CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761406Orig1s000
761406Orig2s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	November 22, 2024
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Prabuddha Sengupta, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment X
Application:	BLA 761406-ORIG-1
Applicant:	Biocon Biologics Inc.
Submission Date:	November 29, 2023
Product:	YESINTEK (ustekinumab-kfce)
Dosage form(s):	Injection
Strength and Container-Closure:	45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe 45 mg/0.5 mL solution in a single-dose vial 130 mg/26 mL (5 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the proposed interchangeable biosimilar to US-Licensed Stelara® injection (SC and IV).
Recommendations:	The prescribing information, medication guide, instructions for use, container labels, and carton labeling are acceptable from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information, medication guide, and instructions for use submitted on November 20, 2024 and container labels and carton labeling submitted on November 21 and 22, 2024, were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on November 21, 2023)
\\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word.docx

Medication Guide (submitted on November 21, 2023)
\\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-medication-guide-tracked-changes-word.docx

Instructions for Use (submitted on November 21, 2023)
\\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-ifu-vial-tracked-changes-word.docx

\\CDSESUB1\EVSPROD\bla761406\0001\m1\us\114-labeling\draft\labeling\draft-labeling-ifu-pfs-tracked-changes-word.docx

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise [redacted] (b) (4) to the qualifying phrase "Manufactured by:" to identify the licensed applicant. To identify the country of origin, we recommend revising to "Product of India". Add the U.S. License number. If space is an issue for the container labels, consider not including "245 Main St 2nd Floor".

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Add the U.S. License Number. The licensed manufacturer should appear as: Manufactured by: Biocon Biologics Inc., 245 Main St 2nd Floor, Cambridge, MA 02142, U.S.A., US License No. 2324 Product of India *The Applicant revised as recommended.*

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength presentation of the vials so that the (b) (4) is not included with the primary expression of strength.

The Applicant revised as recommended.

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: For the 45 mg/0.5 mL vial, consider decreasing the size of "Rx Only" to allow for prominence of other critical information on the PDP. For the 45 mg/0.5 mL and 90 mg/mL prefilled syringes, consider debolding "Rx Only" to allow for prominence of other critical information on the PDP. *The Applicant revised as recommended.*

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

Biocon would like to confirm to the Agency that the stoppers and cap overseal (flip off seals) are non-embossed (i.e. no text is present on components).

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

Biocon would like to confirm to Agency that for the 30 (b)(4) vial there is 9mm space between the ends of the label that remains uncovered for its full length leaving sufficient space vertically for visual inspection of the product. Similarly, in case of (b)(4) vials in the current label the uncovered area was approximately (b)(4) based on Agency recommendation the vial label length has been reduced such that there is a 4.0 mm space between the ends of the label that remains uncovered for its full length leaving sufficient space vertically for visual inspection of the product as shown in figure below. It is be noted that for length reduction only the company logo was adjusted without changing the text, font and spacing of the label.

(b) (4)

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

NDC numbers (container label)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the package type term from "single dose" to include the hyphen as follows "Single-dose"

The Applicant revised as recommended.

No misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No

	☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider deleting [redacted] (b) (4) and adding the net quantity "0.5 mL" to appear with the package type term as follows: " 0.5 mL Single-dose vial". For consistency, consider adding the net quantity similarly to the 26 mL vial and the prefilled syringes.

The Applicant revised as recommended.

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: For space considerations, consider removing the dosage statement [redacted] (b) (4) from the 45 mg/0.5 mL vial which can be considered a partial label. For the 130 mg/26 mL vial, revise the Statement of Dosage to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling format.

The Applicant revised as recommended.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: For consistency, revise the storage information so the dash between 36F and 46 F is changed to "to" and so that the degree symbol is adjacent to the number value to read as follows: "Storage: Refrigerate at 36º F to 46º F (2º C to 8º C) in the original carton to protect from light. Do not freeze. Do not shake."

The Applicant revised as recommended.

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise [redacted] (b) (4) to the qualifying phrase "Manufactured by:" to identify the licensed applicant. To identify the country of origin, we recommend revising to "Product of India". Add the U.S. License number.

Add the U.S. License Number.

The licensed manufacturer should appear as:
Manufactured by: Biocon Biologics Inc.,
245 Main St 2nd Floor, Cambridge, MA 02142, U.S.A.,
US License No. 2324
Product of India

The Applicant revised as recommended.

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No

	☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength presentation of the vials so that the (b) (4) is not included with the primary expression of strength.

The Applicant revised as recommended.

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: For consistency, revise the storage information so the dash between 36F and 46 F is changed to "to" and so that the degree symbol is adjacent to the number value to read as follows: "Storage: Refrigerate at 36º F to 46º F (2º C to 8º C) in the original carton to protect from light. Do not freeze. Do not shake."

The Applicant revised as recommended.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	✓ Yes ☐ No ☐ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure the suffix is added to the proper name in the ingredient list so that it reads as "ustekinumab-xxxx".

Revise the inactive ingredient list to match your prescribing information. To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section

502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients).

The established names for inactive ingredients in the 130 mg/26 mL vial are the USP/NF monographs titles which are: edetate disodium, histidine, L-histidine hydrochloride monohydrate, methionine, Polysorbate 80 and sucrose. Confirm if EDTA disodium salt (b) (4) meets the definition of edetate disodium, USP monograph. If so, then the name and the calculated amount (b) (4) will need to be revised accordingly. Confirm the provided calculation and provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 that includes the calculation between mg of EDTA disodium salt (b) (4) and mg of edetate disodium (b) (4) (labeled as edetate disodium). The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 (i.e., EDTA disodium salt (b) (4)) to the name and quantity presented in the Prescribing Information, container label, and carton labeling (i.e., edetate disodium). Ensure all inactive ingredients with a USP monograph are provided as such.

The established names for inactive ingredients for the 45 mg/0.5 mL prefilled syringe and the 90 mg/mL prefilled syringe are the USP/NF monographs titles which are: histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and sucrose.

Per 21 CFR 201.100(b)(5)(iii), the labeling must bear the quantity or proportion of all inactive ingredients. We ask that you revise the ingredient information to the compendial names for the excipients, histidine and L-histidine hydrochloride monohydrate with its respective individual amount in milligrams. Submit an updated Description and Composition Table in section 3.2.P.1.

Each 0.5 mL prefilled syringe delivers 45 mg ustekinumab-xxxx, histidine, L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 0.5 mL vial delivers 45 mg ustekinumab-xxxx, histidine, L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab-xxxx, histidine, L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

Each 26 mL vial delivers 130 mg ustekinumab-xxxx, edetate disodium ((b) (4) mg), histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

The Applicant revised as recommended.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for ustekinumab products (i.e., there is no specific test method described in regulation for ustekinumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Yesintek because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Although this statement currently appears on the carton labeling of the reference product, Stelara, this inclusion predated the Agency's renewed attention to the labeling requirement in § 610.61(r) as part of FDA's implementation of section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009. The absence of the statement for Yesintek should not be interpreted to mean that the Agency reached different conclusions about whether potency is a factor (within the meaning of § 610.61(r)) for Yesintek and its reference product.

Remove the statement "No U.S. standard of potency" from the carton labeling. Although this statement appears on the carton labeling of the reference product, Stelara, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for Yesintek carton labeling.

The Applicant revised as recommended.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The proprietary name, established name, product strength, route of administration, warning statements should be the most prominent information on the PDP. Considering removing any bolding or large prominence of Rx Only to allow for prominence of other critical information on the PDP.

The Applicant revised as recommended.

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the package type term from "single dose" to include the hyphen as follows "Single-dose".

For the 45 mg/0.4 mL PFS blister label and the 90 mg/mL PFS blister label, relocate the statement "Discard unused portion" to appear after the package type term "Single-dose Prefilled Syringe."

The Applicant revised as recommended.

No misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise Statement of Dosage to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling format.

Add the Statement of Dosage to the 45 mg/0.5 mL vial.

The Applicant revised as recommended.

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: For the 45 mg/0.5 mL vial, revise the medication guide statement to change (b) (4) to "to" so that it reads as "ATTENTION: Dispense the enclosed medication guide to each patient."

For the 45 mg/0.5 mL vial, the 45 mg/0.5 mL prefilled syringe, and the 90 mg/mL prefilled syringe, capitalize "ATTENTION".

The Applicant revised as recommended.

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling*	✓ Yes ☐ No ☐ N/A

Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Micro data do not support the proposed storage of the infusion solution to be completely administered within (b) (4) *hours. The applicant agreed in amendment 0010 (response to item 40) to update the USPI to allow for NMT 4 hours at RT. The Applicant submitted (sec 0010) proposed revisions to the PI as follows:*

(b) (4)

The Applicant revised identifying characteristics to reflect Biocon's product characteristics consistent with the Chemistry, Manufacturing and Controls section of Biocon's application as

clear and colorless to pale yellow. Product Quality Assessor confirmed.

(b) (4)

The package type term "single-dose" is intended to describe the container and has already been placed as a modifier for the word "vial" as "single-dose vial" in pertinent sections of the labeling. Placement of the modifier "single-dose" in this sentence as an action to be taken "for single-dose" may present ambiguity for the intended action. Thus, "single-dose" was revised to indicate the vial is intended for "one-time use in only one patient".

The Applicant revised as recommended.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The Applicant revised identifying characteristics to reflect Biocon's product characteristics consistent with the Chemistry, Manufacturing and Controls section of Biocon's application as clear and colorless to pale yellow. Product Quality Assessor confirmed.

(b) (4)

The Applicant revised as recommended.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**

Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

The Applicant revised identifying characteristics to reflect Biocon's product characteristics consistent with the Chemistry, Manufacturing and Controls section of Biocon's application as clear and colorless to pale yellow. Product Quality Assessor confirmed.

(b) (4)

The Applicant revised as recommended.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients for the 45 mg/0.5 mL prefilled syringe and the 90 mg/mL prefilled syringe are the USP/NF monographs titles which are: histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and sucrose.

Per 21 CFR 201.100(b)(5)(iii), the labeling must bear the quantity or proportion of all inactive ingredients. We ask that you revise the ingredient information to the compendial names for the excipients, histidine and L-histidine hydrochloride monohydrate with its respective individual amount in milligrams. Submit an updated Description and Composition Table in section 3.2.P.1.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in the 130 mg/26 mL vial are the USP/NF monographs titles which are: edetate disodium, histidine, L-histidine hydrochloride monohydrate, methionine, Polysorbate 80 and sucrose.

Confirm if EDTA disodium salt (b) (4) meets the definition of edetate disodium, USP monograph. If so, then the name and the calculated amount (b) (4) will need to be revised accordingly.

Confirm the provided calculation and provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 that includes the calculation between mg of EDTA disodium salt (b) (4) and mg of edetate disodium (b) (4) (labeled as edetate disodium). The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 (i.e., EDTA disodium salt (b) (4)) to the name and quantity presented in the Prescribing Information, container label, and carton labeling (i.e., edetate disodium). Ensure all inactive ingredients with a USP monograph are provided as such.

Confirm the added pH adjusters, hydrochloric acid and sodium hydroxide.

(b) (4)

The Applicant revised as recommended.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**

Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
Add in the 4-letter suffix.

The Applicant deleted (b) (4) *information, this information is not applicable to Biocon's presentation. The Biocon's PFS needle cover is* (b) (4) *Product Quality Assessor confirmed.*

The Applicant revised gauge size to align with Biocon's presentation. The needles used with the PFS are 29 gauge, 0.5-inch, (b) (4) *needle and a novel Rigid Needle Shield,* (b) (4)

Confirm revision to include description of the clarity of solution as clear.

Added the subsection for section 16 (How Supplied).

Revised the subsection to the subsection name accordingly (Storage and Handling).

The Applicant revised as recommended.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise (b) (4) to the qualifying phrase "Manufactured by:" to identify the licensed applicant. To identify the country of origin, use the phrase, "Product of India".

(b) (4)

The Applicant revised as recommended.

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the 4-letter suffix to the proper name.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients for the 45 mg/0.5 mL prefilled syringe and the 90 mg/mL prefilled syringe are the USP/NF monographs titles which are: histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and sucrose.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for

drugs (i.e., drug products and ingredients). The established names for inactive ingredients in the 130 mg/26 mL vial are the USP/NF monographs titles which are: edetate disodium, histidine, L-histidine hydrochloride monohydrate, methionine, Polysorbate 80 and sucrose.

The Applicant revised as recommended.

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise (b) (4) to the qualifying phrase "Manufactured by:" to identify the licensed applicant. To identify the country of origin, we recommend using the qualifying phrase, "Product of India".

Applicant revised as recommended.

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).*	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022). *To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)*	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022). *21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise (b) (4) to the qualifying phrase "Manufactured by:" to identify the licensed applicant. To identify the country of origin, we recommend using the qualifying phrase, "Product of India".

Applicant revised as recommended.

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on November 20, 2024)
  \\CDSESUB1\EVSPROD\bla761406\0039\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean-word.docx

- Medication Guide (submitted on November 20, 2024)
  \\CDSESUB1\EVSPROD\bla761406\0039\m1\us\114-labeling\draft\labeling\draft-labeling-medication-guide-clean-word.docx

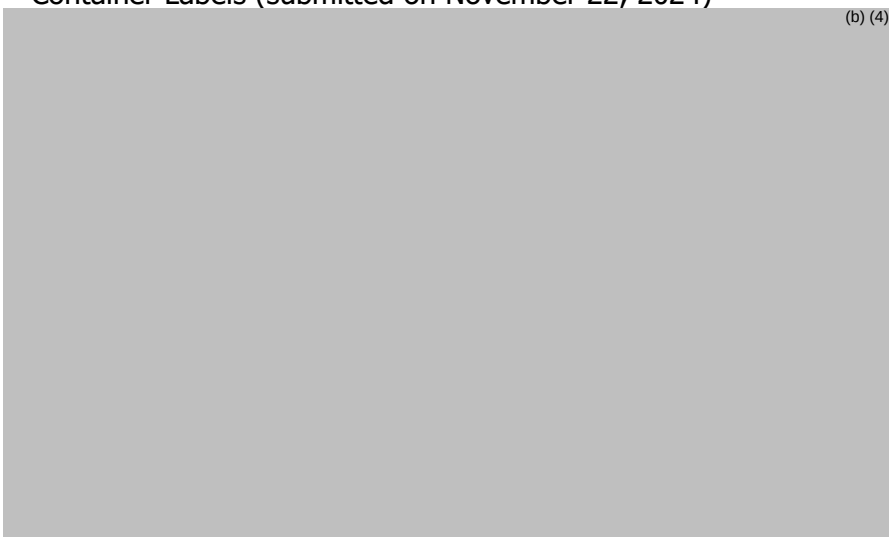
- Instructions for Use (submitted on November 20, 2024)
  \\CDSESUB1\EVSPROD\bla761406\0039\m1\us\114-labeling\draft\labeling\draft-labeling-ifu-vial-word-clean.docx

  \\CDSESUB1\EVSPROD\bla761406\0039\m1\us\114-labeling\draft\labeling\draft-labeling-ifu-pfs-word-clean.docx

- Container Labels (submitted on November 21, 2024)

- Container Labels (submitted on November 22, 2024)

(b) (4)



Diana Pei

Digitally signed by Diana Pei
Date: 11/22/2024 03:32:12PM
GUID: 6352da2c009ad0777a2c3b47ec094b9a

Prabuddha Sengupta

Digitally signed by Prabuddha Sengupta
Date: 11/22/2024 03:36:16PM
GUID: 626b341b016e86a817c5193a7d0ac483

BLA Executive Summary Addendum
Assessment Date: 11/19/2024

1. Application/Product Information

BLA number	761406
Submission Type	Original submission
Regulatory Pathway	Biosimilar 351 (k)
Associated IND/BLA	IND 153118
Review Designation	Standard
Applicant	Biocon Biologics Inc.
Indication	Adult patients with: • moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis. • moderately to severely active Crohn's disease. • moderately to severely active ulcerative colitis. Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis.
Rx/OTC dispensed	Rx
	Proprietary Name: Yesintek

Drug Product Name	**Non-proprietary Name/Code Name:** ustekinumab-kfce/Bmab1200
	OBP Naming: BsMAB: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [Bmab1200]
Drug Product Description	Ustekinumab-kfce is a human IgG1k monoclonal antibody produced in murine cell line (Sp2/0). Ustekinumab-kfce is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to their receptors. The ustekinumab-kfce drug product (DP) is available as a sterile, clear, colorless to pale yellow, preservative-free solution in both single dose pre-filled syringe (PFS) and single dose vial for subcutaneous (SC) use, and in single dose vial for intravenous (IV) use.
Dosage Form	Injection
Strength	Ustekinumab-kfce SC DP presentations: Ustekinumab-kfce PFS DP is supplied in 1 mL single dose USP Type-1 PFS with fill volumes of 0.5 mL (45 mg/0.5 mL PFS) or 1.0 mL (90 mg/1.0 mL PFS), with both PFS presentations containing ustekinumab-kfce at a concentration of 90 mg/mL. The ustekinumab-kfce vial for SC use, i.e., 45mg/0.5 mL vial, is supplied in a single dose USP Type-1 2 mL (2 (b) (4) glass vial with fill volume of 0.5 mL and containing ustekinumab-kfce at a concentration of 90 mg/mL. Ustekinumab-kfce IV DP presentation: The ustekinumab-kfce vial for IV use, i.e., 130mg/26 mL vial, is supplied in a single dose USP Type-1 30 mL (30 (b) (4) glass vial with fill volume of 26 mL and containing ustekinumab-kfce at a concentration of 5 mg/mL.

Route of Administration	Subcutaneous injection, Intravenous infusion		
Primary Container Closure System	Ustekinumab-kfce 45 mg/0.5 mL and 90 mg/1.0 mL PFS are filled in sterile 1 mL USP Type-I glass syringes containing a 29G½ inch staked needle and rigid needle shield. They are stoppered using (b) (4) plunger stopper. Ustekinumab-kfce 45 mg/0.5 mL vial is filled in single dose USP type 1 2 mL (2 (b) (4) glass vial and stoppered using sterile 13 mm (b) (4) rubber stopper and sealed with 13 mm aluminum overseal with plastic flip-off cap component. Ustekinumab-kfce 130 mg/26 mL DP is filled in sterile USP type 1 30 mL (30 (b) (4) glass vial and stoppered using sterile 20 mm (b) (4) rubber stopper and sealed with 20 mm aluminum overseal with plastic flip-off cap component.		
Device Information	Ustekinumab-kfce 45 mg/0.5 mL and 90 mg/1.0 mL PFS are assembled with a needle safety guard to reduce the occurrence of needle-stick injuries post injection.		
Co-packaged Product Information	NA		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Prabuddha Sengupta (OPQ/OPQA III/DPQA XIV)	Xiaoshi Wang (OPQ/OPQA III/DPQA XIV)
	Drug product		
	Immunogenicity Assay		
	Comparative Analytical Assessment		
	Facility	Mike Shanks (OPQ/OPMA) Madushini Dharmasena	Madushini Dharmasena (OPQ/OPMA) Candace Gomez-Broughton

		(OPQ/OPMA) for addendum	(OPQ/OPMA) for addendum
	Microbiology	Reyes Candau-Chacon (OPQ/OPMA)	Madu Dharmasena (OPQ/OPMA)
	RBPM	Hannah Lee (OPQ/OPRO)	
	ATL	Xiaoshi Wang (OPQ/OPQAIII/DPQAXIV)	
OPQ Issued Consults	The final recommendation from CDRH is that the device constituent parts of the combination product are acceptable.		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761406 for Yesintek manufactured by Biocon Biologics Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Yesintek is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Yesintek is highly similar to US-licensed Stelara (i.e., US-Stelara), notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** Biocon Biologics Limited, Bengaluru, India (FEI: 3003981475)
- **Drug Product:** Biocon Biologics Limited, Bengaluru, India (FEI: 3003981475)

b. Fill size and dosage form: Injection

- 45 mg/0.5 mL in single dose PFS
- 90 mg/1.0 mL in single dose PFS
- 45 mg/0.5 mL solution in single-dose vial
- 130 mg/26 mL solution in single-dose vial

c. Dating Period:

- **Drug Product:**
  45 mg/0.5 mL in PFS: 18 months at 5 °C ±3°C
  90 mg/1.0 mL in PFS: 6 months at 5 °C ±3°C
  45 mg/0.5 mL in vial: 12 months at 5 °C ±3°C
  130 mg/26 mL in vial: 12 months at 5 °C ±3°C

- **Drug Substance:** (b) (4) months at (b) (4)
- **Intermediate Substance, if applicable:** NA
- **For packaged products:** NA
- **Stability Option:**
  - Limited stability data: results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
  - For stability protocols: we have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Yesintek is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

Ustekinumab-kfce is a human IgG1k monoclonal antibody produced in murine cell line (Sp2/0). Ustekinumab-kfce is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23, and thereby prevents IL-12 and IL-23 from binding to their receptors. Ustekinumab-kfce is a proposed biosimilar interchangeable with US-Stelara for the same indications. Ustekinumab-kfce DP is supplied as the following strengths and presentations: 45 mg/0.5 mL in PFS, 90 mg/1.0 mL in PFS, 45 mg/0.5 mL in vial for SC injection, and 130 mg/26 mL in vial for IV infusion.

BLA 761406 is recommended for approval from product quality and microbiology perspectives. Refer to the Quality Executive Summary submitted in DARRTS on October 18, 2024, for a summary of the basis of recommendation from product quality and microbial perspectives.

Regarding facility, OPQ initially recommended a Complete Response for BLA 761406 based on the compliance status of Biocon Biologics Limited, Bengaluru, India (FEI: 3003981475) for the DS and DP manufacturing and testing facility for this application. On November 8, 2024, CDER/Office of Compliance (OC)/Office of Manufacturing Quality (OMQ) downgraded the compliance status of Biocon Biologics Limited, Bengaluru, India (FEI: 3003981475) to voluntary action indicated (VAI) after compliance review.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for DS and DP manufacturing and testing facility at Biocon Biologics Limited, Bengaluru, India (FEI: 3003981475). All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status, and recent relevant inspectional coverage.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for ustekinumab (i.e., there is no specific test method described in regulation for ustekinumab that establishes an official standard of potency). We next considered whether potency is a factor for ustekinumab within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Yesintek for purposes of § 610.61(r) because lot variability is not a concern for Yesintek as Yesintek's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

(b) (4)

(b) (4)

- Post-approval stability protocol at (b) (4) up to (b) (4) months, and stability commitment for ongoing stability studies of process validation batches.

ii. Residual risk: None
iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
- Post-approval stability protocol for 45 mg/0.5 mL PFS and 90 mg/1.0 mL PFS at 5 °C ±3 °C up to (b) (4) months, and stability commitment for ongoing stability studies of process validation batches.
- Post-approval stability protocol for 45 mg/0.5 mL vial at 5 °C ±3 °C up to (b) (4) months, and stability commitment for ongoing stability studies of process validation batches.
- Post-approval stability protocol for 130 mg/26 mL vial at 5 °C ±3 °C up to (b) (4) months, and stability commitment for ongoing stability studies of process validation batches.

ii. Residual risk: None
iii. Future inspection points to consider: None

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

Appendix. Comparative Analytical Assessment Summary

The data and information provided in the application supports that ustekinumab-kfce is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. The Applicant adequately established a three-way scientific bridge between ustekinumab-kfce, US-Stelara, and EU-approved Stelara (i.e., EU-Stelara) to support the relevance of the data generated from clinical studies using EU-Stelara as the comparator to the assessment of biosimilarity. The strengths of ustekinumab-kfce 90 mg/mL in single-dose PFS (45 mg/0.5 mL PFS and 90 mg/1.0 mL PFS) and single-dose 45 mg/0.5 mL vial for SC and 5mg/mL in single-dose 130 mg/26 mL vial for IV are the same as the corresponding presentations of US-Stelara. Refer to Quality Executive Summary submitted in DARRTS on October 18, 2024 for a summary of comparative analytical assessment.

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/

XIAOSHI N WANG
11/19/2024 02:33:52 PM

CANDACE GOMEZ-BROUGHTON
11/19/2024 02:48:57 PM

YAN WANG
11/19/2024 02:54:39 PM

BLA Executive Summary
Assessment Date: 10/17/2024

1. Application/Product Information

BLA number	761406
Submission Type	Original submission
Regulatory Pathway	Biosimilar 351 (k)
Associated IND/BLA	IND 153118
Review Designation	Standard
Applicant	Biocon Biologics Inc.
Indication	Adult patients with: • moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis. • moderately to severely active Crohn's disease. • moderately to severely active ulcerative colitis. Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis.
Rx/OTC dispensed	Rx
	Proprietary Name: Yesintek (proposed)

Drug Product Name	**Non-proprietary Name/Code Name:** ustekinumab-kfce/Bmab1200
	OBP Naming: BsMAB: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [Bmab1200]
Drug Product Description	Bmab1200 is a human IgG1k monoclonal antibody produced in murine cell line (Sp2/0). Bmab1200 is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23 and prevents IL-12 and IL-23 from binding to their receptors. The Bmab1200 drug product (DP) is available as a sterile, clear, colorless to pale yellow, preservative-free solution in both single dose pre-filled syringe (PFS) and single dose vial for subcutaneous (SC) use, and in single dose vial for intravenous (IV) use.
Dosage Form	Injection
Strength	Bmab1200 SC DP presentations: The Bmab1200 PFS DP is supplied in 1 mL single dose USP Type-1 PFS with fill volumes of 0.5 mL (45 mg/0.5 mL PFS) or 1.0 mL (90 mg/1.0 mL PFS), with both PFS presentations containing Bmab1200 at a concentration of 90 mg/mL. The Bmab1200 vial for SC use, i.e., 45mg/0.5 mL vial (Bmab1200 SC vial), is supplied in a single does USP Type-1 2 mL (2 (b) (4) glass vial with fill volume of 0.5 mL and containing Bmab1200 at a concentration of 90 mg/mL. Bmab1200 IV presentation: The Bmab1200 vial for IV use, i.e., 130mg/26 mL vial (Bmab1200 IV vial), is supplied in a single does USP Type-1 30 mL (30 (b) (4) glass vial with fill volume of 26 mL and containing Bmab1200 at a concentration of 5 mg/mL.
Route of Administration	Subcutaneous injection, Intravenous infusion

<table>
<tr><td>Primary Container Closure System</td><td colspan="3">Bmab1200 45 mg/0.5 mL and 90 mg/1.0 mL PFS are filled in sterile 1 mL USP Type-I glass syringes containing a 29G½ inch staked needle and rigid needle shield. They are stoppered using (b) (4) plunger stopper.

Bmab1200 45 mg/0.5 mL vial is filled in single dose USP type 1 2 mL (2 (b) (4) glass vial and stoppered using sterile 13 mm (b) (4) rubber stopper and sealed with 13 mm aluminum overseal with plastic flip-off cap component.

Bmab1200 130 mg/26 mL DP is filled in sterile USP type 1 30 mL (30 (b) (4) glass vial and stoppered using sterile 20 mm (b) (4) rubber stopper and sealed with 20 mm aluminum overseal with plastic flip-off cap component.</td></tr>
<tr><td>Device Information</td><td colspan="3">Bmab1200 45 mg/0.5 mL and 90 mg/1.0 mL PFS are assembled with a needle safety guard to reduce the occurrence of needle-stick injuries post injection.</td></tr>
<tr><td>Co-packaged Product Information</td><td colspan="3">NA</td></tr>
<tr><td rowspan="7">OPQ Review Team</td><td>Discipline</td><td>Primary</td><td>Secondary</td></tr>
<tr><td>Drug substance</td><td rowspan="3">Prabuddha Sengupta (OPQ/OPQA III/DPQA XIV)</td><td rowspan="3">Xiaoshi Wang (OPQ/OPQA III/DPQA XIV)</td></tr>
<tr><td>Drug product</td></tr>
<tr><td>Immunogenicity Assay</td></tr>
<tr><td>Facility</td><td>Mike Shanks (OPQ/OPMA)</td><td>Madu Dharmasena (OPQ/OPMA)</td></tr>
<tr><td>Microbiology</td><td>Reyes Candau-Chacon (OPQ/OPMA)</td><td>Madu Dharmasena (OPQ/OPMA)</td></tr>
<tr><td>RBPM</td><td>Hannah Lee (OPQ/OPRO)</td><td></td></tr>
<tr><td>ATL</td><td colspan="2">Xiaoshi Wang (OPQ/OPQAIII/DPQAXIV)</td></tr>
<tr><td>OPQ Issued Consults</td><td colspan="3">The final recommendation from CDRH is that the device constituent parts of the combination product are acceptable.</td></tr>
</table>

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761406 for Bmab1200 manufactured by Biocon Biologics Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Bmab1200 is well-controlled and will lead to a product that is pure and potent. The comparative analytical data support a demonstration that Bmab1200 is highly similar to US-licensed Stelara (i.e., US-Stelara), notwithstanding minor differences in clinically inactive components. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Biocon Biologics Limited to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comment to Be Included in the CR Letter

During a recent inspection of the Biocon Biologics Limited (FEI 3003981475) manufacturing facility for this BLA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this BLA may be approved.

4. Basis for Recommendation

a. Summary:

Bmab1200 is a human IgG1k monoclonal antibody produced in murine cell line (Sp2/0). Bmab1200 is an antagonist of human interleukin 12 (IL-12) and interleukin 23 (IL-23) cytokines. It binds to the p40 subunit shared by IL-12 and IL-23, and thereby prevents IL-12 and IL-23 from binding to their receptors. Bmab1200 is a proposed biosimilar interchangeable with US-Stelara for the same indications.

Bmab1200 DP is supplied as the following strengths and presentations: 45 mg/0.5 mL in PFS, 90 mg/1.0 mL in PFS, 45 mg/0.5 mL in vial for SC injection, and 130 mg/26 mL in vial for IV infusion.

Potency of Bmab1200 is controlled using an ELISA-based p40 binding assay and a cell-based assay that uses HEK-IL-12 cell line to measure the neutralization of IL-12 induced signal transducer and activator of transcription 4 (STAT4) activation in both drug substance (DS) and DP release and stability specifications. Bmab1200 binds to the shared P40 subunit of IL-12 or IL-23

and is unable to bind to the IL-12 or IL-23 molecule already bound to its receptor complex, and thus is not likely to mediate Fc effector functions.

The data and information provided in the application supports that Bmab1200 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. The Applicant adequately established a three-way scientific bridge between Bmab1200, US-Stelara, and EU-approved Stelara (i.e., EU-Stelara) to support the relevance of the data generated from clinical studies using EU-Stelara as the comparator to the assessment of biosimilarity. The strengths of Bmab1200 90 mg/mL in single-dose PFS (45 mg PFS and 90 mg PFS) and vial for SC and 5mg/mL in single-dose vial for IV are the same as the corresponding presentations of US-Stelara. Refer to Appendix of the executive summary for detailed comparative analytical assessment (CAA).

Bmab1200 is manufactured (b) (4)

(b) (4)

The DP manufacturing process for the Bmab1200 SC presentations (45 mg/0.5 mL PFS, 90 mg/1.0 mL PFS and 45 mg/0.5 mL vial) consists of the following steps: (b) (4)

(b) (4)

(b) (4)

The overall Bmab1200 control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for Bmab1200 DS and DP as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern.

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The DP is sterilized using a validated (b) (4) process (b) (4) (b) (4) using equipment and components with a 10^{-6} sterility assurance level.

Although the BLA is recommended for approval from product quality and microbiology perspectives, during a recent inspection of Biocon Biologics Limited, Bengaluru, India (FEI: 3003981475) for the DS and DP manufacturing and testing facility for this application, our field investigators issued 10-item FDA Form 483 conveying deficiencies to the representatives of the facility. Based on the facility compliance review of the facility's response to the FDA Form 483, a withhold is recommended for the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, OPQ is recommending a Complete Response for BLA 761406 during this assessment cycle.

CDRH final recommendation is that the device constituent parts of this combination product are approvable.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Inadequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations
Not applicable as OPQ does not recommend approval of this application.

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

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

The Applicant is seeking licensure of Bmab1200 as a biosimilar interchangeable with US-licensed Stelara (i.e., US-Stelara) for the following: 45 mg/0.5 mL and 90 mg/1.0 mL in a PFS, and 45 mg/0.5 mL in a vial for SC injection, and 130 mg/26 mL in a vial for IV infusion. These strengths, presentations and routes of administration are the same as those approved for US-Stelara.

The Applicant provided results from two three-way CAA studies to support the demonstration that Bmab1200 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components and to establish the analytical component of the scientific bridge between Bmab1200, US-Stelara and EU-approved Stelara (i.e., EU-Stelara). One CAA study was performed on the SC products (45 mg/0.5 mL PFS, 90 mg/1.0 mL PFS and 45 mg/0.5 mL vial). The other CAA study was performed on the IV product (130 mg/26 mL vial).

CAA lot selection and data pooling: 1) The selected US-Stelara lots include 10 lots of 45 mg/0.5 mL PFS, 10 lots of 90 mg/1.0 mL PFS, 11 lots of 45 mg/0.5 mL vial and 15 lots of 130 mg/26 mL vial. The selected EU-Stelara lots include 11 lots of 45 mg/0.5 mL PFS, 10 lots of 90 mg/1.0 mL PFS, 9 lots of 45 mg/0.5 mL vial and 14 lots of 130 mg/26 mL vial. The US-Stelara and EU-Stelara lots selected have an expiry span of June 2020 to August 2025 and across the DP shelf life to capture potential differences or variability over time. US-Stelara and EU-Stelara clinical lots are also included in the CAA. Therefore, the number and selection of US-Stelara and EU-Stelara lots in the CAA studies are appropriate and acceptable. 2) The number of independent Bmab1200 DP

lots studied in the CAA studies include 5 lots of 45 mg/0.5 mL PFS, 2 lots of 90 mg/1.0 mL PFS, 3 lots of 45 mg/0.5 mL vial and 8 lots of 130 mg/26 mL vial. The Bmab1200 DP lots include clinical lots, development lots and process performance qualification (PPQ) lots. Therefore, the number and selection of Bmab1200 DP lots in the CAA studies is also appropriate and acceptable. 3) The Applicant performed comparability assessment to support that various SC strengths and presentations of US-Stelara are comparable, various SC strengths and presentations of EU-Stelara are comparable, and various SC strengths and presentations of Bmab1200 are comparable. Based on results of comparability studies and the same protein concentration of all different SC presentations, the approach of pooling data from different SC strengths and presentations for each product is acceptable.

CAA quality attributes (QAs) selection: the CAA was performed on appropriately selected and ranked QAs based on their potential impact on efficacy, pharmacokinetics (PK)/pharmacodynamics (PD), immunogenicity and safety. The QAs are listed in section B of the summary.

Assessment approach of CAA study results: quality ranges (QRs) are established for methods to allow quantitative analysis. The QAs were classified into two groups using a decision-tree methodology to decide the standard deviation multiplier for each QA. For QAs with very high criticality, a multiplier of 3 is selected for CAA when the method precision is equal or less than 20%, and a multiplier of 2 is selected for CAA when the method precision is >20%. For moderate, low and very low criticality QAs, a multiplier of 3 is selected for CAA. Graphical profiles are compared side-by-side for qualitative methods for which quantitative results are not available. Therefore, the CAA study results assessment approach is reasonable and appropriate.

Overall, our assessment supports the demonstration of Bmab1200 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. The Applicant also employed three-way pairwise comparisons of Bmab1200, US-Stelara and EU-Stelara using the same methods and assessment approach to establish the analytical component of the scientific bridge between Bmab1200, US-Stelara and EU-Stelara to support the relevance of data generated from clinical studies using EU-Stelara as the comparator in the similarity assessment.

B. Results of the Comparative Analytical Assessment

The Applicant assessed the following quality attributes in the CAA.

Physicochemical/functional characteristics and quality attributes	Supports a demonstration of highly similar?	Supports the analytical component

			of scientific bridge?
DP general characteristics	Protein concentration by SoloVPE	Yes	Yes
Primary structure and post-translational modifications (PTM)	Intact protein molecular mass	Yes	Yes
	Reduced mass analysis of light chain	Yes	Yes
	Reduced mass analysis of Heavy chain	Yes	Yes
	Amino acid sequence by reduced peptide mapping	Yes	Yes
	Amino acid sequence by subunit liquid chromatography (LC)-mass spectrometry (MS) analysis	Yes	Yes
	Disulfide mapping	Yes	Yes
	Free cysteine by Ellman's test	Yes	Yes
	PTMs by peptide mapping, C-terminal lysine, methionine oxidation, N-terminal pyro-glutamate, N386 and N317 deamidation	Yes	Yes
Extinction coefficient	Amino acid analysis	Yes	Yes
Secondary structure	Far UV circular dichroism (CD) analysis	Yes	Yes
	Fourier transform infrared (FTIR)	Yes	Yes
Tertiary structure analysis	Near UV CD analysis	Yes	Yes
	Intrinsic fluorescence	Yes	Yes
Thermodynamical analysis	Tm1, Tm2, Tm3 by differential scanning calorimetry	Yes	Yes
Conformational dynamics	Hydrogen Deuterium exchange- mass spectrometry (HDX-MS)	Yes	Yes
Charge variants	isoelectric point, acidic, main and basic variants by Imaged capillary isoelectric focusing (iCIEF) untreated and Carboxypeptidase B (CpB) treated	Yes	Yes

	Acidic, main and basic variants by Ion Exchange High-performance liquid chromatography (IEX-HPLC) untreated and CpB treated	Yes	Yes
Size variants	High molecular weight protein (HMWP) and main peak by Size Exclusion Chromatography (SEC) HPLC	Yes	Yes
	two heavy and one light chain (2H1L), total fragments and monomer by non-reduced CE-SDS	Yes	Yes
	Non glycosylated heavy chain (NgHC) and LC+HC by reduced Capillary electrophoresis-sodium dodecyl sulfate (CE-SDS)	Yes	Yes
Hydrophobic variants	Lower hydrophobic species (LHS) and main variants by Hydrophobic interaction chromatography (HIC) HPLC untreated and CpB treated	Yes	Yes
Glycosylation	Total sialylation	Yes	Yes
	Total terminal galactosylation	Yes	Yes
	Total terminal GlcNAc	Yes	Yes
	Total high mannose	Yes	Yes
	Total afucosylation	Yes	Yes
	Total alpha 1,3-galactose	Yes	Yes
Functional activities	p40 binding by Enzyme-linked immunosorbent assay (ELISA)	Yes	Yes
	IL-12 binding by ELISA	Yes	Yes
	IL-12 affinity by Surface plasmon resonance (SPR)	Yes	Yes
	IL-23 binding by ELISA	Yes	Yes
	IL-23 affinity by SPR	Yes	Yes
	Neutralization of IL-12 induced STAT-4 activation by cell based assay	Yes	Yes

	Neutralization of IL-23 induced STAT-3 activation by cell based assay	Yes	Yes
	FcRn binding by SPR	Yes	Yes
	FcγRIa binding by SPR	Yes	Yes
	FcγRIIa binding by SPR	Yes	Yes
	FcγRIIIa V158 binding by SPR	Yes	Yes
	FcγRIIIa F158 binding by SPR	Yes	Yes
	FcγRIIb binding by SPR	Yes	Yes
	FcγRIIIb binding by SPR	Yes	Yes
	C1q binding	Yes	Yes
	IFN-γ release	Yes	Yes
	IL-17 release	Yes	Yes
	Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)	Yes	Yes
	Complement Dependent Cytotoxicity (CDC)	Yes	Yes
	Binding to IL-12 and IL-23 related proteins like IL-6	Yes	Yes
	Binding to IL-12 and IL-23 related proteins like IL-10	Yes	Yes
	Binding to IL-12 already bound to receptors	Yes	Yes
	Binding to IL-23 already bound to receptors	Yes	Yes
Forced degradations studies	High temperature	Yes	Yes
	Light exposure	Yes	Yes
	Acidity pH 3	Yes	Yes
	Alkalinity pH 9	Yes	Yes
	Shaking 250±30 rpm	Yes	Yes
	Oxidation 0.5% tert-butyl hydroperoxide (tBHP)	Yes	Yes

C. Comparative Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

Two clinical studies were conducted that compared Bmab1200 to US-Stelara and/or EU-Stelara.

- Clinical study BM12H-NHV-01-G-01 is a three-way PK similarity study conducted on healthy volunteers to demonstrate PK similarity of Bmab1200, the EU-Stelara, and the US-Stelara.

- Clinical study BM12H-PSO-03-G-02 was conducted to evaluate the similarity of efficacy, PK, safety and immunogenicity of Bmab1200 and EU-Stelara in patients with moderate to severe Plaque Psoriasis.

To establish the analytical component of the scientific bridge to support the relevance of the clinical data generated using EU-Stelara as the comparator product, the Applicant performed three-way analytical assessment comparing Bmab1200, US-Stelara, EU-Stelara using a comprehensive set of analytical methods. The differences observed in a subset of QAs in the comparative analytical studies (See section D below) do not preclude a determination that the analytical component of the scientific bridge is established.

D. Assessment of Analytical Study Results

CAA criteria were met for all attributes evaluated with the following exceptions:

1. PTMs by multi-attribute monitoring (MAM), charge variants by iCIEF, hydrophobic variants by hydrophilic interaction liquid chromatography (HILIC) with and without CpB treatment.

PTMs: for C-terminal lysine, 70% of Bmab1200 SC batches are within US-Stelara QRs; 60% Bmab1200 SC batches are within EU-Stelara QRs; all Bmab1200 IV batches are within the US-Stelara QR; and 25% of Bmab1200 IV batches are within EU-Stelara QR. The C-terminal lysine content in Bmab1200 (SC 27-48%, IV 27-44%) is slightly lower than the US-Stelara SC QR of 29-60% and EU-Stelara SC QR of 32-57%, and EU-Stelara IV QR of 33-58%. For Met254ox and Met430ox, almost all Bmab1200 batches are outside of the US/EU-Stelara QRs. The Bmab1200 Met254ox (Bmab1200 SC 1.24-2.71%, IV 1.33-1.9%) and Met430ox (Bmab1200 SC 0.33-1.15%, IV 0.49-0.86%) contents are slightly higher than their corresponding US-Stelara QR (Met254ox SC 0.27-1.13%, IV 0.38-0.97%; Met430ox SC 0.11-0.31%, IV 0.02-0.51%) and EU-Stelara QR (Met254ox SC 0.34-1.32%, IV 0.38-0.92%; Met430ox SC 0-0.48%, IV 0.09-0.24%). However, the Met254ox and Met430ox contents in all three products are low (<3%).

Charge variants: the acidic variants of about half of the Bmab1200 IV lots are marginally above the upper limits of the US-Stelara and EU-Stelara QRs. The main variant of 20% Bmab1200 SC batches is outside of US-Stelara QR, and 60% Bmab1200 IV batches is outside of EU-Stelara QR. The main peak of Bmab1200 batches (SC 23.2-41.9%, IV 23.8-38.5%) is higher than US-Stelara QRs (SC 22.1-33.8%, IV 22.0-35.4%) and EU-Stelara QRs (SC 21.6-35.0%, IV 21.4-33.6%), while the basic variants of

Bmab1200 batches (SC 23.6-42.0% and IV 25.4-42.3%) is lower than US-Stelara QRs (SC 30.0-49.2%, IV 30.1-47.7%) and EU-Stelara QRs (SC 29.8-49.4% and IV 32.3-47.8%). However, following CpB treatment, main and basic variants of all Bmab1200 batches are within US-Stelara and EU-Stelara QRs. The differences are mainly due to the lower C-terminal lysine content of Bmab1200 batches compared to US-Stelara and EU-Stelara batches.

Hydrophobic variants: the lower hydrophobic species (LHS) and main variant contents of Bmab1200 are within US-Stelara and EU-Stelara QRs without CpB treatment. However, following CpB treatment which removes C-terminal residues, ~90% of Bmab1200 batches (SC 3.3-6.6%, IV 2.6-6.0%) had higher levels of LHS variants, and slightly lower levels of main variant (Bmab1200 SC 93.4-96.7%, IV 94.0-97.4%) compared to the corresponding CpB treated US-Stelara (LHS SC 0.5-3.9%, IV 1.08-4.2%; main variant SC 96.2-99.5%, IV 95.8-98.9%) and EU-Stelara (LHS SC 0.5-4.3%, IV 1.9-3.4%; main variant SC 95.7-99.5%, IV 96.6-98.2). Based on characterization studies, this difference is due to slightly higher level of Met254ox in Bmab1200 which is detected as LHS variant.

Overall, the differences in charge variants and hydrophobic variants are due to the lower C-terminal lysine and higher level of Met254ox of Bmab1200 batches compared to US-Stelara and EU-Stelara batches. C-terminal lysine truncation occurs readily *in vivo* following both IV and SC administration. The differences in C-terminal lysine levels are not expected to have a clinical impact on the PK. The Met254 residue is located in the Fc CH2 domain which may impact PK and Fc mediated functional activities. However, no differences in FcRn binding were observed between Bmab1200 and US-Stelara and EU-Stelara in CAA studies. Also, Bmab1200 and US-Stelara and EU-Stelara lack ADCC and CDC activities. Therefore, the small differences in the observed PTMs, charge variants and hydrophobic variants between Bmab1200 and US-Stelara and EU-Stelara are not expected to have clinical impact on product quality of drug product, so they do not preclude the determination that Bmab1200 is highly similar to US-Stelara or the establishment of the analytical component of the scientific bridge.

2. N-Glycan profile

Bmab1200 is produced in murine cell line Sp2/0, which is the same cell line as the reference product. The N-glycan profiles of Bmab1200, US-Stelara, and EU-Stelara were assessed by HILIC-UPLC. Among the glycan species evaluated, only the total mannose content of Bmab1200 met the US-Stelara and EU-Stelara QRs. The differences observed in levels of other glycans are discussed below.

Total sialylation: the major sialyation form in Bmab1200, US-Stelara and EU-Stelara is N-glycolylneuraminic acid (NGNA) which is potentially immunogenic for human. For SC batches, total sialylation of nearly all the Bmab1200 batches are outside the US-Stelara

and EU-Stelara QRs. Total sialyation level is lower in SC Bmab1200 (range: 15.5-19%) than the QR of 19-29.5% for both US-Stelara and EU-Stelara. For IV presentation, the total sialyation of all the Bmab1200 batches is within the US/EU-Stelara QRs, but the values are at the lower end of the QRs. Bmab1200 has lower level of NGNA than US-Stelara and EU-Stelara. Therefore, the immunogenicity risk is expected to be lower for Bmab1200. The levels of total sialylation can also potentially impact PK and Fc-mediated bioactivity. However, no differences in FcRn binding were observed between Bmab1200 and US-Stelara and EU-Stelara in CAA studies. Also, Bmab1200, US-Stelara, and EU-Stelara lack ADCC and CDC activities.

Total terminal galactose: 40% of Bmab1200 SC batches and 60% of Bmab1200 IV batches were within US-Stelara and EU-Stelara QRs. Total terminal galactose level is slightly lower in Bmab1200 (both SC and IV 46-53%) than QR of 49-63% for both US-Stelara and EU-Stelara SC, and QR of 47.5-64% for both US-Stelara and EU-Stelara IV. Differences in galactosylation could potentially impact C1q binding and CDC activity. However, the observed differences are small, and Bmab1200, US-Stelara and EU-Stelara show similar C1q binding activity. In addition, Bmab1200, US-Stelara and EU-Stelara do not have CDC activity. Therefore, this difference is expected to have minimal clinical impact.

Total terminal GlcNAc: total terminal GlcNAc of all Bmab1200 SC batches are outside the US-Stelara and EU-Stelara QRs. Bmab1200 SC batches (81-85%) have higher levels of terminal GlcNAc compared to QR of 66-80% for both US-Stelara and EU-Stelara SC. Although total terminal GlcNAc of all Bmab1200 IV batches are within the US/EU-Stelara QRs, the values are at the higher end of the US-Stelara and EU-Stelara QRs. Terminal GlcNAc glycan may impact PK and Fc-mediated activities. However, no differences in FcRn binding were observed between Bmab1200, US-Stelara, and EU-Stelara in the CAA studies. Additionally, Bmab1200, US-Stelara, and EU-Stelara lack ADCC and CDC activities.

Afucosylation: 90% of Bmab1200 SC batches were outside of US-Stelara QR, and 70% batches were outside of EU-Stelara QR. 40% of Bmab1200 IV batches were outside of US-Stelara QR, and 75% batches were outside of EU-Stelara QR. Bmab1200 batches (3-6% for both SC and IV batches) have lower afucosylation than US-Stelara and EU-Stelara SC QR (4-7% for both) and US-Stelara IV QR (4-7%) and EU-Stelara IV QR (5-7%). Level of afucosylation of IgG antibodies has been reported to be directly proportional to binding affinity for FcγRIIIa and FcγRIIa receptors, and to impact ADCC activity. However, Bmab1200, US-Stelara and EU-Stelara lacks ADCC activity, therefore, the differences are not expected to have clinical impact on the biological activities of the three products.

Alpha-1,3 galactose: all Bmab1200 batches were outside US-Stelara and EU-Stelara QRs. The α-1,3 galactose level is lower in Bmab1200 (SC 1.4-2%, IV 1.9-2.1%) than

QR of 3-8% for both US-Stelara and EU-Stelara SC, and US-Stelara and EU-Stelara IV QR (3-9% for both). α-1,3 galactose is expected to be produced by murine cells. It is reported that α-1,3 galactose on Fab portion of a monoclonal antibody can potentially impact immunogenicity. However, the differences observed are related to α-1,3 galactose located on the Fc portion of the product which is enclosed in a cavity in the Fc region and is not readily accessible. Therefore, the differences are not expected to impact safety (e.g., increased immunogenicity) of Bmab1200.

Overall, there were differences in total sialylation, total terminal galactose, total terminal GlcNAc, afucosylation and alpha-1,3 galactose levels between Bmab1200 and US-Stelara and EU-Stelara. However, these analytical differences are expected to have minimal impact on safety, efficacy, PK, and immunogenicity, so they do not preclude the determination that Bmab1200 is highly similar to US-Stelara or the establishment of the analytical component of the scientific bridge.

3. Size variants

HMWP and main peak by SEC-HPLC: Bmab1200 SC batches have a slightly higher level of HMWP (0.25-0.79%) coupled with slight lower level of main peak (99.1-99.7%) than US-Stelara SC (HMWP QR 0.2-0.4%, main peak QR 99.3-99.9%) and EU-Stelara SC (HMWP QR 0.1-0.5%, main peak 99.0-100%). Bmab1200 IV batches have a marginally lower level of HMWP (0.12-0.3%) than US-Stelara IV (QR 0.16-0.43%) and EU-Stelara IV (QR 0.14-0.41%). However, the absolute differences are small and the HMWP levels are low (<0.8 % for Bmab1200 SC presentations, <0.3% for Bmab1200 IV presentation). Characterization of isolated HMWP fractions from both Bmab1200 and US-Stelara also showed that the HMWP species are predominantly dimers and a small amount of trimers, so the immunogenicity risk from the HMWP species is relatively low. Therefore, the small differences in HMWP and main peak levels between Bmab1200 and US-Stelara and EU-Stelara are expected to have minimal impact on product quality of drug product, so they do not preclude the determination that Bmab1200 is highly similar to US-Stelara or the establishment of the analytical component of the scientific bridge.

2H1L, total fragments and monomer by CE-SDS (NR): for SC presentations, a marginally higher level of 2H1L was observed in 30% of Bmab1200 SC batches compared to US-Stelara SC QR. For IV presentations, the total fragment content is lower and monomer content is marginally higher in 60% of Bmab1200 batches than US-Stelara and EU-Stelara. The 2H1L (≤1.08%) and total fragments (≤2.62%) contents are low for all three products. Therefore, the marginal differences in 2H1L, fragments and monomer between Bmab1200 and US-Stelara and EU-Stelara are expected to have minimal impact on product quality of drug product, so they do not preclude the determination of similarity.

NgHC, LC+HC and by CE-SDS (R): a slightly higher level of NgHC was observed in Bmab1200. 40% of Bmab1200 SC batches are within both US-Stelara and EU-Stelara SC and IV QRs. 25% of Bmab1200 IV batches were within US-Stelara IV QR. 37.5% of Bmab1200 IV batches were within EU-Stelara IV QR. The LC+HC level are within the US-Stelara and EU-Stelara QRs. The NgHC level (≤0.71%) is low for all three products. In addition, Bmab1200, US-Stelara and EU-Stelara do not have significant Fc-mediated functional activities. Therefore, the small differences in NgHC between Bmab1200 and US-Stelara and EU-Stelara are expected to have minimal impact on product quality of drug product, so they do not preclude the determination that Bmab1200 is highly similar to US-Stelara or the establishment of the analytical component of the scientific bridge.

4. Binding to Fc receptors

4.1 FcγRIIIa-V158 binding: lower binding affinities to FcγRIIIa-V158 were observed for Bmab1200 (SC 8.3×10^{-8}-1.8×10^{-6}, IV 7.9×10^{-8}-1.25×10^{-7}) compared to US-Stelara (QR SC 5.2×10^{-8}-1.2×10^{-7}, IV 5.5×10^{-8}-9.7×10^{-8}) and EU-Stelara (QR SC 5.4×10^{-8}-1.1×10^{-7}, IV 6.8×10^{-8}-8.6×10^{-8}).

4.2 FcγRIIIa-F158 binding: lower binding affinities to FcγRIIIa-F158 were observed for Bmab1200 (SC 1.6×10^{-7}-2.3×10^{-7}, IV 1.0×10^{-7}-2.3×10^{-7}) compared to US-Stelara (QR SC 7.8×10^{-8}-1.6×10^{-7}, IV 6.0×10^{-8}-1.5×10^{-7}) and EU-Stelara (QR SC 8.3×10^{-8}-1.6×10^{-7}, IV 4.3×10^{-8}-1.9×10^{-7}).

4.3 FcγRIIb binding: lower binding affinities to FcγRIIb were observed for Bmab1200 SC batches (3.0×10^{-6}-5.9×10^{-6}) compared to US-Stelara SC QR of 2.1×10^{-6}-5.4×10^{-6}.

4.3 FcγRIIIb binding: lower binding affinities to FcγRIIIb were observed for Bmab1200 (SC 1.3×10^{-6}-2.8×10^{-6}, IV 2.3×10^{-6}-3.4×10^{-6}) compared to US-Stelara (QR SC 8.4×10^{-7}-1.8×10^{-6}, IV 1.2×10^{-6}-2.5×10^{-6}) and EU-Stelara (QR SC 1.0×10^{-6}-1.8×10^{-6}, IV 1.3×10^{-6}-2.0×10^{-6}).

The lower binding affinities (i.e., higher dissociation constants Kd) to the above Fc receptors are due to lower afucosylation level observed in Bmab1200. However, Bmab1200, US-Stelara and EU-Stelara lack ADCC activity, so the differences are expected to have minimal clinical impact on the biological activities of the three products.

Overall conclusion

Taken together, the totality of the CAA supports the following conclusion:

- Bmab1200 is highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components.

- For attributes with minor differences, the sources of the differences were adequately evaluated, and residual uncertainties were risk-assessed. The differences are expected to have minimal clinical impact on safety, PK, efficacy and immunogenicity. Therefore, the differences do not preclude a demonstration that Bmab1200 is highly similar to US-Stelara or the establishment of the analytical component of the scientific bridge.

E. Same Strengths

Bmab1200 has the same dosage form and routes of administration as US-Stelara. Comparative protein concentration (mg/mL) was assessed as part of the CAA. The deliverable volume (mL) and fill weight data were assessed as part of manufacturing process controls. Based on the CAA and manufacturing data, the proposed strengths of Bmab1200 have the same total content of drug substance in mass in a container closure, and the same concentration of drug substance in mass per volume as the corresponding strengths of US-Stelara. Based on above, the strengths of Bmab1200 in 90 mg/1.0 mL and 45 mg/0.5 mL in PFS, 45 mg/0.5 mL in vial, and 130 mg/26 mL in vial are the same as those of US-Stelara.

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/

XIAOSHI N WANG
10/17/2024 11:07:52 PM

MADUSHINI N DHARMASENA
10/18/2024 08:40:24 AM

YAN WANG
10/18/2024 09:10:42 AM