CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761406Orig1s000
761406Orig2s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 17, 2025
Requesting Office or Division:	Office of Therapeutic Biologics and Biosimilars (OTBB)
Application Type and Number:	BLA 761406/Ori-2
Product Name, Dosage Form, and Strength:	Yesintek (ustekinumab-kfce) injection, Prefilled syringe: 45 mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL (5 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Biocon Biologics Inc.
FDA Received Date:	January 15, 2025
TTT ID #:	2025-13034
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Yesintek (ustekinumab-kfce) injection BLA 761406/Original 2 for interchangeability designation of Yesintek prefilled syringes (45 mg/0.5 mL and 90 mg/mL) and vials (45 mg/0.5 mL and 130 mg/26 mL), the Office of Therapeutic Biologics and Biosimilars (OTBB) requested that we review the proposed Yesintek Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Yesintek (ustekinumab-kfce) is a proposed 351(k)(4) interchangeable and the US-licensed Reference Product (RP) is Stelara (ustekinumab), BLA 125261 and BLA 761044.

2 CONCLUSION

The Yesintek Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling remain unchanged from what DMEPA previously found acceptable for BLA 761406/Ori-1.[a,b] We have no recommendations at this time.

[a] Patel, M. Label and Labeling Review for Yesintek (BLA 761406). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 24. TTT ID No.: 2023-7314.

[b] Patel, M. Review of Revised Label and Labeling for Yesintek (BLA 761406). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 NOV 26. TTT ID No.: 2023-7314-2.

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/s/

MADHURI R PATEL
04/17/2025 08:09:20 AM

YEVGENIYA M KOGAN
04/18/2025 07:26:35 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 26, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761406
Product Name, Dosage Form, and Strength:	Yesintek (ustekinumab-kfce) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe, 45 mg/0.5 mL vial, and 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Biocon Biologics Inc
FDA Received Date:	November 21, 2024 and November 22, 2024
TTT ID #:	2023-7314-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Biocon Biologics Inc submitted revised container labels and carton labeling received on November 21, 2024 and November 22, 2024 for Yesintek. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Yesintek (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Biocon Biologics Inc implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, M. Review of Revised Label and Labeling for Yesintek (BLA 761406). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 NOV 19. TTT ID: 2023-7314-1.

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/s/

MADHURI R PATEL
11/26/2024 10:34:56 AM

YEVGENIYA M KOGAN
11/26/2024 04:32:11 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 19, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761406
Product Name, Dosage Form, and Strength:	Yesintek (ustekinumab-kfce) injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe, 45 mg/0.5 mL vial, and 130 mg/26 mL (5 mg/mL) vial
Applicant Name:	Biocon Biologics Inc
FDA Received Date:	November 15, 2024
TTT ID #:	2023-7314-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Biocon Biologics Inc submitted revised container labels and carton labeling received on November 15, 2024 for Yesintek. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Yesintek (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The container labels and carton labeling are unacceptable from a medication error perspective. We note the color for the 90 mg/mL strength differentiation was revised to a (b) (4) color and we also note the 130 mg/26 mL strength differentiation is another shade of (b) (4). Per the Applicant's response dated November 15, 2024, "The product identifiers human readable form and machine-readable form (2D data matrix barcode) GTIN and S/N is updated in cartons for all presentations." However, we are unable to locate the 2D data matrix on the carton labeling. We note the updates to the proprietary name, nonproprietary name, and strength on the container labels and carton labeling since our previous review and have provided additional recommendations to ensure prominence of important information.

3 RECOMMENDATIONS FOR BIOCON BIOLOGICS INC

A. General Comments (Container Label(s) and Carton Labeling)

1. Consider revising the color differentiation used for either the 90 mg/mL or the 130 mg/26 mL strength as the (b) (4) colors may lack adequate differentiation.
2. Given the location, size, and color of Biocon Biologics™, the proprietary name lacks prominence on the principal display panel for the 130 mg/26 mL (5 mg/mL) and 45 mg/0.5 mL vial container labels and carton labeling and the strength lacks prominence on the prefilled syringe container labels. The proprietary name and nonproprietary name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). Consider reducing the size and relocating Biocon Biologics™ to increase the prominence of the proprietary name and strength. *See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

B. Container Labels

1. As currently presented, the nonproprietary name lacks prominence on the principal display panel for the 45 mg/0.5 mL and 90 mg/mL prefilled syringe

[a] Patel, M. Label and Labeling Review for Yesintek (BLA 761406). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 15. TTT ID: 2023-7314.

container labels. The proprietary name and nonproprietary name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend improving the legibility of the nonproprietary name. You could consider utilizing a larger font size or heavier type or other means. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

2. Ensure the proprietary name and nonproprietary name along with the product strength, route of administration are legible on the prefilled syringe container labels and the 45 mg/0.5 mL vial container label. Per 21 CFR 201.10(i), small labels are required to have the following minimum amount of information: proprietary name, established name, product strength, Identifying lot or control number, name of manufacturer, packer, or distributor, and expiration date. Therefore, to create additional white space, consider removing the following: (b) (4)

3. For the 130 mg/26 mL vial container label, the net quantity statement is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to over-dosing. We recommend relocating the statement "26 mL Single-dose vial Discard unused portion" away from and less prominent than the product strength, such as to the bottom of the principal display panel under "Must be diluted." See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

C. Carton Labeling

1. For the 45 mg/0.5 mL and 90 mg/mL prefilled syringe blister labeling, revise the net quantity to include the full strength (e.g. "1 x 45 mg/0.5 mL single-dose prefilled syringe. Discard unused portion" and "1 x 90 mg/mL single-dose prefilled syringe. Discard unused portion").

2. Per your response dated November 15, 2024, "The product identifiers human readable form and machine-readable form (2D data matrix barcode) GTIN and S/N is updated in cartons for all presentations." However, we are unable to locate the 2D data matrix. Please clarify the location of the 2D data matrix on the carton labels. We continue to request you add a place holder to the carton labeling.

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/s/

MADHURI R PATEL
11/19/2024 02:57:01 PM

YEVGENIYA M KOGAN
11/19/2024 04:03:51 PM

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

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

Memorandum

Date: November 15, 2024

To: Kimberle Searcy, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Tong Li-Masters, Clinical Reviewer, DDD

Suzette Peng, Clinical Reviewer, DDD

Sandhya Apparaju, Clinical Reviewer, DDD

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for YESINTEK™ (ustekinumab-xxxx) injection, for subcutaneous or intravenous use

BLA: 761406

Background:
In response to DDD's consult request dated July 18, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide and Instructions for Use's (IFU) for the original BLA submission for YESINTEK™ (ustekinumab-xxxx) injection, for subcutaneous or intravenous use [Yesintek].

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 14, 2024 and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide and IFU's, and comments were sent under separate cover on November 14, 2024.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at Elvy.Varghese@fda.hhs.gov.

38 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ELVY M VARGHESE
11/15/2024 08:53:56 AM

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:	November 14, 2024
To:	Kim Searcy Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFUs)
Drug Name (established name):	YESINTEK (ustekinumab-kfce)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761406
Applicant:	Biocon Biologics, Inc.

[1]YESINTEK has been developed as a proposed biosimilar to US-licensed STELARA (ustekinumab). The proposed proprietary name, YESINTEK, was found conditionally acceptable on February 23, 2024. The nonproprietary name, ustekinumab-kfce, was found conditionally acceptable on August 7, 2024.

1 INTRODUCTION

On November 30, 2023, Biocon Biologics, Inc. submitted for the Agency's review A Biologics License Application (BLA) 761406 for YESINTEK (Ustekinumab-kfce) injection, a proposed biosimilar product to US-licensed STELARA (ustekinumab) injection (BLA 125261).

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 Dermatology and Dentistry on November 30, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for STELARA (ustekinumab) injection, for subcutaneous or intravenous use.

2 MATERIAL REVIEWED

- Draft YESINTEK (ustekinumab-kfce) injection MG and IFUs received on November 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 13, 2024.
- Draft YESINTEK (ustekinumab-kfce) injection Prescribing Information (PI) received on November 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 13, 2024.
- Approved US-licensed STELARA (ustekinumab) injection labeling dated March 18, 2024.

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%.

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.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG are IFUs 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFUs meet the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the MG is consistent with the approved labeling for the US-licensed STELARA (ustekinumab) injection where applicable.

4 CONCLUSIONS

The MG and IFUs 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 IFUs 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.

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/s/

MARIA T NGUYEN
11/14/2024 03:21:45 PM
DMPP-OPDP review of ustekinumab-kfce (YESINTEK) BLA 761406 MG and IFUs

ELVY M VARGHESE
11/14/2024 03:31:48 PM

LASHAWN M GRIFFITHS
11/14/2024 03:35:14 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 23, 2024

TO: Jill Lindstrom, M.D.
Director
Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspections of Fortrea Clinical Research Unit Ltd., Leeds, United Kingdom and Medicines Evaluation Unit Ltd., Manchester, United Kingdom

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged clinical inspections of study BM12H-NHV-01-G-01 (BLA 761406) conducted at Fortrea Clinical Research Unit Ltd., Leeds, United Kingdom and Medicines Evaluation Unit Ltd., Manchester, United Kingdom.

No Form FDA 483 was issued at the inspection close-out at either site. However, there was one discussion item at Fortrea Clinical Research Unit Ltd., and one discussion item at Medicines Evaluation Unit Ltd. After reviewing the inspectional findings, exhibits provided in EIRs, and the firm's response to the discussion items per the EIRs, there are no identified concerns for Fortrea Clinical Research Unit or Medicines Evaluation Unit regarding reliability of the data or human subject protection for inspected study BM12H-NHV-01-G-01 for the review division's consideration.

2. Inspected Studies:

BLA 761406

Study Number: BM12H-NHV-01-G-01
Study Title: "A phase 1, randomized, double-blind, 3-arm, parallel design study in healthy subjects to evaluate pharmacokinetics, safety, tolerability, and immunogenicity of Bmab 1200 after single subcutaneous injection in comparison with EU-approved Stelara and US-licensed Stelara."
Dates of study conduct: 04/20/2022 – 03/13/2023

Clinical site 001: Fortrea Clinical Research Unit Ltd.
Drapers Yard, Marshall Street, Holbeck
Leeds, LS11 9EH, West Yorkshire, UK

Clinical site 002: Medicines Evaluation Unit Ltd.
The Langley Building, Southmoor Road,
Wythenshawe, Manchester, M23 9QZ
Greater Manchester, UK

3. Inspectional Findings

Fortrea Clinical Research Unit Ltd., Leeds, UK

ORA investigator Matthew C. Watson inspected Fortrea Clinical Research Unit Ltd., Drapers Yard, Marshall Street, Holbeck, Leeds, West Yorkshire, UK from September 2-6, 2024.

3.1 Previous Inspection

This was the first OSIS inspection of Fortrea Clinical Research Unit Ltd. under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs) and subject source records
-Informed consent forms
-Protocol compliance
-Standard operating procedures
-Test article accountability and storage
-Randomization scheme
-Adverse event reporting

-Collection, processing, and storage of subject samples
-Facility floor plans
-Equipment records

3.3 Inspection findings

At the conclusion of the inspection, investigator Matthew C. Watson did not issue Form FDA 483 to the clinical site. However, there was one discussion item addressed at the inspection close out. The discussion item, the firm's response per the EIR, and my evaluation are presented below.

3.3.1. Discussion Item

Discussion item 1:
The delegation log shows dates of study personnel activities were prior to the dates study activities were delegated by the CI.

OSIS Evaluation:
The OII investigator reviewed source records, including job descriptions and training records, of the identified individuals who conducted study activities. The OII investigator confirmed that the study personnel were qualified to conduct their delegated tasks and found no issues with the task delegation. Therefore, I conclude that this discussion item has no impact on data integrity or subject safety.

Firm's Response:
The site management agreed with the discussion item. The site previously identified the issue with the delegation logs, and has since established a new process in which there is a specific individual in charge of the review of delegation logs, ensuring they are completed accurately.

Medicines Evaluation Unit Ltd., Manchester, UK

ORA investigator Matthew C. Watson inspected Medicines Evaluation Unit Ltd., The Langley Building, Southmoor Road, Wythenshawe, Manchester, M23 9QZ, Greater Manchester, UK from August 27-30, 2024.

3.1 Previous Inspection

This was the first OSIS inspection of Medicines Evaluation Unit Ltd. under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs) and subject source records
-Informed consent forms
-Protocol compliance
-Standard operating procedures
-Test article accountability and storage
-Randomization scheme
-Adverse event reporting
-Collection, processing, and storage of subject samples
-Facility floor plans
-Equipment records

3.3 Inspection findings

At the conclusion of the inspection, investigator Matthew C. Watson did not issue Form FDA 483 to the clinical site. However, there was one discussion item addressed at the inspection close out. The discussion item, the firm's response per the EIR, and my evaluation are presented below.

3.3.1. Discussion Item

Discussion item 1:
The testing site collected and maintained reserve samples in accordance with UK/EU requirements. The OII investigator recommended that the site management include USFDA retention requirements in their procedures in case there are any discrepancies between the USFDA requirements and the UK/EU requirements.

OSIS Evaluation:
Per FDA Guidance for Industry "Questions and Answers on Biosimilar Development and the BPCI Act" (September 2021), the Agency recommends that the *sponsor* of a proposed biosimilar product retain reserve samples for at least 5 years following the date of completion of a comparative clinical PK and/or PD study of the reference product and the proposed biosimilar product. There is no regulatory requirement that the clinical site maintain reserves for proposed biosimilar products. In addition, this discussion item is purely a recommendation rather than an observation of an objectionable condition regarding the retention of reserves. I conclude that this discussion item has no impact on data reliability.

Firm's Response:
The CI and testing site management agreed to update their procedures to assure USFDA requirements are fully represented within their procedures.

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 10/21/2024, 10/22/2024
Edit: MO 10/22/2024

OSIS File #: BE 10224

eNSpect Assignment ID: 244521
eNSpect OpID: 286333 (Fortrea); 286332 (MEU)

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/s/

MAKINI COBOURNE-DUVAL
10/23/2024 12:34:17 PM

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10/23/2024 01:00:50 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/17/2024

TO: Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761406

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

(b) (4): OSIS conducted an inspection for the analytical site in (b) (4). The inspection was conducted under the following submission: BLA Non-responsive.

The following objectionable conditions were observed:

NON-RESPONSIVE

After review of the objectionable conditions and the written response from the site, OSIS concluded that data from the reviewed studies were reliable. (Final OSIS Review – (b) (4)

Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

FELECIA P HAGOOD
09/17/2024 11:42:04 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	May 15, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761406
Product Name, Dosage Form, and Strength:	Yesintek (ustekinumab-xxxx)[a] injection, 45 mg/0.5 mL and 90 mg/mL prefilled syringe, 45 mg/0.5 mL vial, and 130 mg/26 mL (5 mg/mL) vial
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Biocon Biologics Inc.
FDA Received Date:	November 29, 2023
TTT ID #:	2023-7314
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder ustekinumab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

As part of the approval process for Yesintek (ustekinumab-xxxx) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Yesintek Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Yesintek (ustekinumab-xxxx) is a proposed 351(k) biosimilar and the US-licensed Reference Product (RP) Stelara (ustekinumab), BLA 125261 and BLA 761044.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761406.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Yesintek Prescribing Information (PI), Patient Package Insert (PPI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Dermatology and Dentistry (DDD) in Section 4 and for Biocon Biologics Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) – General Issues			
1.	The nonproprietary name suffix is denoted by the placeholder '-xxxx' or '(ustekinumab)'.	A distinguishable nonproprietary name will facilitate accurate identification of the biological product by	We recommend replacing '-xxxx' with the conditionally acceptable nonproprietary name suffix when it is determined and including the nonproprietary name suffix in

Table 2. Identified Issues and Recommendations for the Division of Dermatology and Dentistry (DDD)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		healthcare providers and patients.	all other instances where appropriate.

5 RECOMMENDATIONS FOR BIOCON BIOLOGICS INC.

Table 3. Identified Issues and Recommendations for Biocon Biologics Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The expiration date placeholder is currently displayed as a YYYY-MM format.	We are unable to assess the proposed expiration date format from a medication safety perspective.	Clarify whether MM is intended to indicate a 2-letter abbreviation (e.g., JU) for the month or 2-digit (e.g., 01). 2-letter abbreviations have led to confusion for the months of March vs May and June vs July. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date 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

Table 3. Identified Issues and Recommendations for Biocon Biologics Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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 forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
2.	The "Rx only" statement appears more prominent than other critical information [route of administration and strength] on the principal display panel.	The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel.	We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
3.	For the vial container labels, the 130 mg/26 mL (5 mg/mL) vial carton labeling, and both prefilled syringe blister and carton labeling, the terminology within the statement of dosage statement (i.e., "usual dosage", "package insert") is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Dosage: see Prescribing Information" or "Recommended Dosage: see Prescribing Information". Additionally, we recommend adding the dosage statement to the 45 mg/0.5 mL vial carton labeling.

Table 3. Identified Issues and Recommendations for Biocon Biologics Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	The net quantity statement on the 90 mg/mL prefilled syringe container label is in close proximity to the product strength.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to over-dosing.	We recommend relocating the net quantity statement away from and less prominent than the product strength, such as to the bottom of the principal display panel. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
2.	For the prefilled syringe container labels, as currently presented, "BFXXXX/XX" is located in close proximity to the expiration date.	Numbers or codes located in close proximity to the expiration date may be mistaken as the expiration date.	We recommend you ensure that there are no other numbers located in close proximity to the expiration date.
Carton Labeling			
1.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC,	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

Table 3. Identified Issues and Recommendations for Biocon Biologics Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Yesintek received on November 29, 2023 from Biocon Biologics Inc., and the US-licensed Reference Product (RP).

Table 4. Relevant Product Information for Yesintek and the US-licensed Reference Product (RP).

Product Name	Yesintek	Stelara[b]
Initial Approval Date	N/A	September 25, 2009 (BLA 125261) September 23, 2016 (BLA 761044)
Nonproprietary Name	ustekinumab-xxxx	ustekinumab
Indication	Psoriasis (Ps) treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Psoriatic Arthritis (PsA) treatment of patients 6 years or older with active psoriatic arthritis. Crohn's Disease (CD) treatment of adult patients with moderately to severely active Crohn's disease. Ulcerative Colitis treatment of adult patients with moderately to severely active ulcerative colitis.	
Dosage Form	injection	
Strength	Subcutaneous: Prefilled syringe: 45 mg/0.5 mL, 90 mg/mL Vial: 45 mg/0.5 mL Intravenous: 130 mg/26 mL (5 mg/mL)	
Route of Administration	subcutaneous, intravenous	

[b] Stelara [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. March 2023. [cited 2024 APR 04]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125261s158lbl.pdf.

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Yesintek and the US-licensed Reference Product (RP).</th></tr>
<tr><td>Product Name</td><td>Yesintek</td><td>Stelara[b]</td></tr>
<tr><td>Dose and Frequency</td><td colspan="2">Psoriasis (Ps)
<u>Subcutaneous Adult:</u>
• For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
• For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.
In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects
<u>Subcutaneous Pediatric:</u>
Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.
The recommended dose for pediatric patients (6-17 years old) based on body weight is shown below.
<table>
<tr><th>Body Weight of Patient at the Time of Dosing</th><th>Recommended Dose</th></tr>
<tr><td>less than 60 kg*</td><td>0.75 mg/kg</td></tr>
<tr><td>60 kg to 100 kg</td><td>45 mg</td></tr>
<tr><td>more than 100 kg</td><td>90 mg</td></tr>
</table>
*For pediatric patients weighing less than 60 kg… withdraw the appropriate volume from the single-dose vial.

Psoriatic Arthritis (PsA)
<u>Subcutaneous Adult:</u>
• The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
• For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.
<u>Subcutaneous Pediatric:</u>
Administer subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.
The recommended dose for pediatric patients (6-17 years old) based on body weight is shown below.</td></tr>
</table>

<table>
<tr><td colspan="3">Table 4. Relevant Product Information for Yesintek and the US-licensed Reference Product (RP).</td></tr>
<tr><td>Product Name</td><td>Yesintek</td><td>Stelara[b]</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><th>Body Weight of Patient at the Time of Dosing</th><th>Recommended Dose</th></tr>
<tr><td>less than 60 kg*</td><td>0.75 mg/kg</td></tr>
<tr><td>60 kg or more</td><td>45 mg</td></tr>
<tr><td>greater than 100 kg with co-existent moderate-to-severe plaque psoriasis</td><td>90 mg</td></tr>
</table>
*For pediatric patients weighing less than 60 kg... withdraw the appropriate volume from the single-dose vial.

Crohn's Disease (CD) and Ulcerative Colitis
Intravenous Induction Adult:
A single intravenous infusion dose using the weight-based dosage regimen.
<table>
<tr><th>Body Weight of Patient at the time of dosing</th><th>Dose</th><th>Number of 130 mg/26 mL (5 mg/mL) vials</th></tr>
<tr><td>55 kg or less</td><td>260 mg</td><td>2</td></tr>
<tr><td>more than 55 kg to 85 kg</td><td>390 mg</td><td>3</td></tr>
<tr><td>more than 85 kg</td><td>520 mg</td><td>4</td></tr>
</table>
Subcutaneous Maintenance Adult:
The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
</td></tr>
</table>

Table 4. Relevant Product Information for Yesintek and the US-licensed Reference Product (RP).		
Product Name	Yesintek	Stelara[b]
How Supplied	sterile, preservative-free, colorless to pale yellow solution. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials <u>For Subcutaneous Use</u> *Prefilled Syringes* • 45 mg/0.5 mL (NDC 83257-023-41) • 90 mg/mL (NDC 83257-025-41) Each prefilled syringe is equipped with a 29 gauge fixed ½ inch needle, a needle safety guard, and a needle cover (b) (4) *Single-dose Vial* • 45 mg/0.5 mL (NDC 83257-024-11) <u>For Intravenous Infusion</u> *Single-dose Vial* • 130 mg/26 mL (5 mg/mL) (NDC 83257-026-11)	sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials <u>For Subcutaneous Use</u> *Prefilled Syringes* • 45 mg/0.5 mL (NDC 57894-060-03) • 90 mg/mL (NDC 57894-061-03) Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber. *Single-dose Vial* • 45 mg/0.5 mL (NDC 57894-060-02) <u>For Intravenous Infusion</u> *Single-dose Vial* • 130 mg/26 mL (5 mg/mL) (NDC 57894-054-27)

Table 4. Relevant Product Information for Yesintek and the US-licensed Reference Product (RP).		
Product Name	Yesintek	Stelara[b]
Storage	vials and prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Store vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use after the expiration date on the carton or on the prefilled syringe.	
Container Closure	Prefilled Syringe: Each prefilled syringe is equipped with a 29 gauge fixed ½ inch needle, a needle safety guard, and a needle cover (b) (4) Vial: N/A	Prefilled Syringe: Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber Vial: N/A

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

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

- Prescribing Information received on November 29, 2023, available from \\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word.docx
- Medication Guide received on November 29, 2023, available from \\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-medication-guide-tracked-changes-word.docx
- Instructions for Use received on November 29, 2023, available from \\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-ifu-vial-tracked-changes-word.docx and \\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-ifu-pfs-tracked-changes-word.docx
- Container label(s) received on November 29, 2023
- Carton labeling received on November 29, 2023

B.2 Container Label(s) and Carton Labeling Images

Container label(s)

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

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/s/

MADHURI R PATEL
05/15/2024 02:12:14 PM

YEVGENIYA M KOGAN
05/16/2024 07:40:09 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	3/27/2024		
To:	Hannah Lee		
Requesting Center/ Office	CDER/OPQ	**Clinical Review Division** OPRO/DRBPMI/RBPMB2	Other
From	Sangeetha Rajesh OPEQ/OHT3/DHT3C		
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR:00961727 ICC:2301148 Submission: BLA761406 Sponsor: Biocon Biologics Inc. Drug/Biologic: Ustekinumab Indications for Use: Treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.		
Recommendation	**Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
	Comments to Review Team: The sponsor has tested the safety features of the device per the requirements of ISO 23908:2011 Sharps Injury protection. The design verification testing report provided is acceptable. There are no additional concerns or requirements from the sponsor.		
	PMC/PMR or CR Deficiencies:		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**
Sangeetha Rajesh -S 2024.03.29 07:34:36 -04'00'	Shruti N. Mistry -S	2024.03.29 10:31:10 -04'00'

1. PURPOSE

This review provides an assessment of the needle safety device constituent part[1] of the prefilled syringe product.

This review will cover the following review areas:

☒ Needle safety device constituent performance [1]

CDRH Quality Systems Assessment / Facilities consult not required per internal MAP 5017.7

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[2]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

Bmab1200 (Ustekinumab) is being developed by Biocon Biologics as a proposed biosimilar product to US and EU licensed Stelara® (Ustekinumab) and are proposed to be presented in prefilled syringes (PFS) and vials. Bmab1200 is presented as a single-use, fixed dose, manually operated, single-user prefilled syringe designed to deliver a total of 45mg/0.5mL and 90mg/mL (same syringe with two different fill volumes) of Bmab1200 drug through subcutaneous injection. The final combination product will be available in the market only on prescription (Rx).

Each prefilled syringe is fitted with a passive needle safety guard designed to reduce the occurrence of accidental needle sticks. Device constituent parts (Prefillable Syringe, Plunger stopper, Plunger Rod, and Passive needle guard) are designed and manufactured by (b) (4). The final combination product consists of Bmab1200 drug with (b) (4) prefillable syringe, (b) (4) Plunger Rod (White), (b) (4) Plunger Stopper and (b) (4) Passive Needle Guard. (b) (4) supplies the Syringe components to Biocon Biologics (b) (4) (The needle is supplied staked to the glass syringe barrel). Biocon Biologics is responsible to (b) (4). Biocon Biologics is the legal manufacture for final combination product.

An Illustration of the Bmab1200 Combination Product, as Received by the User

(b) (4)

[1] The scope of this review will be limited to the device constituent performance in accordance with ISO 23908:2011 Sharps Injury Protection and FDA guidance Medical Devices with Sharps Injury Prevention Features. Therefore, for a PFS with a needle safety device constituent the review will be limited to needle safety performance requirements and will not cover functions of the primary container (container content, breakloose force, glide force, needle shield removal force, etc.,).

[2] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Container Closure System/Device Components (Section 3.2.P.7 of the submission)

The Bmab1200 DP is [redacted] filled into PFS device composed of ready to use [redacted] 1mL USP type 1 glass syringe with 29-gauge half inch hypodermic stainless-steel staked needle. The needle is protected by an [redacted] shield. The PFS is stoppered [redacted] with a ready to use [redacted] grey [redacted] plunger stopper [redacted] on the product contact side. The syringe barrel and the plunger stopper are the primary container closure parts that remain in contact with the product. The PFS is assembled with a passive needle guard and a plunger rod. The plunger rod is white in color [redacted]. The needle guard consists of a transparent [redacted] body, a transparent [redacted] guard and a stainless-steel spring, which enables passive actuation after dose administration. The plunger rod and needle guard do not come into contact with the drug product.

Bmab1200 drug product (DP)is filled into sterile 1 mL [redacted] USP Type-I glass syringe fitted with a staked needle and stoppered with a [redacted] plunger stopper. A plunger rod is assembled onto the plunger stopper on the side that does not come in contact with the product and helps in extruding the product out from the syringe. The needles used with the PFS are 29 gauge, 0.5-inch, [redacted] and a novel Rigid Needle Shield, [redacted] that helps to preserve needle point integrity.

As the Design Authority, [redacted] is the holder of the drug master file (DMF) for the components of the Bmab1200 PFS (DMF [redacted] & DMF [redacted]) which is on file with the Centre for Devices and Radiological Health (CDRH). Biocon Biologics hold the device Design History File [DHF] and have overall responsibility for manufacturing activities, including the Drug Substance (DS), Drug Product (DP), final assembly and Packaging.

Table 3.2.P.2.4/ 2: A Summary of the User Steps of the Bmab1200 Combination Product from the IFU

User Step	Summary
(b) (4)	

Proposed IFU (presented in Section 1.1.4(PFS)):

(b) (4)

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Table 3.2.P.7/ 1: Overview of the Bmab1200 Container Closure/Device Components

Device Component	Constituent Component	Material	Compliance status	Sterilization Method	Sterilization Location	Supplier	DMF reference no.
Syringe: (b) (4)	Glass syringe barrel	(b) (4)	(b) (4) (USP <660>, Ph. Eur. 3.2.1	(b) (4)	(b) (4)	(b) (4)	DMF: (b) (4) (Type III)[a]
	Needle		ISO 9626	Product meets 10^{-6} Sterility Assurance Level (SAL)			
	Rigid Needle shield – consisting of needle shield skirt (inner cap) and rigid shield (outer cap)		USP <381>, Ph. Eur. 3.2.9; ISO 8871-2				
Plunger stopper: (b) (4)	Plunger stopper		Ph. Eur. 3.2.9, USP <381>, ISO 10993	(b) (4) Product meets 10^{-6} SAL	(b) (4)		STN (b) (4)
			Ph.Eur./USP- (b) (4) monograph, ISO 10993				
Needle guard: (b) (4)	Body		Not applicable as it does not come in contact with the product.	Not applicable	Not Applicable		DMF (b) (4) (Type III)[a]
	Guard						
	Spring						
Plunger rod: (b) (4)	Plunger rod			Not applicable	Not Applicable		

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	The design of the Bmab1200 PFS allows health care providers, care giver and users to administer their prescribed dose of Bmab1200 into subcutaneous tissue.
Needle connection (e.g. luer, slip tip, staked)	Staked
Needle safety type (active or passive)	Passive

3. FILING REVIEW (optional)

Checklist	Present		
Item	**Yes**	**No**	**N/A**
Device Description	x		
Letters of Authorization	x		
Design Verification Summary and reports for needle safety attributes	x		

4. DEVICE PERFORMANCE REVIEW

4.1. Performance Data

Performance Requirement	Specification	Confidence / Reliability	Verification Data Acceptable (Y/N)
Needle Safety Activation force	(b) (4) *N* *Min* (b) (4) *N, Max–* (b) (4) *N*	☒ (b) (4) %	*n=30* (b) (4) % - **Y**

Needle safety lockout force/override force/safe mode challenge	Not performed on final product. Adequate justification and testing performed on the (b) (4) (b) (4) Passive Needle Guard in safe made per ISO 23908 provided by sponsor is acceptable	☒ (b) (4)%	**Y**
Needle Safety Pre-activation	*Actuation of the safety device*	☒ (b) (4)%	N=60, attribute test - **Y**
Needle safety Access in safe mode	Not performed on final product. Adequate justification and testing performed on the (b) (4) (b) (4) Passive Needle Guard in safe made per Annex B of ISO 23908 provided by sponsor is acceptable	*Tested*	*Sphere test Method Described in ISO 23908 Annex B.* **-Y**

Reviewer Comments:

- The sponsor has set the specification limit in compliance with the ISO23908 standard for the needle safety activation force and has tested 72 samples and has provided the min and max values. However, the sponsor hasn't provided the K vale or indicated the confidence and reliability intervals.
- The actuation of the device is tested, and it complies with the standard. However, only 15 samples were tested. The number of samples tested will not ensure (b) (4)% confidence and reliability and no rationale or justification is provided.
- Override force testing might not be needed as the sponsor has clearly indicated for single use, and re-use of the needle is discouraged but have included an IR to evaluate the sponsor's justification for not performing this test based on their design control.
- Testing the risk of accidental access to a sharp once in safe mode per Annex B has not been provided.

Information Request #1	(b) (4)

	(b) (4)
Sponsor Response	The sponsor responses are provided below.
Reviewer Comments	The sponsor responses are adequate and acceptable
Response Adequate:	☑ **Yes** ☐ **No, See IR # 1**

Reviewer Comments: The sponsor has tested the safety features of the device per the requirements of ISO 23908:2011 Sharps Injury protection. The design verification testing report provided is acceptable. There are no additional concerns or requirements from the sponsor.

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/

HANNAH A LEE
03/29/2024 10:44:44 AM
CDRH review is uploaded on behalf of CDRH assessors.

USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSIS REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 13, 2024
Product Therapeutic Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	IND 153118 and BLA 761406
Product Type:	Combination Product (Biologic-Device)
Product Name, Dosage Form and Strength:	Bmab 1200[a] (ustekinumab-xxxx)[b] injection, 45 mg/0.5 mL and 90 mg/mL
Device Constituent:	Pre-filled syringe (PFS)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biocon Biologics Inc. (Biocon)
FDA Received Date:	February 17, 2023, November 02, 2023, November 29, 2023
TTT ID #:	2023-3777 and 2023-7316
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

[a] Bmab 1200 has been developed as a proposed interchangeable biosimilar to US-licensed Stelara (ustekinumab). At the time this review was written, a proprietary name has not yet been approved. The proprietary name placeholder Bmab 1200 is used throughout the review.

[b] The proposed nonproprietary name suffix has not yet been conditionally accepted. We therefore refer to the proposed product as "ustekinumab-xxxx" throughout this review in place of the nonproprietary name suffix for this product.

1 REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA) and threshold analyses (hereafter called comparative analyses) submitted under IND 153118 and BLA 761406 for Bmab 1200 Prefilled Syringe (PFS) to determine whether Biocon needs to submit the results of a comparative use human factors study to support their marketing application seeking interchangeable biosimilarity to US-licensed Stelara (hereafter called Stelara).

1.1 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix/Section
Product Information/Prescribing Information	Section 1.2
Background Information Previous HF Reviews (DMEPA) and FDA/Sponsor Interactions	Section 2
Use-Related Risk Analysis, Comparative Analyses and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Label and Labeling	Appendix C

1.2 PRODUCT INFORMATION

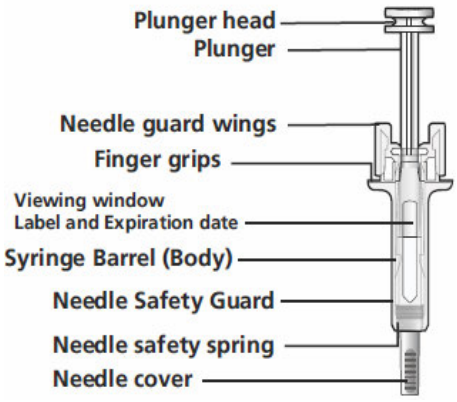
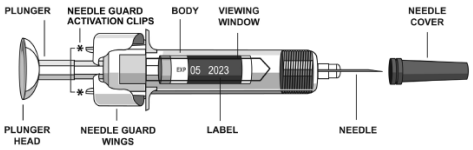
Table 2 presents relevant product information for Bmab 1200 received on 11/29/2023 From Biocon Biologics Inc.

Table 2. Relevant Product Information for Bmab 1200 and Stelara		
Product Name	Bmab 1200	Stelara[c] (BLA 761044)
Initial Approval Date	N/A	September 25, 2009
Active Ingredient	ustekinumab-xxxx	ustekinumab
Therapeutic Drug Class	monoclonal antibody, interleukin (IL) inhibitors	
Indication	Adult patients: • moderate to severe plaque psoriasis (Ps) who are	Adult patients: • moderate to severe plaque psoriasis (Ps) who are

[c] Stelara [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 OCT 18. [action date 2023 MAR 06] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761044s009lbl.pdf

	candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) alone or in combination, with methotrexate • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis <u>Pediatric patients 6 years and older with:</u> • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy.	candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis <u>Pediatric patients 6 years and older with:</u> • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis.
Route of Administration	• Subcutaneous • Intravenous Infusion	
Dosage Form	Injection	
Strength	<u>Subcutaneous Injection:</u> • 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe (PFS) • 45 mg/0.5 mL solution in a single-dose vial <u>Intravenous Infusion:</u> • 130 mg/26 mL (5 mg/mL) solution in a single-dose vial	
Dose and Frequency	<u>Psoriasis Adult Subcutaneous:</u> • weighing 100 kg or less: 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. • weighing more than 100 kg: 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. <u>Psoriasis Pediatric Subcutaneous:</u> • weighing 60 kg or less: 0.75 mg/kg initially, 4 weeks later, then every 12 weeks. • weighing 60 kg to 100 kg: 45 mg initially, 4 weeks later, then every 12 weeks. • weighing more than 100 kg: 90 mg initially, 4 weeks later, then every 12 weeks. <u>Psoriatic arthritis (PsA) Adult Subcutaneous:</u> • 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. • For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, 90 mg initially and 4 weeks later, followed	

<table>
<tr><td></td><td colspan="2">by 90 mg every 12 weeks.
<u>Psoriatic arthritis (PsA) Pediatric Subcutaneous:</u>
• weighing 60 kg or less: 0.75 mg/kg initially, 4 weeks later, then every 12 weeks.
• weighing 60 kg to 100 kg: 45 mg initially, 4 weeks later, then every 12 weeks.
• weighing more than 100 kg with co-existent moderate-to-severe plaque psoriasis: 90 mg initially, 4 weeks later, then every 12 weeks.
<u>Crohn's Disease and Ulcerative Colitis:</u>
• Intravenous Induction:
o weighing 55 kg or less: 260 mg (2 vials)
o weighing more than 55 kg to 85 kg: 390 mg (3 vials)
o weighing more than 85 kg: 520 mg (4 vials)
• Subcutaneous Maintenance:
o 90 mg, 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.</td></tr>
<tr><td>How Supplied</td><td>Bmab 1200 injection is a sterile, preservative-free, colorless to pale yellow solution. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.
<u>For Subcutaneous Use:</u>
• Prefilled Syringes
o 45 mg/0.5 mL (NDC 00000-000-00)
o 90 mg/mL (NDC 00000-000-00)
Each prefilled syringe is equipped with a 29-gauge fixed ½ inch needle, a needle safety guard, and a needle cover.
• Single-dose Vial
o 45 mg/0.5 mL (NDC 00000-000-00)
<u>For Intravenous Infusion</u>
• Single-dose Vial
130 mg/26 mL (5 mg/mL)
(NDC 00000-000-00)</td><td>Stelara injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.
<u>For Subcutaneous Use:</u>
• Prefilled Syringes
o 45 mg/0.5 mL (NDC 57894-060-03)
o 90 mg/mL (NDC 57894-061-03)
Each prefilled syringe is equipped with a 27-gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.
• Single-dose Vial
o 45 mg/0.5 mL (NDC 57894-060-02)
<u>For Intravenous Infusion</u>
• Single-dose Vial
o 130 mg/26 mL (5 mg/mL) (NDC 57894-054-27)</td></tr>
</table>

Storage	Bmab 1200 vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store Bmab 1200 vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use Bmab 1200 after the expiration date on the carton or on the prefilled syringe.	Stelara vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store Stelara vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use Stelara after the expiration date on the carton or on the prefilled syringe.
Container Closure/Device Constituent (including figure)		
Intended Users	Adult Patients, Pediatric Patients, or Healthcare professionals (HCPs).	
Intended Use Environment	Non-clinical (i.e., Home), Clinical (i.e., Hospital or HCP Office)	

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

On October 17, 2023, and subsequently on December 18, 2023, we searched for previous DMEPA reviews and FDA/Biocon interactions relevant to this current review using the terms, "*IND 153118*", "*BLA 761406*", "*Bmab 1200*" and "*ustekinumab*". See details below.

- On January 28, 2021, Biocon submitted a Biosimilar Biological Product Development (BPD) Type 2 Meeting request under IND 153118 to discuss the proposed development plan for Bmab 1200, a proposed biosimilar to US-licensed Stelara, to support a future 351 (k) biosimilar Biologic License Application (BLA) submission. We granted the meeting request, and, on April 26, 2021, we had a teleconference meeting with Biocon. In the meeting minutes dated May 17, 2021, we recommended Biocon submit a comprehensive use related risk analysis, comparative analyses, and justification for not submitting Human Factors (HF) validation study results.
- On February 17, 2023, Biocon submitted a comparative analyses under IND 153118 for Bmab 1200. The submission did not include a URRA. As such, on October 31, 2023, we issued an information request to obtain the URRA and Biocon submitted the URRA for review on November 02, 2023.
- On November 29, 2023, Biocon submitted BLA 761406 for Bmab 1200, as a proposed interchangeable biosimilar to US-licensed Stelara. We note Biocon did not wait for our review and response to the URRA and comparative analyses submitted under IND 153118 before submitting their BLA. Instead, Biocon submitted the same URRA and comparative analyses under their BLA, which are the subject of this review.

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis (URRA) and comparative analyses.

2.1 USE-RELATED RISK ANALYSIS

Biocon submitted a URRA for their proposed product.

We reviewed the URRA for the proposed product and, based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what Biocon proposes for the design and intended use of this product. Furthermore, for the tasks evaluated in the URRA, we did not identify any additional use-related issues that were not analyzed. Based on Biocon's identified use-related risks for this product, we determined the risks are mitigated by the proposed labels and labeling.

2.2 COMPARATIVE ANALYSES

The proposed product has the same indications, intended user populations (adult and pediatric patients, caregivers, and healthcare professionals) and the same use environments (non-clinical (i.e., home) and clinical (i.e., hospital or healthcare professional office) as Stelara.

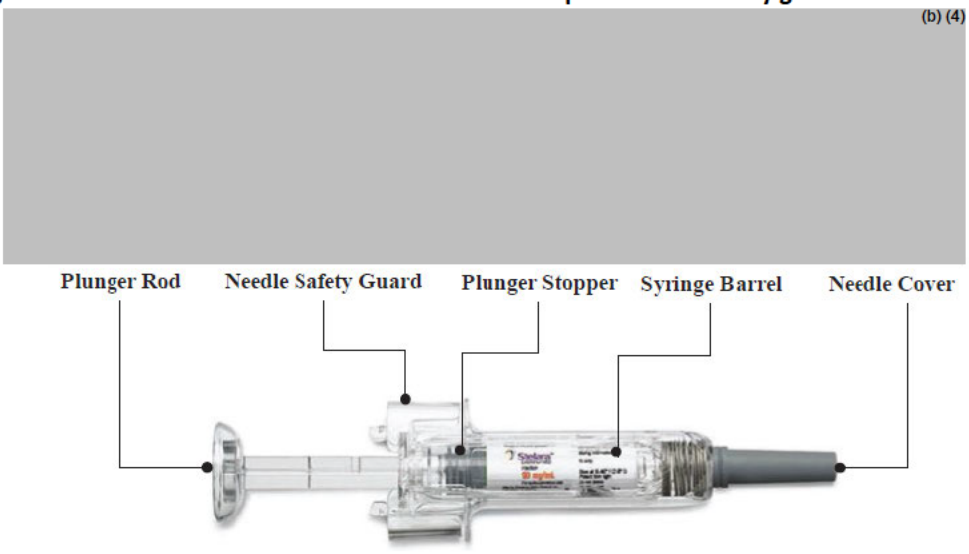
2.2.1 PHYSICAL COMPARISON

Biocon did not identify any "other" design differences in the physical comparison between the proposed Bmab 1200 and the reference product Stelara.

Biocon identified the following physical differences between Bmab 1200 and Stelara as "minor".

- Bmab 1200 PFS's needle gauge size is 29-gauge as compared to Stelara PFS's needle gauge size which is 27-gauge. In their justification for the "minor" design difference, Biocon stated that the "*syringe barrel with staked needle remains common, the difference is on the needle size which does not have impact of the user-interaction of the device*". Additionally, Biocon stated that the "*29 -gauge barrel needle used in the proposed Bmab 1200 PFS is designed for decrease pain pricking and penetration force which improve user experience*". Our review of the needle gauge size difference determined that the difference in needle gauge size is not likely to pose risk of usability concerns.
- The Bmab 1200 PFS needle safety guard activation clips are present within the activation wings as compared to Stelara PFS needle safety guard activation clips are present outside the activation wings. In their justification for the "minor" design difference, Biocon states that, "*In Bmab 1200 PFS, the activation clips are present within the activation wings to avoid accidental trigger of the needle guard. This provides additional safety feature to the proposed Bmab 1200 PFS when compared to the reference product Stelara. This difference does not impact the user-interaction tasks between the proposed and the reference product.*" (see Figure 1 below).

Figure 1. Bmab 1200 PFS and Stelara PFS activation clips of needle safety guard



We disagree with Biocon that the above design differences are "minor" as they may impact the performance of critical tasks for this specific product. As such, we determined that these differences are "other" design differences. Based on our independent expert review, we determined that the identified differences are unlikely to negatively impact users'

ability to complete critical tasks needed to use this product safely and effectively in the context of a proposed interchangeable biosimilar product to Stelara. Therefore, we determined that these differences do not warrant data from a comparative use human factors study.

Furthermore, we note Biocon provided device specifications. We defer the review of the acceptability of the device specifications to the Center for Devices and Radiological Health (CDRH). Depending on the outcome of their review, additional HF data considerations may apply if differences are identified that raise concerns regarding design validation.

2.2.2 COMPARATIVE TASK ANALYSES

Biocon did not identify task differences between the proposed product and Stelara. We did not identify any other new, differing, or unique tasks for the proposed product as compared to Stelara.

2.2.3 LABELING COMPARISON

Biocon's labeling comparison considered the Instruction for Use (IFU), Prescribing Information (PI), Medication Guide (MG), container labels and carton labeling.

Biocon did not identify any "other" design differences in the labeling comparison between the proposed Bmab 1200 PFS and the Stelara PFS.

However, Biocon identified minor labeling differences in corporate design colors, product manufacturer name, proprietary name, drug substance suffix, formulation, NDC number, barcode, logo, and formatting between the proposed product and Stelara. We agree with Biocon's determination to categorize the differences in formatting and differences mentioned above in the IFU, PI, MG, container labels and carton labeling between the proposed user interface as compared to the Stelara user interface as minor. As a general matter, graphics/illustrations, location of certain information and formatting of certain information can impact the performance of critical tasks. However, from a medication error perspective, we do not think these differences warrant data from a comparative use human factors (CUHF) study.

Note that the DMEPA 1 naming and labeling review team will evaluate the product specific labels and labeling under a separate cover.

3 CONCLUSION

Our review of the use-related risk analysis and comparative analyses did not identify any new, differing, or unique risks for the proposed product Bmab 1200 PFS as compared to US-licensed Stelara PFS. As such, no further information, or data (e.g., data from a CUHF study) is needed to support this marketing application for Bmab 1200, a proposed interchangeable biosimilar to US-licensed Stelara. We have no HF recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. USE RELATED RISK ANAYLYSIS, COMPARATIVE ANALYSES AND HF-RELATED SUPPORTING DOCUMENTS

IND 153118 submissions dated February 17, 2023:

- IND 153118 Bmab 1200 PFS Use-Related risk analysis (URRA) submission dated November 02, 2023, can be accessible in EDR via: \\CDSESUB1\EVSPROD\ind153118\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5354-other-stud-rep\drd-tr-lr-19-0079-22-002\use-related-risk-analysis.pdf
- IND 153118 Bmab 1200 Comparative Analyses submission dated February 17, 2023, can be accessible in EDR via: \\CDSESUB1\EVSPROD\ind153118\0019\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5354-other-stud-rep\drd-tr-lr-19-0079-22-002\drd-tr-lr-19-0079-22-002-study-report.pdf

BLA 761406 submissions dated November 29, 2023:

- Bmab 1200 PFS Use-Related risk analysis (URRA) can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761406\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5354-other-stud-rep\drd-tr-lr-19-0079-22-002\drd-tr-lr-19-0079-22-002-report-body-2.pdf
- Bmab 1200 PFS Comparative Analyses can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761406\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5354-other-stud-rep\drd-tr-lr-19-0079-22-002\drd-tr-lr-19-0079-22-002-report-body-1.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On October 31, 2023, we issued an information request (IR) to obtain the use-related risk analysis for the proposed Bmab 1200 prefilled syringe. Biocon provided an acceptable response on November 02, 2023, that can be accessible in EDR via: \\CDSESUB1\EVSPROD\ind153118\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\plaque-psoriasis\5354-other-stud-rep\drd-tr-lr-19-0079-22-002\use-related-risk-analysis.pdf

APPENDIX C. PRODUCT SAMPLE, LABEL AND LABELING

C.1 Product Sample

The product samples were submitted for our review, and we did not identify any recommendations for improvement at this time.

C.2 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following labels and labeling submitted by Biocon Biologics Inc., on November 29, 2023, under the BLA 761406.

- Container label
- Carton labeling
- Instructions for Use (image not shown) on page 147 of the Comparative analyses document
- Prescribing Information on page 144 to 145 of the Comparative analyses document

C.3 Label and Labeling images

Container label – PFS

(b) (4)

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

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

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/s/

AVINASH KONKANI
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OLUWAMUREWA OGUNTIMEIN
02/13/2024 04:34:04 PM

ARIANE O CONRAD
02/13/2024 04:53:31 PM

JASON A FLINT
02/13/2024 05:12:41 PM