD, BCPS

[a] The nonproprietary name "ropeginterferon alfa-2b-njft" has been found conditionally acceptable for this BLA on July 26, 2021.

Reference ID: 4879002

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761166 for Besremi (ropeginterferon alfa-2b-njft).

1.1 PRODUCT DESCRIPTION

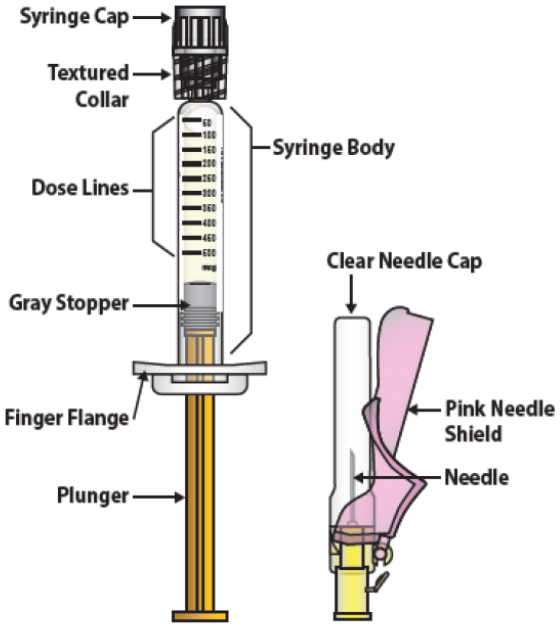
This is a combination product with a proposed prefilled syringe (PFS) device constituent part that is intended for the treatment of adults with polycythemia vera without symptomatic splenomegaly. The proposed starting dose is 100 mcg (b) (4) as a subcutaneous injection. The dose should be gradually titrated by 50 mcg every two weeks until stabilization of the hematological parameters is achieved. The maximum dose is 500 mcg every two weeks. The dose at which stabilization of the hematological parameters is achieved should be maintained at a two-week administration interval for at least (b) (4); after that time, the dosing interval may be expanded to every 4 weeks.

The Applicant proposes to supply Besremi in a carton containing one single-dose PFS and one 30 gauge ½ inch injection needle. The PFS includes a rigid syringe tip cap, Luer Lock adapter, a plunger stopper, a plunger rod, and a finger flange. The PFS has graduated dose markings at 50 mcg, 100 mcg, 150 mcg, 200 mcg, 250 mcg, 300 mcg, 350 mcg, 400 mcg, 450 mcg, and 500 mcg. Depending on the prescribed dose, the amount of dose in the syringe may need to be adjusted by discarding some of the medication prior to administration. The safety hypodermic needle is attached to the syringe through luer lock mechanism.

We note that compared to the user interface evaluated in the previous BLA review cycle (BLA submission dated March 13, 2020), the Applicant redesigned the graduated dose markings on the PFS to increase visibility and introduced a new carton insert in the currently proposed user interface. When end users pull the clear plastic tray containing the PFS and needle out of the carton, the new carton insert and the instructions for use (IFU) are on top of the PFS and needle. The new carton insert informs end users of the need to adjust the amount of medicine in the syringe to the prescribed dose (see Appendix F for carton insert image).

See Figure 1 below. For additional product information see Appendix A.

Figure 1.



BESREMi prefilled syringe

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On August 5, 2019, PharmaEssentia submitted an HF protocol as an appendix in a Type B Pre-BLA meeting package under IND 119047.[b] At that time, the Agency recommended that PharmaEssentia submit their HF study protocol separately to the existing IND and request a separate meeting.[c]

On September 11, 2019, PharmaEssentia submitted an HF protocol as part of a Type C WRO meeting request.[d] As part of the meeting request, PharmaEssentia inquired regarding use of (b) (4) to be evaluated in the HF study. October 10, 2019, we denied the meeting request and informed PharmaEssentia that their protocol submission was incomplete.[e] We provided PharmaEssentia with the protocol deficiencies and recommended they submit a new request for an HF validation study protocol review with their complete protocol submission. However, PharmaEssentia chose not to submit a complete HF validation study protocol under the IND for our review.

[b] Type B Pre-BLA Meeting Briefing Document Appendix 8.3: IND 119047. Taipei, Taiwan. PharmaEssentia US, LLC; 2019 AUG 05. Available from: \\CDSESUB1\evsprod\ind119047\0050\m1\us\16-meetings\ap-8-3-hu-fctr.pdf.
[c] Aisida, B. Type B pre-BLA Meeting Minutes for ropeginterferon-a-2b (P1101). Silver Spring (MD): FDA, CDER, OPQ, OBP (US); 2019 AUG 28. IND 119047.
[d] Type B Pre-BLA Meeting Briefing Document Appendix C: IND 119047. Taipei, Taiwan. PharmaEssentia US, LLC; 2019 SEP 11. Available at: \\CDSESUB1\evsprod\ind119047\0052\m1\us\112-other-correspondence\appendix_c_human-factor-engineering-study-protocol_v2-clean.pdf
[e] Wu, L. Correspondence: Meeting Request Denied. Silver Spring (MD): FDA, CDER, OSE (US); 2019 OCT 10. IND 119047.

On March 13, 2020, PharmaEssentia submitted their marketing application under BLA 761166, which included an HF validation study results report.

Our review of the HF validation study results concluded that the "*study demonstrated several failures, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient.*" We provided recommendations for PharmaEssentia to implement prior to conducting another HF validation study to demonstrate that the product can be used safely and effectively.[f] On December 29, 2020, PharmaEssentia submitted their updated HF validation study protocol for their additional HF validation study. Our review of the updated HF validation study protocol included recommendations for the study methodology and the instructions for use (provided by DMPP/PLT).[g]

BLA 761166 received a complete response on March 12, 2021 due to HF and facility inspections.

The Applicant resubmitted their BLA on May 13, 2021, and the Class 2 Resubmission includes the results of the additional HF validation study for the revised user interface, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E

[f] DeGraw, S. Human Factors Study Report and Label and Labeling Review for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-503 and 2020-519.

[g] DeGraw, S. Human Factors Validation Study Protocol Review for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 24. RCM No.: 2020-2727.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed , and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

We note that while no caregiver user group was proposed in the HF validation study protocol submitted December 29, 2020 for the Agency's review, the Applicant revised the study protocol to include a caregiver user group on their own. We further note this added caregiver user group only included 15 caregiver participants (10 injection experienced and 5 injection naïve, see Table 2 below). We generally expect a minimum of 15 participants per distinct user group (e.g., 15 injection experienced caregiver participants and 15 injection naïve caregiver participants). However, in this case, we did not identify unique differences between patients and caregivers that would significantly impact usability of the proposed product, and both patients and caregivers are lay users. Considering that the HF validation study included 15 participants in each of the injection experienced patient and the injection naïve patient user groups, we find that between anticipated lay users (patients and caregivers), the HF validation study included at least 15 injection experienced participants and 15 injection naïve participants. As such, in this case, the addition of 15 caregiver participants does not preclude our review of the HF validation study results.

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design	Details
Participants	n = 60 participants • Patients (n = 30) o 15 injection experienced o 15 injection naïve o (b) (4) [redacted] • Caregiver participants (n = 15) o 10 injection experienced

	o 5 injection naïve • Healthcare providers (HCPs) who treat oncology patients (n = 15)
Training	All participants were untrained.
Test Environment	The test room was setup to simulate a home or clinical office environment using a table and chairs to simulate where patient may go when using the PFS or when receiving a dose from a HCP. Due to local restrictions related to COVID 19, all participants were required to wear face coverings during the study.
Sequence of Study	• Optional familiarization • Product storage task • Simulated use • Subjective feedback/root cause analysis • Knowledge tasks • Subjective feedback/root cause analysis All participants completed a single study session. During the session, they were first given as much time as needed (if they chose) to do whatever they would do upon arriving home from the pharmacy with the prescribed product; or if a caregiver or HCP, to do whatever they would do prior to using the product on a patient. Next, participants were asked to store the product. Next, participants performed all unaided tasks and provided subjective feedback. HCPs were asked to administer a 100 mcg dose. Patients and caregivers were asked to administer a single dose of one of the following doses: 100 mcg, 150 mcg, 200 mcg, 250 mcg, 300 mcg, 350 mcg, 400 mcg, 450 mcg, 500 mcg.

3 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Reference ID: 4879002

Table 3. Identified Issues and DMEPA's Findings for Critical Tasks		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task to store in the original carton, there was 1 use error (1 failure). One injection-experienced caregiver participant stored Besremi and the needle in the refrigerator, but outside of the carton. Regarding subjective feedback, the participant stated that he did not read the instructions for use (IFU) because it was inside the carton and further stated that removing "to protect it from light" from the storage information on the carton would have made the statement more clear, even though he did not read it. The Applicant's root cause analysis (RCA) attributed the use error to the participant not reading the storage information on the carton or in the IFU. The Applicant did not propose mitigations in response to the use error and noted that the carton labeling and IFU have a dedicated storage section. Per the Applicant (b) (4)	Based on the URRA, if this task is omitted or not performed correctly there is risk of reduced medication efficacy/underdose and reduced effectiveness. We agree with the Applicant's RCA that the use error was due to the participant not reading the labeling. Our review of the study results identified subjective feedback that was consistent with the RCA. For example, participant P42 stated, "Because I didn't read the instructions, the instructions are inside the carton." Our review of the user interface (labels and labeling, etc.) finds that both the carton labeling and IFU include a storage statement to store the PFSs in the original carton. Our independent review finds that the information is presented in a manner consistent with other similar marketed products. We reviewed and agree with the Applicant's justification that (b) (4) Thus, we had no concern that this use error requires mitigation, and we did not identify areas of improvement in the user interface. We have no recommendations.
2.	For the task "Check expiration date", there was 1 use error (1 failure) in which one injection-naïve patient participant did not check the expiration date on the carton or state out loud he would check. Regarding subjective feedback, the participant stated they do not remember reading the step to check the expiration date. The Applicant's RCA stated that there is no clear explanation or root cause related to the product user interface for why this participant did not check.	Based on the URRA, if this task is omitted or not performed correctly there is risk of reduced medication efficacy, acute underdosing (which may lead to mild elevations of blood counts), and chronic underdosing (which may lead to inadequate control of blood counts). We agree with the Applicant's RCA that there is no clear explanation to attribute this use failure. Our review of the study results identified subjective feedback that aligns with the RCA. When asked whether they checked for the expiration date, the

Table 3. Identified Issues and DMEPA's Findings for Critical Tasks		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
	The Applicant did not propose mitigations in response to the use error.	participant replied, "Did I check for the expiration date? I probably did not." Our review of the labels and labeling finds that IFU Step 1 provides instruction and a graphic regarding checking the expiration date. We note the expiration date will appear on the container label and carton labeling. We are also aware that as part of the therapeutic monitoring of patients receiving the drug product, hematologic levels (i.e., hematocrit, platelets, leukocytes) are assessed routinely which decreases our concern for risk of patient harm. We did not identify areas of improvement in the user interface to address this use error and we have no recommendations.
3.	For the task "Attach the needle to the Besremi prefilled syringe", there was 1 use error (1 use difficulty). One injection-experienced caregiver participant had difficulty attaching the needle to the PFS. The participant uncapped the syringe, then removed the clear needle cap and inserted the needle into the syringe luer. Then they continued to look at the IFU and realized that he had attempted to attach the needle incorrectly; then the participant re-capped the needle and correctly attached the needle. Regarding the subjective feedback, the participant stated that he was only looking at the illustration in IFU sub-step 5.3 and ignored the instructional text because there was too much text. The participant also stated that all the text in sub-step 5.3 should be replaced with illustrations. The Applicant's RCA attributed the use error to the participant not reading the instructional text. Additionally, following simulated use testing and in response to the question "What difficulty, if any, did you have preparing or dosing with	Based on the URRA, if this task is omitted or not performed correctly there is slight risk of contamination/ local infection, potential for needle-stick injury/local infection, risk of delay of dose and risk of underdose/no or reduced symptom relief. We agree with the Applicant's RCA that the use error was due in part to the participant not reading the instruction. Our review of the study results identified subjective feedback that indicated one participant considered the IFU to be text-heavy and recommended replacing text with graphics. We provide our assessment of the labeling in the paragraph below. Additionally, we note one participant indicated it was difficult to determine whether the needle was secured; however, we note this participant was able to successfully complete the task. Our review of the labels and labeling finds IFU Step 5.3 states "Attach the needle to the prefilled syringe by firmly pushing it into the collar of the syringe and then screwing (turn clock-wise)

Table 3. Identified Issues and DMEPA's Findings for Critical Tasks		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
	this product?", 1 injection-naïve patient participant stated that it was hard to tell if the needle was secure and that it didn't feel secure at first. The Applicant did not propose mitigations in response to the use error and noted the IFU reasonably describes and demonstrates how to attach the needle. The Applicant also states that removal of the clear needle cap is not mentioned until sub-step 7.2.	it on until it feels securely attached" and includes a corresponding graphic. Our review finds that the instructions in the IFU is stepwise in that users are not instructed to remove the cap until IFU step 7.2, Figure W. Furthermore, we note that the previous figures prior to Figure W depict a capped needle. We did not identify areas of improvement in the user interface to address the use error and we have no recommendations.
4.	For the task "Removes clear needle cap", there was 1 use error (1 use difficulty). One injection-naïve caregiver had difficulty removing the clear needle cap. The participant initially held the syringe from the bottom of the clear needle cap with one hand while trying to pull off the clear needle cap with her other hand. The participant eventually reviewed the IFU and successfully removed the cap. Regarding the subjective feedback, the participant stated that she did not initially look at the IFU and was nervous about the needle. The Applicant's RCA attributed the use error to the participant initially not referring to the IFU. The Applicant did not propose mitigations in response to the use error and noted that the IFU describes and demonstrates how to remove the clear needle cap from the syringe.	Based on the URRA, if this task is omitted or not performed correctly there is risk of delay of dose, needle-stick injury/local infection, and potential loss of medication. We agree with the Applicant's RCA that the use error was due in part to the participant not reading the labeling instruction. Our review of the study results identified subjective feedback that aligns with the RCA. For example, the participant stated no additional revisions to the labeling were necessary to prevent this use difficulty from occurring in the future. Our review of the labels and labeling finds IFU Step 7.2 states "Remove the clear needle cap by pulling it straight off" and includes a corresponding graphic. We also note the graphic shows a hand holding the middle of the clear needle cap. We did not identify areas of improvement in the user interface to address the use error and we have no recommendations.
5.	For the task "Set dose", there were 2 use errors (1 failure and 1 close call). The failure involved an injection-naïve caregiver who did not set the dose using the instructed technique; instead, the participant delivered the prescribed dose of 250 mcg by only injecting the correct amount and holding back the remaining amount (and then disposing it). The close call involved an injection experienced patient participant	Based on the URRA, if this task is omitted or not performed correctly there is risk of overdose or underdose. The URRA also notes that overdose might result in flu-like symptoms, acute underdosing (between 1-3 months) might lead to mild elevations of blood counts including the hematocrit, and chronic underdosing might lead to inadequate control of blood counts.

Table 3. Identified Issues and DMEPA's Findings for Critical Tasks		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
	who initially set the dose to 200 mcg rather than her prescribed dose of 300 mcg; the participant realized the error prior to injection and the moderator provided the participant with a new PFS. Regarding subjective feedback, 1 participant who experienced a failure stated that they blanked out and noted it would be helpful to include a star next to this step which will remind him to pay special attention to it. The other participant who experienced a close call indicated that they looked at the bottom of the gray stopper rather than the top outer edge. The Applicant's RCA attributed the failure to the participant not fully reading IFU Step 8 and not following the IFU when dosing, and the Applicant's RCA attributed the close call to the participant being nervous and fixating on the bottom of the gray stopper. The Applicant did not propose mitigations in response to the use error. The Applicant noted that the IFU has a dedicated section regarding how to set the dose, Step 8 is dedicated to setting the dose, and the carton includes a placard insert regarding setting the dose.	We agree with the Applicant's RCA. Our review of the study results notes that all study participants administered the correct dose. Additionally, we didn't identify subjective feedback that indicated confusion regarding how to adjust the PFS to the prescribed dose. For example, when debriefed regarding the close call, the participant stated that "nothing in the instructions is wrong" and "these were actually the most clear instructions she had ever seen." We note that a participant suggested increasing the prominence of IFU Step 8 by [redacted] (b) (4). However, our review of the labels and labeling finds that instructions and graphics for adjusting the PFS to the prescribed dose are presented in multiple locations in the IFU (i.e., the red "Read Me: How to Adjust the Medicine Level…" box located after the Important Information section and in IFU Step 8). We did not identify areas of improvement in the user interface and we have no recommendations to address these use errors. Based on our assessment of the PFS design, we remain concerned regarding the risk of dosing errors. Specifically, we are concerned that the PFS requires users to adjust the dose prior to administration of doses less than 500 mcg. Keeping in mind that HF validation testing is primarily a qualitative rather than a quantitative exercise[h], we are concerned that even with training and labeling mitigations, users prescribed doses less than 500 mcg may not adjust the PFS to the prescribed dose

[h] Guidance for Industry and Food and Drug Administration Staff : Applying Human Factors and Usability Engineering to Medical Devices. Food and Drug Administration. 2016. Available from https://www.fda.gov/media/80481/download.

Table 3. Identified Issues and DMEPA's Findings for Critical Tasks		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
		given the "typical use of PFS is to inject the whole contents of the PFS" in healthcare practice, and may unintentionally administer the entire contents of the syringe. Thus, based on our residual concern and understanding the public health need for the proposed product, we provide a recommendation for DNH in section 4 below to implement an enhanced pharmacovigilance requirement for this product.
6.	For the task "Administer dose", there were 2 use errors (1 failure and 1 close call). The failure involved an injection-naïve patient participant whose needle slipped out of the injection pad while she was injecting resulting in a wet injection. Once she noticed, she reinserted the needle and completed the injection. The close call involved a HCP covering the needle with pink needle shield after setting the dose; the shield is designed to lock in place, so the participant was unable to retract it. The participant obtained a new needle and completed the injection process. Regarding subjective feedback, 1 participant said the needle came out of the pad when she leaned forward and believed it was due to lack of experience and not reading the instructions. The other participant stated that she is used to a different type of syringe, she thought she was protecting the needle by covering it, and that she was not looking at the instructions. The Applicant's RCA attributed the use errors to study artifact, not referring the IFU, and referring to memory and past experience. The Applicant did not propose mitigations in response to the use errors and noted that the current instructions and illustrations are reasonable for all users and clearly communicates how to deliver the dose.	Based on the URRA, if this task is omitted or not performed correctly there is risk of delay of therapy or underdose. We also note the risk of dose omission. We agree with the Applicant's RCA, which attributed the use errors to study artifact, not referring the IFU, and referring to memory and past experience. Our review of the study results identified subjective feedback that indicated that the use errors might have occurred due to lack of familiarity and negative transfer. For example, participant P55 stated she covered the needle out of habit. In both instances, we note the participants were ultimately able to administer a complete dose. Our review of the labels and labeling finds that IFU Step 9 provides instructions and graphics regarding administration and injection technique. Also, Step 7.1 (1) instructs users to pull back the needle shield and (2) informs users that the needle shield will be used after the injection to protect from needle-stick injuries. We did not identify areas of improvement in the user interface to address the use errors and we have no recommendations.

3.1 ANALYSIS OF NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the following non-critical tasks. However based on our review of the available participants' subjective feedback, the Applicant's root cause analysis, and the Applicant's proposed risk mitigation strategy, we determined the residual risk is acceptable. Specifically, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling and in alignment with best labeling practices to instruct the user to wash hands before use and to allow the carton to sit out for 15-30 minutes. In addition, we considered the use tasks of the proposed product as compared with the use tasks in similar marketed products with the same user groups to determine if there are any known concerns of vulnerability to use error and did not identify any concern. Subsequently, we did not identify further need to implement additional risk mitigation strategies at this time to address the use errors related to the following non-critical tasks:

- Allow carton to sit out for 15-30 minutes
- Wash hands

Of note, all of the participants subsequently provided accurate answers to knowledge tasks related to these same observations.

3.2 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the label and labeling received on May 13, 2021, October 4, 2021, and October 12, 2021 , our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 5 was conveyed to the Applicant in a September 29, 2021 Information Request (IR) (see Appendix E), and in light of this, the Applicant submitted revised container label and carton labeling received on October 4, 2021. Our review of the revised container label received October 4, 2021 determined that it was acceptable from a medication error perspective.

Additional carton label recommendations were also conveyed to the Applicant in an October 7, 2021 IR and in an October 22, 2021 IR, and the Applicant submitted revised carton labeling received on October 12, 2021 and October 26, 2021, respectively (see Appendices E and F). Our review of the revised carton labeling received on October 26, 2021 determined that it is acceptable from a medication error perspective.

Table 4: Identified Issues and Recommendations for Division of Non-Malignant Hematology (DNH)			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information			
1.	In Table 1 of Section 2.2 Dose Modifications, the information regarding dose modification for elevated liver enzymes can be improved to increase clarity.	Lack of clarity regarding dose modification might result in user confusion and dosing errors.	Consider revising "Interrupt treatment until recovery, restart at dose 50 mcg lower (b) (4)" to "Interrupt treatment until recovery, restart at dose 50 mcg lower than the previous one".
2.	(b) (4)		

Table 5: Identified Issues and Recommendations for PharmaEssentia			
	Identified Issue	Rationale for Concern	Recommendation
Container Label			
1.	The carton labeling does not contain an "Rx Only" statement.	The "Rx only" statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act.	Revise the label to include the "Rx Only" statement in an area that does not interfere with or compete for prominence with important product identifying information (i.e., product name, product strength).
2.	The format for the expiration date is not defined.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	The container label does not contain the name of the manufacturer.	The name of the manufacturer, packer, or distributor of the drug is required per 21 CFR 201.10(i).	Revise the container label to include the name of the manufacturer.
Carton Labeling			
1.	A Medication Guide statement does not appear on the principal display panel (PDP).	The Medication Guide provides information that is necessary to patients' safe and effective use of the product. Per 21 CFR 208.24(d), the label shall instruct the	Revise the PDP of the carton labeling to include the statement "Dispense the enclose Medication Guide to each patient" or similar statement.

		authorized dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided.	
2.	The Usual Dose statement is not in the correct format.	Per 21 CFR 201.55, "…labels for prescription drugs bear a statement of the recommended or usual dosage." Additionally, the "Usual Dose" statement should be aligned with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement (b) (4) " to read "Recommended Dosage: See Prescribing Information."

4 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation study identified use errors with critical tasks. However, taking into consideration the review of the subjective feedback, root cause analysis, and our independent review of the proposed user interface, we find residual risks associated with these use errors acceptable. Thus, in this specific instance, we accept the simulated HF validation study results.

Our evaluation of the proposed Besremi medication guide and Instructions for Use received on May 13, 2021 did not identify areas of vulnerability that may lead to medication errors. The revised container label received on October 4, 2021, carton labeling insert received on October 12, 2021, and carton labeling received on October 26, 2021 are acceptable from a medication error perspective, and we have no additional recommendations at this time.

While the submitted HF validation study supports that the proposed user interface has been optimized to the extent possible with residual risks at an acceptable level, there are limitations to an HF validation study just like there are limitations to clinical studies. From our postmarketing experience with similar products, we find the proposed PFS, requiring users to adjust the doses less than 500 mcg, poses an inherent risk for dosing errors that can lead to compromised care. As such, we include recommendations for DNH in Section 4.1 below.

4.1 RECOMMENDATIONS FOR DNH

1. We recommend requesting an enhanced pharmacovigilance requirement for this product specifically to ensure that all postmarket medication errors are reported to FDA for this particular product. Based on the single-dose prefilled syringe (PFS) design, we remain concerned about the inherent risk for dosing errors associated with the PFS design. Based on our postmarket experience with other similar products, we remain concerned that Besremi end users prescribed doses less than 500 mcg may unintentionally administer the entire contents of the PFS.
2. We recommend requesting the Applicant explore and develop other designs or presentations post-approval that further facilitate the recommended dosing for Besremi (e.g., consider the most common dose for patients to maintain hematological stabilization).

   While dosing flexibility is necessary with injectable drug products, applicants should determine the appropriate fill sizes, considering how the presentations are likely to be used. Even when appropriately labeled, single-dose prefilled syringe that contain significantly more drug than is required for a single dose may result in the misuse of the leftover drug product.

   It might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

   Guidance on Safety Considerations for Product Design to Minimize Medication Errors

   Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products

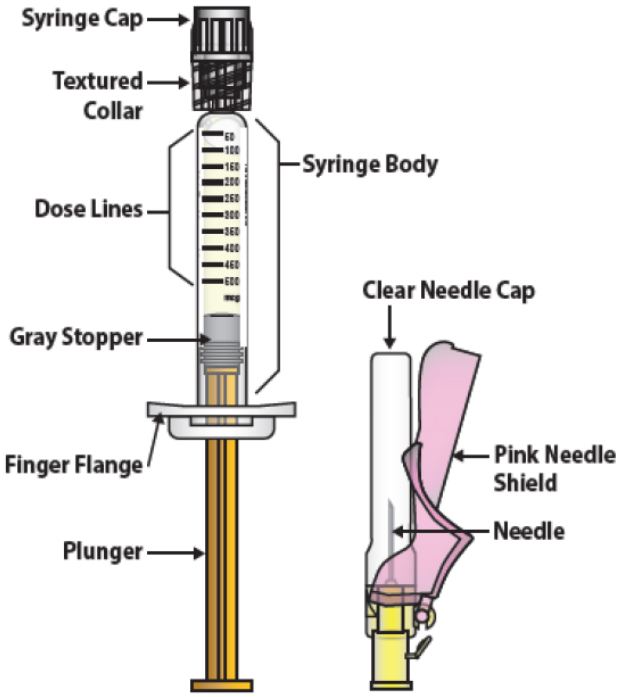
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Besremi that PharmaEssentia submitted on May 13, 2021.

Table 6. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Type I interferon
Active Ingredient (Drug or Biologic)	ropeginterferon alfa-2b-njft
Indication	treatment of adults with polycythemia vera without symptomatic splenomegaly
Route of Administration	subcutaneous
Dosage Form	injection
Strength	500 mcg/mL
Dose and Frequency	<u>Single-Agent Therapy</u>: • The recommended starting dosage for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. • Gradually increase the dose by 50 mcg every two weeks until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L, and leukocytes less than 10 x 10^9/L). • The maximum dose is 500 mcg every two weeks. <u>Combination Therapy</u>: • (b) (4) [redacted] • Gradually increase the dose by 50 mcg every two weeks while gradually decreasing the (b) (4) [redacted] until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L, and leukocytes less than 10 x 10^9/L). • The maximum dose is 500 mcg every two weeks.

Reference ID: 4879002

	Maintain the dose level at which hematological stability is achieved for [redacted] (b) (4). After that time, the dosing interval may be expanded to every 4 weeks.
How Supplied	BESREMi (ropeginterferon alfa-2b-njft) is a sterile, preservative-free, clear and colorless to slightly yellowish solution for subcutaneous administration in a single-dose prefilled syringe. Each carton contains one 500 mcg/mL prefilled syringe with a 30 gauge, ½ inch safety hypodermic needle (NDC 73536-500-01).
Storage	Store in a refrigerator at 36 °F to 46 °F (2 °C - 8 °C) in the original carton to protect from light. Do not freeze.
Container Closure/Device Constituent	 *BESREMi prefilled syringe*
Intended Users	Patients, caregivers, HCPs
Intended Use Environment	Home or clinical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On September 20, 2021, we searched the L:drive and AIMS using the terms, ropeginterferon and BLA 761166 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 3 previous reviews[i,j,k], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\CDSESUB1\evsprod\bla761166\0048\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\pec-hf\pec-hf-report.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On September 7, 2021, we sent an Information Request to the Applicant to request additional information regarding the HF validation study results. The Applicant submitted a response on September 13, 2021. See link:
\\CDSESUB1\evsprod\bla761166\0049\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\pec-hf-ir\resp-human-factors-ir-rcvd-7sept2021.pdf

On September 29, 2021, the Agency sent the combined DMEPA and OBP container label and carton labeling recommendations to the Applicant. The Applicant's response was received on October 4, 2021. See link:
\\CDSESUB1\evsprod\bla761166\0050\m1\us\cover.pdf

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[i] DeGraw, S. Human Factors Study Report and Label and Labeling Review for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-503 and 2020-519.

[j] DeGraw, S. Labeling Memo for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 23 13. RCM No.: 2020-503-1.

[k] DeGraw, S. Human Factors Validation Study Protocol Review for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 24. RCM No.: 2020-2727.

On October 7, 2021, we sent an Information Request to the Applicant requesting additional revisions to the carton labeling. Specifically, we requested that the Medication Guide statement appear on the principal display panel of the carton labeling, and we requested the Applicant submitted the carton labeling insert for Agency review. The Applicant's response was received on October 12, 2021. See link:
\\CDSESUB1\evsprod\bla761166\0053\m1\us\cover.pdf

On October 22, 2021, we sent an Information Request to the Applicant requestion an additional revision to the carton labeling. Specifically, we requested that the carton labeling include a statement that indicates users may to need to adjust the amount of medicine in the syringe to the prescribed dose. See link:
\\CDSESUB1\evsprod\bla761166\0054\m1\us\cover.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[l] along with postmarket medication error data, we reviewed the following Besremi labels and labeling submitted by PharmaEssentia.

- Container label received on May 13, 2021 and October 4, 2021
- Carton labeling received on May 13, 2021, October 12, 2021, and October 26, 2021
- Carton labeling insert received on October 12, 2021
- Instructions for Use received on May 13, 2021. Available from:
  - \\CDSESUB1\evsprod\bla761166\0048\m1\us\draft-instructions-for-use.pdf
- Prescribing Information and Medication Guide (Image not shown) received o on May 13, 2021. Available from:
  - \\CDSESUB1\evsprod\bla761166\0048\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images received on May 13, 2021

Container label

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[l] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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LOLITA G WHITE
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CHI-MING TU
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 26, 2021

To: Carleveva Thompson, MS, Regulatory Project Manager,
Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling,
(DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BESREMi (ropeginterferon alfa-2b-njft) injection, for subcutaneous use

BLA: 761166

In response to DNH's consult request dated June 3, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for BESREMi (ropeginterferon alfa-2b-njft) injection, for subcutaneous use (Besremi).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Carleveva Thompson) on October 13, 2021, and revised PI from DNH (Virginia Kwitkowski) on October 21, 2021, are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed MG and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 12, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 13, 2020
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761166
Product Type:	Combination Product
Drug Constituent Name, Dosage Form, and Strength:	Besremi (ropeginterferon alfa-2b-njft) injection 500 mcg/mL
Device Constituent:	Prefilled Syringe (PFS)
Rx or OTC:	Rx
Sponsor/Sponsor Name:	PharmaEssentia Corporation (PharmaEssentia)
Submission Date:	March 13, 2020, June 12, 2020, and August 25, 2020
OSE RCM #:	2020-503 and 2020-519
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors (Acting):	Jason Flint, MBA, PMP
DMEPA Associate/Deputy Director:	Chi-Ming (Alice) Tu, PharmD

Reference ID: 4684750

1 REASON FOR REVIEW

PharmaEssentia submitted a human factors (HF) validation study report and labels and labeling under BLA 761166 for Besremi (ropeginterferon alfa-2b-njft). We reviewed the HF validation study report and proposed labeling for areas of vulnerability that may lead to medication errors.

1.1 PRODUCT DESCRIPTION

Besremi is intended to treat polycythemia vera (PV) in adults without symptomatic splenomegaly. The proposed starting dose is 100 mcg (b) (4) as a subcutaneous injection. The dose should be gradually titrated by 50 mcg every two weeks until stabilization of the hematological parameters is achieved. The maximum recommended single dose is 500 mcg every two weeks. The dose at which stabilization of the hematological parameters is achieved should be maintained at a two-week administration interval for at least (b) (4).

PharmaEssentia proposes to supply Besremi in a pack containing one single-dose prefilled syringe (PFS) and one injection needle. The PFS is composed of a syringe barrel with plastic rigid tip cap and Luer Lock adapter, a plunger stopper, a plunger rod, and a backstop. The PFS has graduated dose markings at 50 mcg, 100 mcg, 150 mcg, 200 mcg, 250 mcg, 300 mcg, 350 mcg, 400 mcg, 450 mcg, and 500 mcg. The (b) (4) safety hypodermic needle (30G x 12.7mm) is attached to the syringe through Luer Lock mechanism.

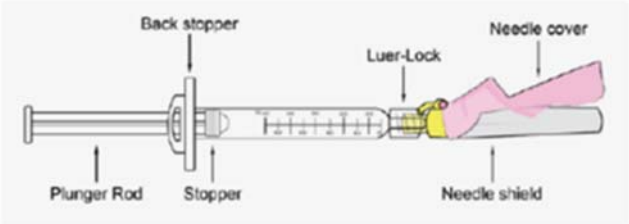

Figure 1. Diagram of the PFS with Needle Attached

Figure 2. PFS

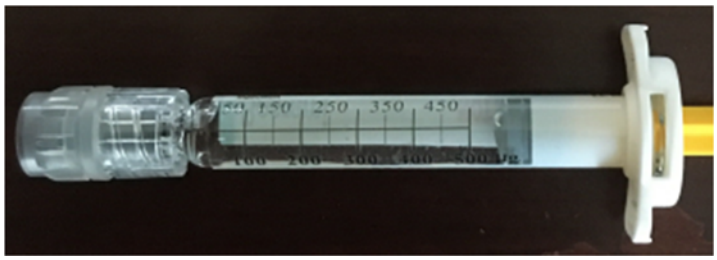

Figure 3. PFS Dose Markings

Reference ID: 4684750

1.2 REGULATORY HISTORY RELATED TO THE HUMAN FACTORS STUDY

On August 5, 2019, PharmaEssentia submitted a human factors (HF) protocol as an appendix in a Type B Pre-BLA meeting package under IND 119047.[1] During the August 28, 2019 meeting, PharmaEssentia noted the HF protocol was submitted (b) (4) the Applicant plans to market the prefilled syringe if approved. PharmaEssentia also asked questions about using (b) (4) to be evaluated in the HF study. At that time, the Agency recommended that PharmaEssentia submit their HF study protocol separately to the existing IND and request a separate meeting.[2]

On September 11, 2019, PharmaEssentia submitted an HF protocol as part of a Type C WRO meeting request.[3] As part of the meeting request, PharmaEssentia again asked questions about using (b) (4) to be evaluated in the HF study. October 10, 2019, we denied the meeting request and informed PharmaEssentia that their protocol submission was incomplete.[4] We provided PharmaEssentia with the protocol deficiencies and recommended they submit a new request for an HF validation study protocol review with their complete protocol submission.

The Sponsor chose not to submit a complete HF validation study protocol under the IND for our review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E

[1] Available at: \\CDSESUB1\evsprod\ind119047\0050\m1\us\16-meetings\ap-8-3-hu-fctr.pdf

[2] Meeting Minutes for 2019 AUG 28 Type B Pre-BLA Meeting. Dated 2019 SEP 20. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8051730d&_afrRedirect=2378998083387324

[3] Available at: \\CDSESUB1\evsprod\ind119047\0052\m1\us\112-other-correspondence\appendix_c_human-factor-engineering-study-protocol_v2-clean.pdf

[4] Park, Linda. Correspondence: Meeting Request Denied. 2019 OCT 10. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8051e901&_afrRedirect=2317670318460693

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Labels and Labeling	F
Packaging	G

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Objective

Evaluate whether the ropeginterferon alfa-2b PFS, as designed, supports safe and effective use by the representative users during subcutaneous injection.

Participants

The study participants included 30 representative users of the ropeginterferon alfa-2b PFS:

- 15 adult polycythemia vera (PV) patients
- 15 healthcare providers (HCPs): licensed nurses who administer injections to patients

The breakdown of participant demographics is described below.

Demographic	PV Patients (n=15)	HCPs [Nurses] (n=15)
Age (Years)		
18-49	0	12
50+	15	3
Gender		
Female	8	14
Male	7	1
Handedness		
Right	14	10
Left	1	5
Injection Experience		
Injection naïve	5	0
Injection experienced	10	15
• Experience with PFS	7	15
• Experience with Pegasys (peginterferon alfa-2a) PFS	3	question not asked

The Sponsor noted that "while caregivers may also inject this product, it is expected that, if a patient and a nurse are capable of injecting the product safely and effectively, then a caregiver would be expected to administer the product safely and effectively as well". As such, a separate caregiver user group was not evaluated as part of the study.

Reference ID: 4684750

Training

All study participants were untrained. The Sponsor noted that *"patients and/or caregivers are expected to receive instructions from their pharmacist, physician, or nurse as a part of prescribing the drug, including walking through the Instructions for Use of the Ropeginterferon alfa-2b Prefilled Syringe. The intended first use of the product is either with a demonstration injection by the HCP or a self-injection supervised by an HCP. Users may be permitted by their HCP to self-administer subsequent doses if the HCP determines that it is appropriate."* Although the Sponsor expects patients and caregivers to receive training and a walk-through demonstration, the Sponsor also recognizes patients may not receive such training in some cases. As such, all study participants were untrained in this HF validation study.

Methodology

- Simulated Use Tasks: Each participant used the product beginning to end, starting with opening the sealed carton and ending with product disposal. Patient participants performed an injection into an injection pad strapped to the patient in the location the patient indicated they would administer the injection. HCP participants performed an injection into an injection pad attached to manikin in the location the HCP indicated they would administer the injection. Tasks were performed in a simulated use environment of a living room (patients) or a patient consultation room (HCPs). Study participants had the IFU available for reference in case they choose to use it during the simulated use testing but were not prompted to use the IFU throughout the session.
- Knowledge Questions: Questions were asked after the simulated use portion of the study was concluded. For this portion of the study, participants were not directed to or asked to refer to the IFU for these tasks; however, the IFU was still available if the participants chose to reference it.
- IFU Assessment: The IFU was evaluated for critical tasks in full as part of the study. Any instance of referring to the IFU during the study was recorded. The IFU was also evaluated with comprehension questions to ensure the information is understandable, perceivable, and supports correct use as part of the usability engineering process.

Of note, to further assess the critical task of measuring doses less than 500 mcg, participants were asked to review Step 14 in the IFU and measure out two additional different doses following the instructions for use in Step 14 after completing the simulated use, knowledge tasks, and subjective feedback portions of the study. For this portion of the study, the participants were provided a new PFS that had already been assembled and asked to imagine that all of the other steps leading up to Step 14 aside from uncapping the syringe have been completed.

3.2 RESULTS AND ANALYSES

Table 2 describes the use errors, use difficulties, and close calls, the Sponsor's analyses of these errors, and our analyses for identified issues for which we have concerns and recommendations for the Sponsor.

Reference ID: 4684750

Table 2. Identified Issues and Recommendations for Sponsor					
Critical Task	Number of Failures/Use Errors[5], Use Difficulties[6], and Close Calls[7]	Description of Failures/Use Errors, Close Calls and Use Difficulties	Summary of Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Patients: Push the plunger to the prescribed dosing mark. Related tasks: Discard excess liquid from the PFS without contaminating the needle. Fully depress the plunger and remove the needle from the injection site.	100 mcg dose: • 8 failures • 3 use difficulties • 1 close call	Failures • 5 users (P04, P10, P03, P05, P15) administered the full contents (500 mcg) • P07 measured 150 mcg • P06 injected 110 mcg and stated he would reuse the PFS • P14 injected 130 mcg and stated he would reuse the PFS Difficulties: • P02 measured 90 mcg • P13 measured 80 mcg • P09 initially measured 120 mcg but self-corrected Close Calls • P01 measured dose while injecting, but measured correctly	Failures • P04 and P10 administered 500 mcg because they assumed the PFS was already measured to the correct dose. • P03 administered 500 mcg because she did not read the instructions on the prescription card to administer 100 mcg. P03 also stated the task was "not real life, so not invested in ensuring correct dose" (study artifact). • P05 administered 500 mcg due to memory lapse likely due to being inebriated • P15 administered 500 mcg because he forgot to perform the step associated with discarding medication. • P07 measured the incorrect amount because she measured as she was injecting and injected too much medication due to difficulties seeing the syringe	Discussion from the HF Report: The related risks were added to the Use-Related Risk Analysis. The risks were reviewed in relation to the Human Factors Validation Study data and it was concluded that the risks are considered acceptable. Proposed mitigations received in the August 25, 2020 response to our information request: • Add an insert to the carton on top of the IFU and PFS emphasizing the need to measure the dose (see figure 4 below). • Revise Step 14: Move the figure of the syringe to top of the step before the text,	We note the potential harm associated with these errors is an underdose or overdose. An underdose may result in the patient receiving inadequate treatment, while an overdose may result in adverse effects, potentially resulting in treatment termination. We acknowledge the Sponsor's proposed labeling mitigations. Based on our review, we've identified additional labeling mitigations to address these errors (see section 4.1). Because these mitigations impact the critical task of measuring and

[5] The Sponsor defined a failure as a 1) incorrect dose resulting in an overdose or underdose 50 mcg or more or 2) incorrect dose measured using the wrong technique

[6] The Sponsor defined a use difficulty as a 1) incorrect dose resulting in an overdose or underdose of less than 50 mcg, 2) correct dose but user notes difficulty, or 3) incorrect dose but self-corrects before administration

[7] The Sponsor defined a close call as a correct dose measured using the wrong technique

Reference ID: 4684750

			markings (was not wearing reading glasses) and she noted the illustration in IFU is unclear. • P06 and P14 measured the incorrect amount because they measured as they were injecting and injected too much medication due to a desire to save the remaining medication for their next dose. P14 noted difficulty reading the markings on the PFS as she was left-handed, and her hand blocked her view of the syringe as she injected the medication. Difficulties: • P02 discarded too much when trying to remove air bubbles. • P13 discarded too much because user had difficulty determining what feature on the stopper to measure from (did not see instructions in IFU). • P09 initially measured 120 mcg but self-corrected (no further explanation provided) Close Calls • P01 measured dose while injecting because she initially thought the PFS would be reused	increase clarity of measuring instructions on the figure of the syringe, and increase the size of the stop sign and bold the red outline around the step (see figure 5 below) • Update the IFU to include additional warnings to not re-use the syringe or needle, even if medication is remaining (see figure 6 below). • Add "Single-Use Only" in red text to the carton labeling. • Update measurement markings & numbering on PFS label to improve visibility (see figure 7 below). • Create a training video for patients. • Create a training guide to assist HCPs with training patients.	administering a dose, we recommend an additional HF validation study be completed to ensure that these mitigations do, in fact, address the observed use errors and do not introduce any new risks.
	250 mcg dose (measured after being prompted to	Failures • P01 measured approximately 300 mcg Difficulties: • P02 measured 225 mcg	Failures • P01 measured incorrectly due to difficulties seeing the syringe markings (specifically the dose markings ending in -50) and the top of the dome of the stopper.		

Reference ID: 4684750

	read step 14 in the IFU): • 1 failure • 5 use difficulties	• P04 correctly measure 250 mcg but noted difficulty • P05 measured 210 mcg • P10 measured 240 mcg • P14 correctly measure 250 mcg but noted difficulty	P01 did not bring reading glasses which she normally wears. Difficulties • P02 discarded too much when trying to remove air bubbles. • P04 expressed difficulty seeing the dome of the stopper and expressed confusion on whether to measure from top or bottom of stopper. • P05 noted difficulty seeing the syringe markings and the liquid inside the syringe. Additionally, P05 was likely inebriated. • P10 misjudged top of the dome of the stopper and noted she would ask her pharmacist to show her how to measure a dose. • P14 was left-handed and noted the numbers were in the wrong area and wrong orientation when she was viewing them.		
	450 mcg dose (measured after being prompted to read step 14 in the IFU): • 6 use difficulties	Difficulties: • P04 measured 425 mcg • P05 measured 410 mcg • P10 measured 440 mcg • P13 measured 430 mcg • P15 measured 440 mcg • P06 measured 50 mcg	Difficulties • P04 noted the numbers on the syringe were not easy to read. P04 also noted she would need her reading glasses. • P05 noted his eyes were not good enough (P05 was wearing glasses) and was likely inebriated. • P10 tried to measure from top of dome but misjudged. • P13 realized he expelled too much medicated (wasn't paying close enough attention) but figured small underdose was ok. P13 also		

			noted he would need a good light to see the top of the dome of the stopper. • P15 believed the dose should be measured from the widest part of the stopper based on previous experience and stated he did not read the instructions in the IFU to measure from the top of the dome of the stopper. • P06 misunderstood the prompt and thought he was simulating an injection of 450 mcg and that it was his habit to measure as he was injecting (would have correctly injected a 450-mcg dose).		
HCPs: Push the plunger to the prescribed dosing mark. Related tasks: Discard excess liquid from the PFS without contaminating the needle. Fully depress the plunger and remove the needle	100 mcg dose: • 5 failures • 7 use difficulties	Failures: • 4 users (N03, N05, N07, N13) administered the full contents (500 mcg) • N08 measured 50 mcg Difficulties: • N01 measured 125 mcg • 2 users (N04, N06) injected 100 mcg without discarding extra medication first • N10 measured 105 mcg then 95 mcg • 3 users (N11, N12, N15) measured 90 mcg	Failures: • N03, N05, N07, and N13 assumed the PFS was already measured to the correct dose. N07 recommended a vial presentation. • N08 measured from the bottom of the stopper rather than the top of the dome. N08 also noted she would have another nurse verify her dose and would likely receive training. Difficulties: • N01 intentionally measured to 125 mcg to account for large air bubble; was able to expel air bubble and measure 100 mcg • N04 and N06 injected the correct dose but did not expel extra medication first. Both N04 and	Discussion from the HF Report: The related risks were added to the Use-Related Risk Analysis. The risks were reviewed in relation to the Human Factors Validation Study data and it was concluded that the risks are considered acceptable. Proposed mitigations received in the August 25, 2020 response to our information request: • Add an insert to the carton on top of the IFU and PFS emphasizing the need to	We note the potential harm associated with these errors is an underdose or overdose. An underdose may result in the patient receiving inadequate treatment, while an overdose may result in adverse effects, potentially resulting in treatment termination. We acknowledge the Sponsor's proposed labeling mitigations. Based on our review, we've identified additional labeling mitigations to address these errors (see section 4.1).

Reference ID: 4684750

from the injection site.			N06 noted they were measuring from the widest part of the stopper, not the top of the dome of the stopper. • N10 measured to 105 mcg but ended up at 95 mcg after removing air bubble. N10 also noted she was measuring from the widest part of the stopper, not the top of the dome of the stopper. • N11, N12, and N15 all measured 90 mcg due to measuring from the widest part of the stopper, not the top of the dome of the stopper.	measure the dose (see figure 4 below). • (b) (4) • Update the IFU to include additional warnings to not re-use the syringe or needle, even if medication is remaining (see figure 6 below). • Add "Single-Use Only" in red text to the carton labeling. • Update measurement markings & numbering on PFS label to improve visibility (see figure 7 below).	Because these mitigations impact the critical task of measuring and administering a dose, we recommend an additional HF validation study be completed to ensure that these mitigations do, in fact, address the observed use errors and do not introduce any new risks.
	250 mcg dose (measured after being prompted to read step 14 in the IFU): • 3 use difficulties	Difficulties: • 2 users (N04, N15) measured 240 mcg • N06 measured 255 mcg	Difficulties: • N04 and N15 measured from the widest part of the stopper, not the top of the dome of the stopper. • N06 held the syringe vertically while discarding the extra medication which made the syringe markings appear differently. N06 noted she was used to dialing doses on pens. N06 recommended making the syringe markings darker.		
	450 mcg dose (measured after being prompted to read step 14 in the IFU): • 4 use difficulties	Difficulties: • 2 users (N04, N08) measured 445 mcg • 2 users (N15, N12) measured 440 mcg	Difficulties: • N04 and N15 measured from the widest part of the stopper, not the top of the dome of the stopper. • N08 thought she measured correctly but noted that stoppers on some syringes have a red mark, so the user knows where to measure. • N12 noted the 50 mcg syringe markings were difficult to see.		

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3.3 ANALYSIS OF OTHER TASK ERRORS

The HF validation study showed use errors, (e.g. failures, difficulties, and close calls) with the following 10 critical tasks[8] (5 safety critical tasks[9], 5 essential tasks[10]) and 14 secondary tasks[11]; however, our assessment of these failures, difficulties, and close calls finds the residual risk is acceptable and thus are not the focus of this review. We do not agree with the categorization of some of the tasks (e.g., choosing an injection site as a secondary task). However, as the Sponsor evaluated all tasks either via simulation or IFU evaluation and reported all the data, we find this acceptable. We reviewed the available participants' subjective feedback, the Sponsor's root cause analysis and Sponsor's proposed risk mitigation strategy to determine acceptability. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the use tasks below; thus, we find no recommendations to further address the use errors or mitigations are necessary at this time to address the use errors related to the following use tasks:

Safety Critical Tasks

1. Store the PFS in the refrigerator
2. Open the PFS carton without damaging the PFS
3. Inspect the PFS liquid for discoloration or particles
4. Choose an appropriate injection site to avoid injecting into a blood vessel
5. Dispose of the PFS in an FDA-cleared sharps container

Essential Tasks

1. Remove the PFS tip cap
2. Remove the needle from the plastic packaging
3. Attach the needle to the PFS luer lock
4. Pull the needle cover away from the needle
5. Remove the plastic needle shield

Secondary Tasks

1. Allow the PFS to warm to room temperature for 15-30 minutes
2. Wash hands
3. Check the expiration date
4. Choose a location on the lower abdomen or front of the thigh
5. Clean the injection site with an alcohol wipe
6. Allow the disinfected site to air dry
7. Avoid touching the PFS septum/connection point
8. Remove the air bubbles from the PFS
9. Pinch the skin around the injection site
10. Insert the needle at a 45-to-90-degree angle

[8] Critical tasks were divided into "safety critical tasks" and "essential tasks".

[9] Safety critical tasks were defined as user tasks necessary to use the device for its intended purpose associated with risks having a severity rating of 3, 4, or 5.

[10] Essential tasks were defined as user tasks necessary to use the device for its intended purpose associated with risks having a severity rating of 1 or 2.

[11] Secondary tasks were defined as user tasks not necessary to use the device for its intended purpose associated with risks having a severity rating of 1 or 2.

Reference ID: 4684750

11. Pull the plunger back slightly to check for blood
12. Do not significantly move the PFS while the needle is inserted into the skin
13. Clean the injection site with an alcohol wipe after the injection
14. Push down on the needle cover until it clicks

3.4 LABELS AND LABELING

DMEPA concludes that the proposed IFU, container label, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. Because this BLA is already in its review cycle, for the purpose of transparency and early communication to the Applicant, we provide recommendations for PharmaEssentia in Section 4.1 below to be implemented, in addition to the Sponsor's proposed labels and labeling revisions, prior to conducting another HF validation study. Additional recommendations for the proposed IFU, container label, and carton labeling that do not need to be implemented prior to conducting the HF validation study will be conveyed to the Sponsor at a later date.

Our recommendations for the Prescribing Information will be provided to the division under separate cover.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several failures, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient. The Sponsor did propose labeling revisions (IFU, container labeling, and carton labeling) to mitigate the risk for use errors; however, our evaluation of the proposed user interface and proposed label and labeling identified additional areas of vulnerability that may lead to medication errors. We provide recommendations in section 4.1 for the Sponsor. We also provide our recommendations for the Sponsor related to the HF validation study in section 4.1 below. We recommend that the Sponsor consider additional design modifications, implement our recommendations, and conduct another HF validation study to demonstrate that the product can be used safely and effectively.

4.1 RECOMMENDATIONS FOR PHARMAESSENTIA CORPORATION

The results of the human factors (HF) validation study demonstrated several use errors, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient. We acknowledge you proposed revisions to the product user interface (instructions for use, container label, and carton labeling); however, our review indicates that additional risk mitigations are necessary. We conclude an additional HF validation study should be conducted to demonstrate the effectiveness of your proposed mitigations and the additional risk mitigations identified below as they affect the critical task of setting and administering doses, and to ensure that these mitigations do not introduce any new risks. Please see our list of recommendations for your study below.

1. We recommend redefining "failure", "close call", and "use difficulty" for the task of pushing the plunger to the prescribed dosing mark as follows:
    - Failure: Participant measures any dose other than the requested prescribed dose. The clinical significance of those failures should be described in your analysis of the failure.

Reference ID: 4684750

- Close call: Participant initially measures an incorrect dose but self-corrects before administration.
- Use difficulty: Participant states or appears as if they are having difficulty measuring the dose but ultimately measures the correct dose, or participant measures the correct dose using the wrong technique (i.e., measures dose while injecting).

2. [redacted] (b) (4)

3. We note that excerpts from the moderator script were included in the HF validation study report. Please provide the full moderator script when you submit the results of your supplemental HF validation study.

In addition, our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. To provide an early communication to you and for transparency, see our list of recommendations for the labels and labeling below that should be implemented, in addition to your proposed revisions to the labels and labeling, prior to conducting another HF validation study. Please note that additional label and labeling comments that do not need to be implemented prior to conducting the HF validation study will be provided at a later date.

A. Instructions for Use (IFU)

1. We note the use of the error-prone abbreviation "µg"[12] throughout the IFU. We recommend replacing "µg" with "mcg" wherever it appears to prevent confusion or misinterpretation.

2. Step 14

   a. As currently presented, the image of the syringe does not accurately reflect the sample syringe provided for our review or the proposed revised syringe label. The [redacted] (b) (4) than the stopper in the sample syringe which has [redacted] (b) (4) . Additionally, the font for the dose markings is different than what is shown in the revised syringe label. Therefore, we recommend revising this image to more accurately reflect the intend-to-market prefilled syringe.

   b. As currently presented, the image of the syringe does not reflect the measurement of a dose less than 500 mcg. We recommend revising the image to show an

[12] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

example dose (e.g., 350 mg). Note, the HF validation study should evaluate doses different from the example dose depicted in IFU to generate robust HF data.

B. Container Label and Carton Labeling

1. We note that strength is expressed as "500 mcg/1.0 mL" on the container label and carton labeling. This format is not in accordance with USP General Chapter <7>. Additionally, the use of "trailing zeros" can lead to 10-fold misinterpretation of numbers (e.g., 1.0 mL *versus* 10 mL).[13] Also the "1" in the denominator is unnecessary as it's commonly understood to be per 1 mL if the strength is expressed as "# mcg/mL". Therefore, revise the strength to read "500 mcg/mL" wherever it appears.

C. Container Label

1. We note the use of the error-prone abbreviation "s.c.".[14] We recommend replacing "s.c. use" with "For Subcutaneous Use Only" to prevent confusion or misinterpretation.

2. We note the use of the error-prone abbreviation "µg".[15] We recommend replacing "µg" with "mcg" to prevent confusion or misinterpretation.

3. We request you add the product's linear barcode to the individual container (syringe) label as required per 21CFR 201.25 and 21 CFR 610.67. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature. The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly and should be placed in an area where it will not be damaged because it appears at a point of label separation. Additionally, the barcode should be oriented in a vertical position. Barcodes placed in a horizontal position may not scan due to syringe curvature.[16]

[13] https://www.ismp.org/tools/errorproneabbreviations.pdf

[14] https://www.ismp.org/tools/errorproneabbreviations.pdf

[15] https://www.ismp.org/tools/errorproneabbreviations.pdf

[16] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Besremi that was submitted by PharmaEssentia on March 13, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class	biologic
Active Ingredient	ropeginterferon alfa-2b-njft
Indication	Treatment of polycythemia vera in adults without symptomatic splenomegaly
Route of Administration	Subcutaneous
Dosage Form	Injection (solution)
Strength	500 mcg/mL
Dose and Frequency	• Recommended starting dose: 100 mcg (b) (4) • Usual dose: 100 mcg to 500 mcg every 2 weeks • Dose should be gradually increased by 50 mcg every 2 weeks
How Supplied	Prefilled syringe (PFS)
Storage	Refrigerated (2°C to 8°C)
Device Constituent	Prefilled syringe
Intended Users	Treatment should be initiated under supervision of a physician experienced in the management of the disease. The medicinal product is intended for long-term treatment as directed by a prescriber and can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections with the prefilled syringe.
Intended Use Environment	Administered: office, home Dispensed from a specialty pharmacy

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On May 26, 2020, we searched the L:/drive and AIMS using the terms, “ropeginterferon”, “119047”, and “761166” to identify human factors or labeling reviews previously performed by DMEPA.

B.1.2 Results

Our search identified zero previous reviews.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The HF validation study protocol is accessible in EDR via:
\\CDSESUB1\evsprod\bla761166\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\pec-hfe\pec-hfe-report.pdf

The Use-Related Risk Analysis is accessible in EDR via:
\\CDSESUB1\evsprod\bla761166\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\use-related-risk\use-related-risk-report.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF validation study results report is accessible in EDR via:
\\CDSESUB1\evsprod\bla761166\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\pec-hf\pec-hf-report.pdf

Reference ID: 4684750

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On August 14, 2020, we sent the following information request to PharmaEssentia:[17]

> We refer to your BLA 761166 submission dated March 13, 2020 for Besremi (ropeginterferon alfa-2b-xxxx) including Human Factors (HF) validation study results.
>
> Our initial review of your HF validation study results identified numerous failures and difficulties associated with the task of pushing the plunger to the prescribed dosing mark for the studied doses (i.e., 100 mcg, 250 mcg, and 450 mcg), including a number of failures which resulted in the participants administering the entire contents of the prefilled syringe (i.e., 500 mcg instead of 100 mcg). We note that the study results, root cause analysis and participants' subjective feedback pointed to:
>
> 1. Overdoses due to participants expecting the prefilled syringe to contain their exact dose,
> 2. Inaccurate measurement of doses due to participants having difficulty reading the syringe markings and deciphering the features of the syringe stopper, and
> 3. Participants measuring doses while injecting in an effort to save remaining product for future doses.
>
> These findings suggest the design of the user interface could be further optimized.
>
> You did not propose any mitigations to address these use errors and difficulties. You state in your study conclusion that the "risks identified in the HF validation study were added to the Use-Related Risk Analysis (URRA)" and "were reviewed in relation to the Human Factors Validation Study data and it was concluded that the [residual] risks are considered acceptable".
>
> We remain concerned about the failures and use difficulties observed in your HF validation study because the risk of underdose or overdose may lead to lack of treatment effect or adverse effects leading to discontinuation of therapy. Thus, we do not agree with your HF validation study conclusion and we find that the currently proposed user interface (i.e., prefilled syringe device, label, and labeling) does not support the safe and effective use of your proposed product, specifically with regard to measuring and administering doses less than 500 mcg.
>
> We recommend you identify additional risk mitigation strategies, based on a re-evaluation of the HF study results, root causes, and participants' subjective feedback, to further optimize the product user interface. We request that you provide your plan and timeline to address the above issues.

On August 25, 2020, PharmaEssentia submitted their response which is accessible in EDR via: \\CDSESUB1\evsprod\bla761166\0018\m1\us\human-factors-response-rfi-14aug2020.pdf

[17] Kacuba, A. Information Request. 2020 AUG 14. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80589172&_afrRedirect=2562526667797886

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[18] along with postmarket medication error data, we reviewed the following labels and labeling submitted by PharmaEssentia.

- Container label received on March 13, 2020 and August 25, 2020
- Carton labeling received on March 13, 2020
- Prescribing Information (image not shown) received on June 12, 2020
  \\CDSESUB1\evsprod\bla761166\0008\m1\us\draft-labeling-text.docx
- Instructions for Use (image not shown) received on June 12, 2020
  \\CDSESUB1\evsprod\bla761166\0008\m1\us\draft-instructions-for-use.docx

E.2 Label and Labeling Images

Container (Syringe) Label

(b) (4)

[18] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MISHALE P MISTRY on behalf of CHI-MING TU
10/13/2020 04:41:19 PM

Division of Nonmalignant Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	BESREMI (ropeginterferon alfa-2b-xxxx) injection, for subcutaneous use
Applicant	PharmaEssentia
Application/Supplement Number	BLA 761166
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	For the treatment of polycythemia vera in adults without symptomatic splenomegaly
Date FDA Received Application	03/13/2020
Review Classification (Priority/Standard)	Standard
Action Goal Date	03/13/2021
Review Date	09/29/2020
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the Warnings and Precautions section of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: This application is for a new molecular entity for ropeginterferon alfa-2b injection (Besremi). The multidisciplinary labeling meetings have not yet been scheduled to review and edit the draft labeling documents (USPI and Medication Guide).

Reviewer Comments: The draft labeling submitted by the Applicant was not consistent with many labeling regulations and guidances. Sections 8.1-8.3 were missing the subsections described in the PLLR guidance. I provided edits to be consistent with regulations and guidances, added comments explaining these edits and comments advising the Applicant to make revisions themselves with links to the guidances to follow. Also, the Instructions for Use document was included in [redacted] (b) (4) which is not

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

correct. In a Day 74 letter comment, I asked the Applicant to develop a separate IFU document. My review was conducted prior to multidisciplinary review, so the labeling will undergo further editing before it is ready to be sent to the Applicant.
I sent an Information Request on 9/29/20 asking the Applicant to revise sections 8.1-8.3 to be consistent with the PLLR labeling guidance. Once that response is submitted, we can paste the revised text/formatting into the active draft labeling.

Attachments: Revised labeling with track changes edits and bubble comments explaining the revisions.

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VIRGINIA E KWITKOWSKI
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 16, 2021

To: Carleveva Thompson, MS, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DNH

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Besremi (ropeginterferon alfa-2b-njft) injection, for subcutaneous use

BLA: 761166

This memo is in response to DNH's labeling consult request dated October 30, 2020. Reference is made to a Complete Response letter that was issued on March 12, 2021. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DNH submit a new consult request during the subsequent review cycle. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	March 4, 2021
To:	Carleveva J. Thompson Regulatory Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)]
Drug Name (established name):	BESREMI (ropeginterferon alfa-2b-njft)
Dosage Form and Route:	Inection, for subcutaneous use
Application Type/Number:	BLA 761166
Applicant:	PharmaEssentia Corporation c/o PharmaEssentia US, LLC

Reference ID: 4756991

1 INTRODUCTION

On March 13, 2020, PharmaEssentia Corporation c/o PharmaEssentia US, LLC submitted for the Agency's review an original Biologics License Application (BLA) 761166 for BESREMI (ropeginterferon alfa-2b-njft) injection, indicated to treat adult patients with polycythemia vera (PV) without systematic splenomegaly in the U.S. On October 30, 2020, the Division of Nonmalignant Hematology (DNH) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) amd Instructions for Use (IFU) for BESREMI (ropeginterferon alfa-2b-njft) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for BESREMI (ropeginterfero alfa-2b-njft) injection.

2 CONCLUSIONS

Due to outstanding Human Factors deficiencies, DNH plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A comprehensive review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

Reference ID: 4756991

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/s/

SHARON R MILLS
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HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 24, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761166
Product Type:	Combination Product
Drug Constituent Name and Strength:	Besremi (ropeginterferon alfa-2b-njft) injection 500 mcg/mL
Device Constituent:	Prefilled Syringe (PFS)
Rx or OTC:	Rx
Applicant/Sponsor Name:	PharmaEssentia
FDA Received Date:	December 22, 2020 and December 29, 2020
OSE RCM #:	2020-2727
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader (Acting):	Colleen Little, PharmD
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate/Deputy Director:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study protocol submitted under BLA 761166 for Besremi (ropeginterferon alfa-2b-njft). Besremi (ropeginterferon alfa-2b-njft) is intended to treat polycythemia vera (PV) in adults without symptomatic splenomegaly.

1.1 PRODUCT DESCRIPTION

Besremi is a combination product proposed to be supplied as a pack containing one single-dose prefilled syringe (PFS) and one injection needle (see Figure 1 below). The PFS has graduated dose markings at 50 mcg, 100 mcg, 150 mcg, 200 mcg, 250 mcg, 300 mcg, 350 mcg, 400 mcg, 450 mcg, and 500 mcg. The (b) (4) safety hypodermic needle is attached to the syringe through Luer Lock mechanism. The proposed starting dose is 100 mcg (b) (4) as a subcutaneous injection. The dose should be gradually titrated by 50 mcg every two weeks until stabilization of the hematological parameters is achieved. The maximum recommended single dose is 500 mcg every two weeks.

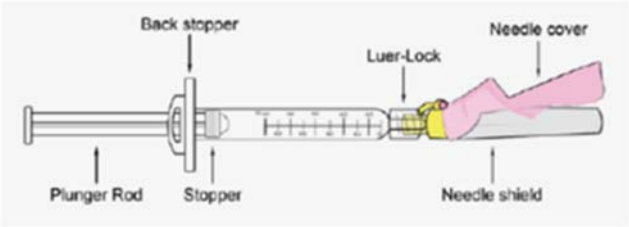

Figure 1: Diagram of the PFS with Needle Attached

1.2 REGULATORY HISTORY RELATED TO HUMAN FACTORS

On September 11, 2019, PharmaEssentia submitted an HF protocol as part of a Type C WRO meeting request.[a] We recommended they submit a new request for an HF validation study protocol review with their complete protocol submission. The Sponsor did not to submit a complete HF validation study protocol under the IND for our review.

On March 13, 2020, PharmaEssentia submitted their marketing application under BLA 761166, which included an HF validation study results report. Our review of the HF validation study results concluded that the "*study demonstrated several failures, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient.*" We provided recommendations for PharmaEssentia to implement prior to conducting another HF validation study to demonstrate that the product can be used safely and effectively.[b]

On December 22, 2020, PharmaEssentia submitted their revised labels and labeling (i.e. container label, carton labeling, and Instructions for Use) under BLA 761166. On December 29, 2020, PharmaEssentia submitted their HF validation study protocol for their additional HF validation study, which is the subject of this review.

[a] Available at: \\CDSESUB1\evsprod\ind119047\0052\m1\us\112-other-correspondence\appendix_c_human-factor-engineering-study-protocol_v2-clean.pdf

[b] DeGraw, S. Human Factors Study Report and Label and Labeling Review for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-503 and 2020-519.

Reference ID: 4752998

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH) and FDA/Sponsor Interactions	B
Human Factors Validation Study Protocol	C
Information Requests Issued During the Review	D – N/A
CDRH Human Factors Consult Review	E – N/A
Product Sample, Label and Labeling, Packaging	F

3 REVIEW SUMMARY AND DISCUSSION

Our overall assessment of the HF validation study protocol contained in the submission indicated that the protocol requires revisions to ensure that adequate data regarding the safe and effective use of this product is collected.

In addition, we evaluated the proposed product user interface including product sample, labels and labeling, and packaging. See Appendix F for more information. Based on the available information at the time of this review, we have identified areas of concern that may lead to medication errors. Please see table below in section 5.1 for our evaluation and recommendations.

We also consulted the Division of Medical Policy Programs (DMPP), Patient Labeling team (PLT) to review the instructions for use (IFU) and they provided their evaluation and recommendations under a separate cover[c]. We note that the January 25, 2021 DMPP review contained comments seeking DMEPA's input for the following areas in the IFU: consistency between the proposed prescribing information and the IFU, labeling of figures, terminology for the labeling of device parts, revising language describing device assembly, and addition of figures to supplement certain preparation and administration steps. We discussed these items with the DMPP reviewer on February 10, 2021 and reached alignment on our recommendations. The aligned recommendations shown in tracked changes for the IFU are included after the table in section 5.1.

[c] Mills, S. Review of Patient Labeling: Instructions for Use for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OMP, DMPP (US); 2021 JAN 25.

Reference ID: 4752998

4 COMMUNICATION OF DMEPA'S ANALYSIS TO OFFICE OF NEW DRUGS

DMEPA communicated our findings to the Division of Nonmalignant Hematology (DNH) via e-mail on February 23, 2021. At that time, we also requested concerns that could inform our review. Per e-mail correspondence from DNH on February 23 and 24, 2021, they stated no additional concerns and did not have additional feedback regarding DMEPA's recommendations.

5 CONCLUSION & RECOMMENDATIONS

We find that the HF validation study protocol is not acceptable. Please see section 5.1 for our recommendations. We advise that the Sponsor implement our recommendations prior to commencing their HF validation study.

5.1 RECOMMENDATIONS FOR PHARMAESSENTIA

Our review of the human factors validation study protocol identified several areas of concern. Please see the **Identified Issues and Recommendations** table. In addition, please see the recommendations from Division of Medical Policy Programs (DMPP) and DMEPA on the IFU below. We recommend that you implement all recommendations before commencing your human factors validation study.

Reference ID: 4752998

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Identified Issues and Recommendations for Sponsor			
	Identified Issue	**Rationale for Concern**	**Recommendation**
HF Validation Study Methodology			
1.	We find that your study protocol does not adequately define distinct user groups because you aim to recruit at least 5 participants with injection experience in the surrogate patient user group.	We believe participants' previous injection experience may impact usability (e.g., due to the potential risk of negative transfer). Based on the results of your previous HF study, injection-experienced patient end users experienced several use errors, close calls, and use difficulties associated with critical administration tasks that may result in harm to the patient. Thus, the potential risk of negative transfer should be assessed in the patient user group. Additionally, we note that the patient user group consisted of polycythemia vera (PV) patients in your previous HF study included. Since this HF study will be conducted with surrogate patients, the pool of participants is larger for recruitment into separate injection-naïve and injection-experienced participant user groups. As such, we consider surrogate patient participants that are injection-naïve and injection-experienced to be distinct user groups[d] for your proposed product.	Revise your study protocol to include the following untrained surrogate patient user groups: • n=15 injection-experienced surrogate patient participants • n=15 injection-naïve surrogate patient participants Furthermore, you should specify what devices/medications the participants have experience with and how long they have used the products for the injection-experienced surrogate patient participants in your study results report.

[d] Guidance for Industry: Applying Human Factors and Usability Engineering to Medical Devices. Food and Drug Administration. 2016. Available from: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

2.	(b) (4)		Revise your study protocol to include 15 untrained HCP participants who are representative of intended users.
3.	(b) (4)		Revise the simulated use portion of your study protocol so that the surrogate patient participants are asked to measure and administer a different dose (e.g., 150 mcg). HCP participants may still be asked to measure and administer (e.g., 100 mcg) as this is the typical starting dose for patients.
4.	Your study protocol and data sheets describe inconsistent test session formats. For example, your study protocol describes the test session format as: (b) (4)	Inconsistency between the HF protocol and the data sheets may cause confusion in collecting and interpreting the data.	Please confirm your study session format. Revise your study protocol and data sheets to address this discrepancy and ensure that the test session format is aligned. As noted in our previous review of your HF validation study results, we maintain that you may or may not choose to ask

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[redacted] (b) (4)		participants to read [redacted] (b) (4) of the IFU before measuring 1 or 2 additional doses to evaluate the effectiveness of the revisions made to [redacted] (b) (4) If you do choose to ask participants to read [redacted] (b) (4) of the IFU then this would be considered part of your IFU evaluation rather than a simulated use task as it is not representative of real-world use.

General Recommendations

1. Your study protocol states that you plan to create a training video for patients and HCPs. Please clarify if/how your proposed training video will be referenced in your product packaging and labeling, and if the content will differ from the IFU.

2. Additionally, please note the Agency expects that you conduct a robust root cause analysis to determine whether additional risk mitigation strategies/modifications are necessary to address the observed use errors, close calls, and use difficulties in your HF study. Depending on the nature of changes and the risk, you may need to perform additional human factors validation study to demonstrate the effectiveness of the changes. If you determine that an additional HF validation study is not required, include your justification for not conducting an additional HF study in your HF results report. The acceptability of your justification will be a matter of review.

3. Furthermore, to ensure that you provide the complete content of your HF validation study report, we recommend that you refer to our draft guidance *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*[e]. In addition, Appendix D, within the draft guidance, provides a hypothetical example of the results and associated analysis of human factors validation study data in a tabular format that can facilitate an efficient Agency review.

[e] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Reference ID: 4752998

Guidance on human factors procedures to follow can be found in the following guidance documents[f]:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[f]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

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

Below are the recommendations for the instructions for use (IFU) via tracked changes.

ropeginterferon
alfa-2b-njft (Besremi)

Reference ID: 4752998

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Besremi submitted by PharmaEssentia on March 13, 2020.

Table 3. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class	biologic
Active Ingredient	ropeginterferon alfa-2b-njft
Indication	Treatment of polycythemia vera in adults without symptomatic splenomegaly
Route of Administration	Subcutaneous
Dosage Form	Injection (solution)
Strength	500 mcg/mL
Dose and Frequency	• Recommended starting dose: 100 mcg (b) (4) • Usual dose: 100 mcg to 500 mcg every 2 weeks • Dose should be gradually increased by 50 mcg every 2 weeks
How Supplied	Prefilled syringe (PFS)
Storage	Refrigerated (2°C to 8°C)
Device Constituent	Prefilled syringe
Intended Users	Treatment should be initiated under supervision of a physician experienced in the management of the disease. The medicinal product is intended for long-term treatment as directed by a prescriber and can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections with the prefilled syringe.
Intended Use Environment	Administered: office, home Dispensed from a specialty pharmacy

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On February 2, 2021, we searched FDA previous reviews using the terms, "Besremi", "ropeginterferon", "BLA 761166" and "IND 119047" to identify reviews previously performed by DMEPA for Besremi.

B.1.2 Results

Our search identified one previous review.[g]

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

Application	Meeting Type	Date	Summary
IND 119047	Type B Pre-BLA	2019 AUG 05 2019 AUG 28	PharmaEssentia submitted a human factors (HF) protocol as an appendix in the meeting package. During the meeting, PharmaEssentia noted the HF protocol was submitted (b) (4) the Applicant plans to market the prefilled syringe if approved. PharmaEssentia also asked questions about using (b) (4) At that time, the Agency recommended that PharmaEssentia submit their HF study protocol separately to the existing IND and request a separate meeting.[h] Note, DMEPA was not consulted for this meeting.
IND 119047	Type C WRO	2019 SEP 11	PharmaEssentia submitted an HF protocol as part of a Type C WRO meeting request.[i] As part of the meeting request, PharmaEssentia asked questions about using (b) (4) to be evaluated in the HF study.

[g] DeGraw, S. Human Factors Study Report and Label and Labeling Review for Besremi (ropeginterferon-alfa-2b-njft). BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-503 and 2020-519.
[h] Meeting Minutes for 2019 AUG 28 Type B Pre-BLA Meeting. Dated 2019 SEP 20. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8051730d&_afrRedirect=2378998083387324
[i] Available at: \\CDSESUB1\evsprod\ind119047\0052\m1\us\112-other-correspondence\appendix_c_human-factor-engineering-study-protocol_v2-clean.pdf

		2019 OCT 10	We denied the meeting request and informed PharmaEssentia that their protocol submission was incomplete.[j] We provided PharmaEssentia with the protocol deficiencies and recommended they submit a new request for an HF validation study protocol review with their complete protocol submission. The Sponsor chose not to submit a complete HF validation study protocol under the IND for our review.

[j] Park, Linda. Correspondence: Meeting Request Denied. 2019 OCT 10. Available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8051e901&_afrRedirect=2317670318460693

APPENDIX C. HUMAN FACTORS VALIDATION STUDY PROTOCOL

The following Human Factors documents are accessible in EDR via:

HF Validation Study Protocol:
\\CDSESUB1\evsprod\bla761166\0033\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\pec-hf\validation-study-protocol.pdf

HF Validation Study Data Sheets and Moderator Script:
\\CDSESUB1\evsprod\bla761166\0033\m5\53-clin-stud-rep\535-rep-effic-safety-stud\polycythemia-vera\5354-other-stud-rep\pec-hf\validation-study-sheets.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW – N/A

APPENDIX E: CDRH HUMAN FACTORS CONSULT REVIEW – N/A

APPENDIX F. PRODUCT SAMPLE, LABELS AND LABELING, PACKAGING

F.2 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Besremi labels and labeling submitted by PharmaEssentia on December 22, 2020.

- Container label
- Carton insert
- Carton labeling
- Instructions for Use (IFU) [image not shown] accessible in EDR via:
  PDF: \\CDSESUB1\evsprod\bla761166\0031\m1\us\draft-instructions-for-use.pdf
  Word: \\CDSESUB1\evsprod\bla761166\0031\m1\us\draft-instructions-for-use.docx

F.2.1 Label and Labeling Images

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 23, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761166
Product Name, Dosage Form, and Strength:	Besremi (ropeginterferon alfa-2b-njft) injection 500 mcg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	PharmaEssentia Corporation (PharmaEssentia)
FDA Received Date:	March 13, 2020 and June 12, 2020
OSE RCM #:	2020-503-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

PharmaEssentia submitted BLA 761166 for Besremi (ropeginterferon alfa-2b-njft) injection on March 13, 2020. Besremi is proposed for the treatment of polycythemia vera (PV) in adults without symptomatic splenomegaly. We evaluated the proposed Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

PharmaEssentia submitted results of a human factors (HF) validation study on March 13, 2020 under BLA 7671166. We reviewed the HF validation study results under separate cover on October 13, 2020.[a] Our review recommended that "the Sponsor consider additional design modifications, implement our recommendations, and conduct another HF validation study to demonstrate that the product can be used safely and effectively". The review included recommendations for the HF validation study, as well as, preliminary container label, carton labeling, and IFU recommendations. This review provides recommendations for the Besremi PI only.

PharmaEssentia submitted revised labeling (i.e., container label, carton labeling, instructions for use) on December 22, 2020 and an HF validation study protocol on December 29, 2020. Our review of the protocol and revised labeling will be provided under separate cover.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other: Information Request	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

[a] DeGraw, S. Human Factors Results and Label and Labeling Review for Besremi (ropeginterferon alfa-2b-njft) BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-503 and 2020-519.

Reference ID: 4751264

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI for Besremi to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI identified areas that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. General Comments
    1. We note some whole numbers are expressed with trailing zeros (e.g., 1.0). We recommend removing all trailing zeros (e.g., 1) to avoid a ten-fold misinterpretation.[b]
    2. We recommend replacing the error-prone abbreviation "µg" wherever it appears with the "mcg" abbreviation to prevent confusion or misinterpretation.[c]
    3. We recommend revising the nonproprietary name placeholder with the full conditionally acceptable nonproprietary name "ropeginterferon-alfa-2b-njft".

B. Highlights of Prescribing Information
    1. Dosage and Administration
        a. We recommend revising the recommended dosage statement to improve clarity and to reduce the length of this section. Revise to read:
            - The recommended starting dose for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. Titrate dose up by 50 mcg every 2 weeks until hematological parameters are stabilized (2.x).
            - (b) (4) [redacted]

    2. Dosage Forms and Strengths
        a. We recommend revising the dosage form and strength statement to reflect the correct dosage form and package type term. Revise to read, "Injection: 500 mcg/mL solution in a single-dose prefilled syringe".

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf
[c] https://www.ismp.org/tools/errorproneabbreviations.pdf

C. Dosage and Administration [2]

1. We recommend revising the subheadings to read "2.1 Recommended Dosage", "2.2 Dosage Modifications for Adverse Reactions", and "2.3 Preparation and Administration".
2. Recommended Dosage [2.1]
    a. To improve clarity of the information presented, we recommend revising the dosage information. For example, revise as follows:

    Single-Agent Therapy:

    - The recommended starting dosage for single-agent therapy is 100 mcg by subcutaneous injection every two weeks.
    - Gradually increase the dose by 50 mcg every two weeks until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L, and leukocytes less than 10 x 10^9/L).
    - The maximum dose is 500 mcg every two weeks.

    Combination Therapy:

    - [redacted] (b) (4) .
    - Gradually increase the dose by 50 mcg every two weeks while gradually decreasing [redacted] (b) (4), until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L, and leukocytes less than 10 x 10^9/L).
    - The maximum dose is 500 mcg every two weeks.

    Maintain the dose level at which hematological stability is achieved for [redacted] (b) (4). After that time, the dosing interval may be expanded to every 4 weeks.

3. Preparation and Administration [2.3]
    a. To improve clarity of the information presented, we recommend revising the instructions for reconstitution and dilution. For example, revise as follows:

    Besremi is intended for use under the guidance of a healthcare provider. After proper training, a healthcare provider may determine patient self-administration or administration by a caregiver is appropriate. Training should aim to demonstrate to those patients and caregivers how to measure the dose using the prefilled syringe, and the focus should be on ensuring that a patient or caregiver can successfully perform all of the steps in the Besremi Instructions for Use. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the

product successfully, you should consider whether the patient is an appropriate candidate for self-administration of Besremi.

Besremi is administered subcutaneously via a single-dose prefilled syringe.

Prior to use, remove the carton from the refrigerator and allow the Besremi prefilled syringe to reach room temperature at 15˚C to 25˚C (59˚F to 77˚F) for 15-30 minutes.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or particulates are observed.

Use aseptic technique.

Twist the gray rubber cap off the syringe barrel.

Attach the needle to the syringe by pushing and twisting clockwise and pull the needle shield straight off.

Remove air bubbles from the syringe.

If less than the full syringe volume is needed to administer the prescribed dose, gently push the plunger rod until the dome of the stopper reaches the dose measurement.

Inject into the front of the thigh or abdominal skin avoiding the space within 5 cm of the navel. Avoid areas that are irritated, reddened, bruise, infected, or scarred.

Press the plunger rod in completely to ensure the entire dose is delivered before removing the needle.

After administration, use your finger, thumb, or hard surface to push the needle cover forward over the needle until it clicks.

Discard unused portion.

4. Dosage Forms and Strengths [3]
    a. We recommend revising the dosage form and strength statement to reflect the correct dosage form and package type term and to provide a description of the solution. Revise to read, “Injection: 500 mcg/mL clear, colorless to slightly yellowish solution in a single-dose prefilled syringe”. (b) (4)

5. How Supplied/Storage and Handling [16]
    a. We recommend revising the subheadings to read “16.1 How Supplied” and “16.2 Storage and Handling”.
    b. We recommend revising the “How Supplied” statements to include the non-proprietary name, dosage form, identifying characteristics, route of

administration, carton contents, and NDC number. Revise to read "Besremi (ropeginterferon alfa-2b-njft) injection is a sterile, preservative-free, clear and colorless to slightly yellowish solution for subcutaneous administration in a single-dose prefilled syringe. Each carton contains one 500 mcg/mL prefilled syringe with a 30 gauge, ½ inch safety hypodermic needle (NDC # XXX-XXXX-XX)."

c. We recommend expressing the storage information in both Celsius and Fahrenheit. Revise to read "Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze."
d. We recommend deleting the subheading (b) (4) and the information contained within the subheading as it is already stated in sections *16.1 How Supplied* and *3 Dosage Forms and Strength*.
e. We recommend deleting the subheading (b) (4) and the information contained within the subheading as it is already stated in section *2.2 Preparation and Administration*.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ropeginterferon alfa-2b-njft received on March 13, 2020 from PharmaEssentia.

Table 2. Relevant Product Information for Besremi	
Initial Approval Date	N/A
Active Ingredient	ropeginterferon alfa-2b-njft
Indication	Treatment of polycythemia vera in adults without symptomatic splenomegaly
Route of Administration	Subcutaneous
Dosage Form	Injection (solution)
Strength	500 mcg/mL
Dose and Frequency	• Recommended starting dose: 100 mcg (b) (4) • Usual dose: 100 mcg to 500 mcg every 2 weeks • Dose should be gradually increased by 50 mcg every 2 weeks
How Supplied	Prefilled syringe (PFS)
Storage	Refrigerated (2°C to 8°C)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 19, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Besremi', 'ropeginterferon', and 'BLA 761166'. Our search identified one previous review[d], and we confirmed that our previous recommendations were implemented.

[d] DeGraw, S. Human Factors Results and Label and Labeling Review for Besremi (ropeginterferon alfa-2b-njft) BLA 761166. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 13. RCM No.: 2020-503 and 2020-519.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following labels and labeling submitted by PharmaEssentia.

- Prescribing Information (image not shown) received on June 12, 2020 \\CDSESUB1\evsprod\bla761166\0008\m1\us\draft-labeling-text.docx

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	January 25, 2021
To:	Lubna Merchant, Pharm D Acting Director **Division of Medication Error Prevention and Analysis (DMEPA)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	BESREMI (ropeginterferon alfa-2b-njft)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761166
Applicant:	PharmaEssentia Corporation c/o PharmaEssentia US, LLC

1 INTRODUCTION

On August 25, 2020, PharmaEssentia Corporation, c/o PharmaEssentia US, LLC, submitted for the Agency's review a response to an Agency Information Request (IR) dated August 14, 2020, regarding the Applicant's submission of Human Factors (HF) validation study results as part of their submission of an original Biologics License Application (BLA) 761166 for BESREMI (ropeginterferon alfa-2b-njft) injection. On December 22, 2020, the Applicant amended their BLA to provide revisions to the carton labeling and Instructions for Use, to ensure alignment related to the Human Factors study as well as current labeling guidance, formatting and usability as recommended by the Agency. We note that the Applicant's proposed proprietary name, BESREMI, was found to be conditionally acceptable by the Agency on June 9, 2020. The non-proprietary name ropeginterferon alfa-2b-njft was determined by the Agency to be conditionally acceptable on September 3, 2020.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Medication Error Prevention and Analysis (DMEPA) on January 8, 2021 for DMPP to review the Applicant's proposed Instructions for Use (IFU) for BESREMI (ropeginterferon alfa-2b-njft) injection to be used in the Human Factors Validation Study Protocol.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- DRAFT BESREMI (ropeginterferon alfa-2b-njft) IFU as presented in the Human Factors Validation Study Protocol received on December 22, 2020, and received by DMPP on January 8, 2021.
- Sample BESREMI (ropeginterferon alfa-2b-njft) prefilled syringe received on January 13, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our review of the IFU we:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information

- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

- This review of the BESREMI (ropeginterferon alfa-2b-njft) IFU provides recommendations regarding clarification of instructions, comprehension, readability, and patient friendly language.

- Revisions to the BESREMI (ropeginterferon alfa-2b-njft) IFU may be required during this or a future BLA review cycle for consistency with the Prescribing Information if DMEPA determines that the findings of the Applicant's proposed Human Factors Validation Study are acceptable.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the IFU is appended to this memorandum. Consult DMPP regarding any additional revisions that need to made to the IFU once the results of the proposed Human Factors Validation Study have been submitted.

Please let us know if you have any questions.

23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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CLINICAL INSPECTION SUMMARY

Date	July 22, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Patricia Oneal, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Director Alice Kacuba, RN, Regulatory Project Manager Division of Nonmalignant Hematology (DNH /OCHEN)
BLA	761166
Applicant	PharmaEssentia US
Drug	Besremi™ (ropeginterferon alpha 2b)
NME	Yes
Division Classification	Pegylated interferon
Proposed Indication	Treatment of polycythemia vera in adults without symptomatic splenomegaly
Consultation Request Date	May 11, 2020 (Priority Review)
Summary Goal Date	July 31, 2020
Action Goal Date	November 15, 2020
PDUFA Date	November 15, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from Study 2012-005259-18 (PROUD-PV and CONTINUATION-PV) was submitted to the Agency in support of a Biologic License Application (BLA 761166) for ropeginterferon for treatment of polycythemia vera in adults without symptomatic splenomegaly.

PharmaEssentia US (Sponsor) and [redacted] (b) (4) (CRO) were inspected for a single study and its continuation trial, Study 2012-005259-18, in support of BLA 761166.

Based on the results of the above inspections, PharmaEssentia US and [redacted] (b) (4) are in compliance with Good Clinical Practice, and the study in support of this application appears to have been conducted adequately. PharmaEssentia US and [redacted] (b) (4) (CRO) maintained adequate oversight of Study 2012-005259-18.

II. BACKGROUND

Ropeginterferon (AOP2014) is a third generation pegylated interferon. The coupling of pegylation and interferon in already registered/marketed second generation products was not at the optimal site, therefore resulting in a relatively short half-life. Ropeginterferon (AOP2014) is a next generation pegylated interferon (Peg-P-IFN-α-2b), with the addition of proline in the N-terminal end allowing monopegylation.

PharmaEssentia submitted an application for ropeginterferon alfa-2b injection solution. The proposed indication is for the treatment of polycythemia vera in adults without symptomatic splenomegaly. Ropeginterferon alfa-2b (P1101) was granted orphan drug designation (#12-3670).

This application is the first BLA for this Sponsor and the efficacy results are based primarily on a single study and its continuation trial: 2012-005259-18 (PROUD-PV and CONTINUATION-PV).

Study 2012-005259-18 (PROUD-PV and CONTINUATION-PV)

Study 2012-005259-18 was a randomized, open-label, multicenter, controlled, parallel arm, Phase 3 study assessing the efficacy and safety of ropeginterferon (P1101) vs. hydroxyurea in the treatment of patients with polycythemia vera.

The primary objective of this phase III study was to compare the efficacy and safety of hydroxyurea with a Peg-P-IFN-α-2b in patients with polycythemia vera. Two populations were assessed: hydroxyurea naïve patients and patients undergoing treatment or pre-treated with hydroxyurea for less than 3 years.

The primary endpoint was the complete hematological response defined as hematocrit less than 45% without phlebotomy in the previous two months, platelet count 400 x 10^9/L or WBC count 10 x 10^9/L (10,000/uL) or less, normal spleen size and absence of thromboembolic events at 12 months.

A total of 257 study subjects were enrolled at 48 sites in 13 countries and 254 patients' data were analyzed. Study 2012-005259-18's (PROUD-PV) initiation date was October 4, 2013. Study completion date was April 8, 2016. Data was locked on January 23, 2017.

Patients could enroll in 2012-005259-18 (CONTINUATION-PV) as an extension study which evaluated long-term safety, tolerability, and durability of effect of ropeginterferon alfa-2b (P1101) treatment compared to hydroxyurea or best available therapy.

The CONTINUATION-PV Study was conducted in 45 sites globally.

III. RESULTS (by site)

1. PharmaEssentia US (Sponsor)
35 Corporate Drive, Suite 325
Burlington, MA 01803

Inspection dates: June 29 to July 7, 2020

This inspection evaluated compliance with the sponsor responsibilities concerning the conduct of Study 2012-005259-18 (PROUD-PV and CONTINUATION-PV).

The inspection included review of organizational charts, vendor oversight, contracts, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, adverse events evaluation and reporting, protocol deviations, standard operating procedures, monitoring logs, Form FDA-1572, delegation of authority log, drug accountability, record retention, and the evaluation of the adequacy of monitoring and corrective actions taken by the firm.

Sponsor performed routine audits. The study monitoring plan appeared to be adequate. Study site monitoring files were reviewed for these two clinical sites: site 11 and site 32. There was no evidence of adverse event underreporting to the FDA.

A Form FDA 483 was not issued at the end of the study inspection. In general, the sponsor appeared to be in compliance with Good Clinical Practice. PharmaEssentia US maintained adequate oversight of clinical trials.

2. (b) (4)

Inspection dates: (b) (4)

(b) (4) was the contract research organization (CRO) that for Study 2012-005259-18 (PROUD-PV and CONTINUATION-PV).

This inspection evaluated compliance with the CRO's responsibilities; specifically, converting the SAS analytical dataset into an FDA-required format. Documents reviewed included the following: organization chart, training records of the staff who conducted SAS programing activities, storage of data, and protection of electronic records. No refusals were encountered.

The study datasets were provided by the sponsor via SharePoint, a web-based collaborative platform. All electronic records were stored in the CRO's server and located at the inspected facility. Documents were placed in a locked room where only the president and the head of Information Technology (IT) had room access. The server had onsite back up every 15 minutes and a remote backup every day at midnight. The server for the remote backup is located in (b) (4)

The Document Management SOP did not specify how long the firm would keep records. However, CRO explained that they would keep the records indefinitely.

A Form FDA 483 was not issued at the end of the study inspection. In general, the CRO appeared to be in compliance with Good Clinical Practice.

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