CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761436Orig1s000
761436Orig2s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 15, 2025
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Prabhavathi Srinivasan, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761436
Applicant:	Biocon Biologics Inc.
Submission Date:	September 13, 2024
Product:	Bosaya (denosumab-kyqq) Aukelso (denosumab-kyqq)
Dosage form(s):	Injection
Strength and Container-Closure:	Bosaya: 60 mg/mL solution in a single-dose prefilled syringe Aukelos: 120 mg/1.7 mL (70 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Bosaya (denosumab-kyqq) a biosimilar to US-licensed PROLIA (denosumab) and Aukelos (denosumab-kyqq) a biosimilar to US-licensed XGEVA (denosumab).
Recommendations:	The prescribing information, medication guide, 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 Bosaya prescribing information submitted on September 10, 2025, Bosaya medication guide submitted on September 15, 2025, Aukelso prescribing information submitted on September 12, 2025, and container labels and carton labeling submitted on September 10, 2025 were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide for Bosaya prefilled syringe (submitted on September 16, 2024)
  \\CDSESUB1\EVSPROD\bla761436\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word-pfs.docx

- Prescribing Information for Aukelos vial (submitted on September 16, 2024)
  \\CDSESUB1\EVSPROD\bla761436\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word-vial.docx

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

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), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
On the 120 mg/1.7 mL vial container, the dosage form is currently located beneath the strength. Consider relocating the dosage form to appear beneath the proper name or to the right of the proper. The size of the dosage form is large. Consider reducing the size of "Injection".
The Applicant revised as recommended.

On the 60 mg/mL prefilled syringe, the dosage form and the route of administration are on the same line. Consider moving the route of administration to appear beneath the dosage form.
The Applicant relocated the strength the right of the proprietary name to appear beneath the dosage form. The route of administration was then relocated to appear beneath the strength which is acceptable.

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

[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.

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:
The manufacturer's name is currently bolded. The proprietary name, established name, product strength, route of administration, and warning statements should be the most prominent information on the Principal Display Panel (PDP). Consider removing any bolding of the manufacturer's name to allow for prominence of other critical information on the PDP.
The Applicant revised as recommended.

There is currently placeholders for the U.S. license number. Add in the U.S. License number.
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

Comment/Recommendation:

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

Comment/Recommendation:

[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."

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

Comment/Recommendation:

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:

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

Comment/Recommendation:

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: The Division of Medication Error Prevention and Analysis (DMEPA) recommended removing non-critical information as the label may be too small to accommodate all the information

proposed by the Applicant. Thus, the "Rx only" statement was removed as the label is small and could be considered a partial label.

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

Comment/Recommendation: The label is small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).

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

Comment/Recommendation: The container is enclosed in a package.

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

Comment/Recommendation: The product contains a container label.

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

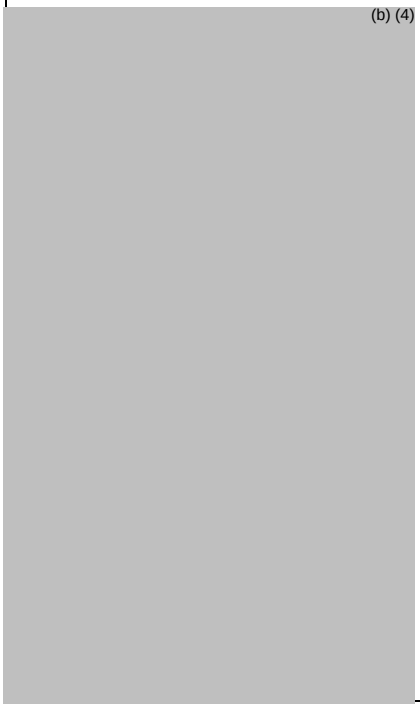
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The Applicant's response: Biocon would like to confirm to the Agency that the ferrule and the cap overseal (flip off seals) of the vials are non-embossed (i.e. no text is present on components).*

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.
The Applicant's response: Based on the Agency recommendation of the vial label length has been reduced such that there is a 4mm 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 below figure.

(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

Comment/Recommendation:

On the 60 mg/mL prefilled syringe, the dosage form and the route of administration are on the same line. Consider moving the route of administration to appear beneath the dosage form.
The Applicant relocated the strength the right of the proprietary name to appear beneath the dosage form. The route of administration was then relocated to appear beneath the strength which is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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:
On the 60 mg/mL prefilled syringe container label, the package type term is bolded. 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 of "Single-dose Prefilled Syringe. Discard unused portion" to allow for prominence of other critical information on the PDP.
The Applicant removed the package type term. The Division of Medication Error Prevention and Analysis (DMEPA) recommended removing non-critical information as the label may be

too small to accommodate all the information proposed by the Applicant. Thus, the package type term was removed as the label is small and could be considered a partial label.

On the 120 mg/1.7 mL vial container label, the package type term and net quantity are bolded. The proprietary name, established name, product strength, route of administration, warning statements should be the most prominent information on the PDP. Consider removing any bolding of "(b) (4)" to allow for prominence of other critical information on the PDP.
The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: The label does not display text in Spanish.

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

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

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

Comment/Recommendation:

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

Comment/Recommendation:

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:

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:
On the 60 mg/mL prefilled syringe container label, the current statement of dosage says "(b) (4)". Update the Statement of Dosage to read "Dosage: See Prescribing Information" to be in alignment with PLR labeling format. *The Applicant removed the statement of dosage. The Division of Medication Error Prevention and Analysis (DMEPA) recommended removing non-critical information as the label may be too small to accommodate all the information proposed by the Applicant. Thus, the statement of dosage was removed as the label is small and could be considered a partial label.*

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

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:

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

Comment/Recommendation:

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The dosage form is located under the strength. Consider relocating the dosage form to the right of or beneath the proper name.
The Applicant revised as recommended.

On the 60 mg/mL blister labeling, the dosage form and the route of administration are on the same line. Consider moving the route of administration to appear beneath the dosage form.
The Applicant revised as recommended.

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:
The U.S. license number currently has placeholders. Add the U.S. license number.
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

[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.

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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:

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:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: The product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

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:
Revise the inactive ingredients so that the units are all in milligrams.
The Applicant revised as recommended.

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

Comment/Recommendation:

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 denosumab products (i.e., there is no specific test method described in regulation for denosumab 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 Bosaya and Aukelso 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.

Remove the statement "No U.S. standard of potency" from the carton and blister labeling because our view is that 21 CFR 610.61(r) is not applicable.
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:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g), 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

Comment/Recommendation:

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:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: The label does not display text in Spanish.

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

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

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

Comment/Recommendation: The drug product does not contain phenylalanine.

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

Comment/Recommendation: The drug product does not contain sulfites.

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

Comment/Recommendation:
Revise the net quantity to state the volume so that it says "1 x Single-Dose Vial" and "1 x Single-Dose Prefilled Syringe".
The Applicant revised as recommended.

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

Comment/Recommendation:

On the carton labeling, the statement of dosage reads "(b) (4) ". Revise the statement of dosage to read "Dosage: See prescribing information" to be alignment with PLR labeling format. *The Applicant revised as recommended.* On the Blister labeling, the statement of dosage reads "(b) (4)". Revise the statement of dosage to read "Dosage: See prescribing information" to be alignment with PLR labeling format. *The Applicant revised as recommended.*

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

Comment/Recommendation:

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

Comment/Recommendation:
The Medication Guide statement currently reads as "Attention: Dispense the accompanying Medication Guide to each patient". Revise the to read as follows: "ATTENTION: Dispense the enclosed Medication Guide to each patient." Please note that "ATTENTION" is capitalized. *The Applicant revised as recommended.*

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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 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:

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:
The statement "(b) (4) s" was removed. The statement "(b) (4)" was revised to "visible particles".

(b) (4)

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:

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Information on sterility and preservatives or lack thereof is not required in Section 3. Thus, the information was deleted. This information is stated in Section 11.
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:

(b) (4)

Ensure the 4-letter suffix is added.
The Applicant revised as recommended.

Revised so the inactive ingredients are in the same units.
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 in your products are the USP/NF monographs titles, glacial acetic acid, polysorbate 20, sorbitol, and sodium acetate.
Confirm [redacted] (b) (4) meets the definition of the sodium acetate, USP monograph. If so, then the name and the calculated amount (calculated on the dried basis [redacted] (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 [redacted] (b) (4) (labeled as sodium acetate). The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 [redacted] (b) (4) to the name and quantity presented in the Prescribing Information, container label, and carton labeling (i.e., sodium acetate).
The Applicant revised as recommended.

Inactive ingredients were also reordered to appear in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients.
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

Comment/Recommendation:

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:

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: Add in US License number. Revised misspelling of "license". *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

Comment/Recommendation: Ensure the 4-letter suffix is added. *The Applicant revised as recommended.*

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

Comment/Recommendation:

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:
Ensure the 4-letter suffix is added.
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 in your products are the USP/NF monographs titles, glacial acetic acid, polysorbate 20, sorbitol, and sodium acetate.
The Applicant revised as recommended.

Inactive ingredients were also reordered to appear in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients.
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:

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.

Diana Pei

Digitally signed by Diana Pei
Date: 9/16/2025 08:05:57AM
GUID: 6352da2c009ad0777a2c3b47ec094b9a

Prabhavathi Srinivasan

Digitally signed by Prabhavathi Srinivasan
Date: 9/16/2025 10:43:52AM
GUID: 65d667ce005a4789046b033f16cce63c

BLA Executive Summary
Assessment Date: 08/18/2025

1. Application/Product Information

BLA number	761436
Submission Type	Original
Regulatory Pathway	351(k)
Associated IND/BLA	IND 153805
Review Designation	Standard review
Applicant	Biocon Biologics Inc.
Indication	Bosaya is indicated for the treatment: • of postmenopausal women with osteoporosis at high risk for fracture • to increase bone mass in men with osteoporosis at high risk for fracture • of glucocorticoid-induced osteoporosis in men and women at high risk for fracture • to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer • to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer Aukelso is indicated for: • Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Bosaya and Aukelso
	Non-proprietary Name/Code Name denosumab-kyqq
	OBP Naming MAB HUMAN (IGG2) ANTI O14788 (TNF11_HUMAN) [BMAB 1000]
Drug Product Description	Denosumab-kyqq (Bmab 1000) is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab-kyqq has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Bosaya (denosumab-kyqq) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow

	solution for subcutaneous use. Bosaya is a proposed biosimilar to US-licensed Prolia. Bosaya for subcutaneous injection is supplied in a single-dose prefilled syringe (PFS) containing 60 mg denosumab-kyqq in 1 mL. The excipient concentrations of Bmab 1000 in the PFS are glacial acetic acid (0.234 mg/mL), polysorbate 20 (0.1 mg/mL), sodium acetate (1.075mg/mL) and sorbitol (47 mg/mL) and may contain sodium hydroxide/acetic acid to adjust pH of 5.2. Aukelso (denosumab-kyqq) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous use. Aukelso is a proposed biosimilar to US-licensed Xgeva. Aukelso for subcutaneous injection is supplied in a single-dose vial containing 120 mg denosumab-kyqq in 1.7 mL. The excipient concentrations of Bmab 1000 in the vial are glacial acetic acid (0.234 mg/mL), polysorbate 20 (0.1 mg/mL), sodium acetate (1.075 mg/mL) and sorbitol (47 mg/mL) and may contain sodium hydroxide/acetic acid to adjust pH of 5.2.		
Dosage Form	Injection		
Strength	Bosaya (Bmab 1000-P): 60 mg/mL PFS Aukelso (Bmab 1000-X): 120 mg/1.7mL (70 mg/mL) vial		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	Bosaya (Bmab 1000-P): 60 mg/mL PFS • 1 mL (b) (4) glass syringe with a staked stainless-steel needle and closed with (b) (4) elastomer plunger-stopper and an elastomeric needle shield (inner cap) and elastomeric rigid shield (outer cap). Aukelso (Bmab 1000-X): 120mg/1.7mL (70 mg/mL) vial • (b) (4) glass vial closed with a 13 mm (b) (4) elastomeric stopper and aluminum seal with plastic flip-off seal		
Device Information	The PFS has a 29-gauge fixed ½ inch staked-in-place stainless steel needle and is assembled with a finger flange, plunger rod and fitted with a passive safety needle guard.		
Co-packaged Product Information	N/A		
	Discipline	Primary	Secondary
	Drug substance	Yigong (George) Bu	Xu (Michael) Di
	Drug product	Prabhavathi Srinivasan	Hailin (Sheena) Wang

OPQ Review Team	Comparative analytical assessment	Joao Pedras-Vasconcelos	Hailin (Sheena) Wang
	Immunogenicity Assay	Md Kamal Hossain	Joao Pedras-Vasconcelos
	Facility/ Microbiology	DS: Priscilla Amaral	Virginia Carroll
		DP: Jiangsong Jiang	Virginia Carroll
	OPQAIII labeling	Diana Pei	
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang	
	Tertiary	Frances Namuswe	
OPQ Issued Consults	The final recommendation from CDRH is that the device safety feature of the combination product is acceptable. There are no PMC/PMR from CDRH.		

2. Recommendation and Conclusion on Approvability
   Recommendation: Approval with PMCs

   The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761436 for Bosaya and Aukelso manufactured by Biocon Biologics Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Bosaya and Aukelso is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Bosaya and Aukelso is highly similar to US-licensed Prolia and US-licensed Xgeva, respectively, 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 - 560099, India. FEI: 3003981475.
      - Drug Product:
        Bosaya (Bmab 1000-P) and Aukelso (Bmab 1000-X)
        Biocon Biologics Limited, Bengaluru-560099, India. FEI: 3003981475.

   b. Fill size and dosage form:
      - 60 mg/mL in a single-dose prefilled syringe
      - 120mg/1.7mL (70 mg/mL) in a single-dose vial

   c. Dating Period:

- Drug Product:
  Bosaya (Bmab 1000-P) and Aukelso (Bmab 1000-X)
  36 months at 2-8°C including an in-use period of 30 days below 25°C
- Drug Substance:
  (b) (4) months at (b) (4) °C
- For packaged products: Not packaged
- Stability Option:
  - For stability protocols:
    - We have approved the stability protocol(s) 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: Bosaya and Aukelso are exempted from lot release per FR 95-29960. The overall control strategy, including manufacturing and release controls, is adequate to control lot-to-lot variability and product quality over the proposed shelf-life.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable:
   CMC PMC#1 (4889-1):
   To implement appropriate positive controls for the container closure integrity test (CCIT) method for Bmab 1000 pre-filled syringe (PFS) to provide the assurance that these positive controls are not subjected to potential leaks larger than the intended breach size of ≤ 20 µm diameter.

   Final report submission date: 12/2025

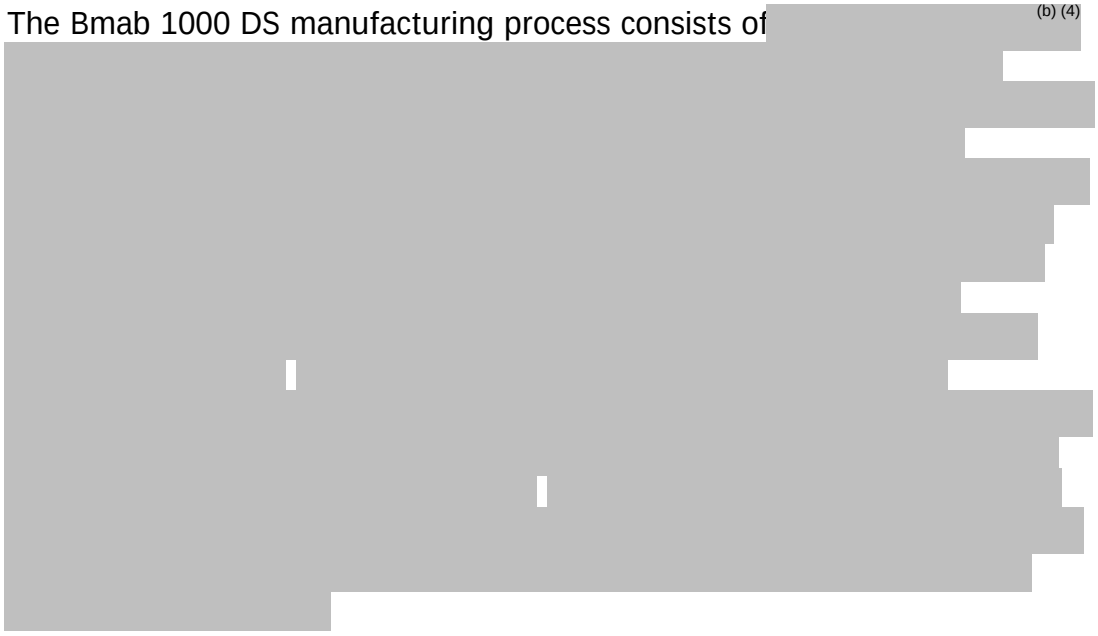
4. Basis for Recommendation
   a. Summary:

   Bmab 1000 (denosumab-kyqq) is a recombinant human IgG2 directed against human RANKL (receptor activator of nuclear factor kappa-B ligand). It is a proposed interchangeable biosimilar to US-Prolia and US-Xgeva for the same indications. Denosumab binds to RANKL, preventing RANKL from activating its only receptor (RANK) on the surface of osteoclasts and their precursors, independent of the bone surface. Denosumab-mediated blocking of RANK-RANKL interaction inhibits NF-κB activation leading to inhibition of differentiation of monocyte/macrophage lineage to osteoclasts, thereby preventing osteoclastogenesis and decreasing bone resorption.

Potency of Bmab 1000 is controlled using an ELISA-based RANKL binding assay and a cell-based functional signaling assay that monitors IκB degradation during drug substance (DS) and drug product (DP) release and stability testing. For the binding assay, denosumab bound to immobilized RANKL on multi-well ELISA plates is detected using a secondary antibody conjugated to horseradish peroxidase (HRP) that can be quantitated using a colorimetric reaction. For the cell-based functional signaling assay, relative potency is determined using a DiscoverX PathHunter U2OS RANK-IκB functional assay with engineered cells containing two β-galactosidase fragments that produce luminescence when complemented. RANKL treatment normally activates NF-κB by degrading the IκB subunit and prevents enzyme complementation, reducing signal output. When denosumab binds to RANKL, it blocks this degradation, allows enzyme complementation, and produces increased luminescence that correlates with drug potency.

The totality of the evidence from the comparative analytical assessment supports that Bmab 1000-P/X (denosumab-kyqq) is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components. The strengths of Bmab 1000-P 60 mg/mL in the single-dose PFS for subcutaneous injection and Bmab 1000-X 120 mg/1.7mL (70 mg/mL) in a single-dose vial for subcutaneous injection are the same as those of US-Prolia and US-Xgeva in the same presentations and routes of administration. Refer to Appendix for detailed summary of the comparative analytical assessment.

The Bmab 1000 DS manufacturing process consists of (b) (4)



The overall Bmab 1000 (denosumab-kyqq) control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Bmab 1000 (denosumab-kyqq) 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.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Biocon Biologics Limited (FEI: 3003981475) proposed for Bmab 1000 (denosumab-kyqq) DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage by Remote Regulatory Assessment (RRA).

The BLA is recommended for approval from the product quality, immunogenicity, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assays	-	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 Bosaya and Aukelso (i.e., there is no specific test method described in regulation for Bosaya and Aukelso that establishes an official standard of potency). We next considered whether potency is a factor for Bosaya and Aukelso 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 Bosaya and Aukelso for purposes of § 610.61(r) because lot variability is not a concern for Bosaya

and Aukelso as Bosaya's and Aukelso's manufacturing processes are 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
      Comments: N/A

   b. Drug Substance:
      i. Protocols approved:
         1. (b) (4) validation protocol
         2. (b) (4) validation protocol
         3. (b) (4) validation protocol
         4. (b) (4) validation protocol
         5. Master cell bank (MCB) and working cell bank (WCB) stability protocols
         6. Qualification protocol for a new WCB
         7. Stability protocols of primary reference standard (PRS) and secondary reference standard (SRS)
         8. Qualification protocol of a new PRS
         9. Qualification protocol of a new SRS
         10. Stability protocols for DS clinical and PPQ batches
         11. Post-approval drug substance annual stability and shelf-life extension protocol
      ii. Residual risk: None
      iii. Future inspection points to consider: None

   c. Drug Product:
      i. Protocols approved for both Bmab 1000-P (PFS) and Bmab 1000-X (vial)
         1. Leachable study protocol
         2. Stability protocol for DP process validation (PV) batches and clinical batches
         3. Post-approval stability commitment and protocol with the potential for shelf-life extension
      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.

II. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

Biocon Biologics is seeking licensure of Bmab 1000 as an interchangeable biosimilar to U.S.-licensed Prolia and US-licensed Xgeva (referred to hereafter as US-Prolia and US-Xgeva) for these strengths and presentations: Bmab 1000-P 60 mg/1.0 mL in a single-dose prefilled syringe (PFS) with safety guard and Bmab 1000-X 120 mg/1.7 mL (70 mg/mL) in a single-dose vial for subcutaneous injection. These are the same strengths, dosage form, and route of administration, currently available for US-Prolia and US-Xgeva.

To support a demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva, Biocon Biologics performed a pair-wise comparative analytical assessment (CAA) between Bmab 1000 and US-Prolia and US-Xgeva. Additional arms of the CAA include comparisons between Bmab 1000 and EU-approved Prolia/Xgeva (referred to hereafter as EU-Prolia and EU-Xgeva), and comparisons between US-Prolia and US-Xgeva and EU-Prolia and EU-Xgeva. Since the comparative clinical studies supporting biosimilarity only included US-Prolia, the CAA review focused solely on the CAA between Bmab1000-P/X and US-Prolia/Xgeva, which compared both PFS and vial presentations based on the following data:

- 14 lots of US-Prolia with expiration dates ranging from November 2020 through August 2025; 11 lots of US-Xgeva with expiration dates ranging from November 2020 through December 2025.
- 5 lots of Bmab 1000-P PFS drug product (DP) manufactured between Sept-2021 to Nov-2023; and 5 lots of Bmab 1000-X vial DP manufactured between Dec-2022 to Oct-2023, resulting in a total of 10 independent drug substance (DS) lots. Note one additional PFS lot and two additional vial lots from non-independent DS lots are included in the CAA for protein concentration and size variant/HMWP assessment.

Clinical studies used only PFS DP materials. The CAA includes all PFS DP lots from clinical studies and two Bmab1000 PPQ lots for each strength and presentation. The CAA excludes one PPQ lot each for PFS and vial DP presentations where multiple pooled DS lots were used in manufacturing. US-Prolia and US-Xgeva ages at testing were sufficient to detect potential differences or variability over time.

The CAA compared physicochemical and functional quality attributes (QAs) of Bmab 1000 and US-Prolia/Xgeva using orthogonal methods, as well as their degradation profiles under forced degradation conditions. Bmab 1000-P/X and US-Prolia/Xgeva data are pooled for the comparative assessment of attributes not impacted by DP

manufacturing process or strength differences. Separate analyses for protein concentration and size variants are conducted for the different presentations. Method validation or qualification study results support the suitability of the methods used in the analytical assessment. The Applicant used criticality-based data analysis to evaluate the analytical results that was consistent with FDA recommendations. The approach included the following: QAs amenable to statistical analysis were compared to quality ranges (QRs) of mean ± 2 (very high criticality) or 3 (high and moderate criticality) * standard deviations (SD) established from US-Prolia/Xgeva. In addition, for certain low criticality attributes, results are also evaluated against the QR of mean±3SD of US-Prolia/Xgeva to support similarity. If a result exceeded the predefined comparative assessment criteria, the magnitude and the criticality of the observed differences were discussed and justified. QAs not amenable to quantitative analysis or otherwise justified were analyzed by a qualitative comparison (e.g. visual comparison).

For the comparative stability studies, the Applicant conducted studies under forced degradation conditions (thermal stress at 25°C and 40°C for up to 24 days, shear stress, photo stress, oxidation and hydrolytic degradations). The comparative forced degradation studies show similar degradation pathways and degradation rates among Bmab 1000-P/X, US-Prolia/Xgeva.

Our assessment of the Bmab 1000 and US-Prolia and US-Xgeva comparative analytical data supports the determination that Bmab 1000 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components. Bmab 1000 has the same strengths, dosage form and route of administration as US-Prolia and US-Xgeva. The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of Bmab 1000 and US-Prolia/US-Xgeva to support the demonstration that the products are highly similar. The number of lots tested and data analysis approaches used were appropriate or justified as needed to allow for a meaningful evaluation of the results of the analytical studies. The differences observed in a subset of the quality attributes do not preclude a determination that Bmab 1000 and US-Prolia and US-Xgeva are highly similar.

B. Comparative Analytical Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?
Primary Structure	Amino acid sequence by peptide mapping by LC-MS	Yes
	Intact mass by LC-MS	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?
	Reduced and deglycosylated mass of HC and LC	Yes
Post Translational Modifications	Methionine Oxidation	Yes
	Deamidation	Yes
	Prolyl amidation	Yes
	HC and LC Glycation	Yes
	Isomerization	Yes
	C-terminal Lys truncation	Yes
Purity and impurities	Size variants by SEC-HPLC	Yes
	Size variants by SEC-MALS	Yes
	Size variants by SV-AUC	Yes
	Size variants by reduced CE-SDS	Yes
	Size variants by non-reduced CE-SDS	Yes
	Non-glycosylated HC	Yes
	Charge variants by icIEF	Yes
	Hydrophobic variants by HIC-HPLC	Yes
Glycosylation by HILIC-UPLC	Afucosylation	Yes
	Total mannosylation	Yes
	Total galactosylation	Yes
	Total sialylation	Yes
High Order Structure	Deuterium Exchange MS	Yes
	Disulfide mapping by non-reduced peptide mapping	Yes
	Disulfide isoforms by RP-HPLC	Yes
	Free cysteine by Ellman's assay	Yes
	Secondary structure FTIR and far UV spectra	Yes
	Tertiary Structure by near UV spectra	Yes
	Tertiary structure by DSC	Yes
Biological activities	RANKL binding	Yes
	NF-κB signaling activation	Yes
	RANKL Induced Osteoclast Differentiation (IOD)	Yes
	Membrane Bound RANKL Binding	Yes
	FcRn binding	Yes
	FcγRI binding	Yes
	FcγRIIa binding	Yes
	FcγRIIb binding	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?
	FcγRIIIa (F158) binding	Yes
	FcγRIIIb binding	Yes
	C1q binding	Yes
	Lack of Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes
	Lack of Complement-dependent cytotoxicity (CDC)	Yes
Drug Product Attribute	Protein concentration	Yes
Drug Substance Attribute	Extinction coefficient	Yes
Forced degradation studies	Thermal stress	Yes
	Mechanical stress	Yes
	Photo degradation	Yes
	Chemical oxidation	Yes
	Hydrolytic degradation	Yes

C. Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product:

Not Applicable

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment criteria were met for all attributes evaluated with the following exceptions:

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Charge variants (acidic and basic variants)	The icIEF results show lower levels of acidic species and higher levels of basic species for Bmab 1000 that fall outside of QR (mean±3SD) established based on US-Prolia/Xgeva. Bmab 1000 contained up to 13% lower levels of acidic species, ~11% higher levels of main peak species, and ~5% higher levels of basic species compared to US-Prolia/Xgeva. Additional characterization of the enriched charge variant species suggests the difference in charge variant profiles between Bmab 1000 and US-Prolia/Xgeva are predominantly due to reduced levels of asparagine deamidation in non-CDR sites for acid variants, while higher levels of basic peaks in Bmab 1000 result from high levels of proline

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	amidation on both heavy chains in Bmab 1000 as compared to the reference products. Characterization of enriched charge variant fractions supports the following: • The multi-attribute monitoring (MAM) analysis of enriched IEC-HPLC fractions of acidic peaks, main peak, and basic peaks from both products contain the same PTMs (oxidation, isomerization, deamidation, proline amidation, C-terminal Lys, etc.) at the same amino acid residues and similar levels, except for a relatively lower level of deamidation (not in CDR) and higher level of proline amidation, which are addressed below. The observed differences do not preclude a demonstration of highly similar. • Acidic peaks in both products are mostly enriched with deamidated species of HC N390/391 and HC N422/435. Characterization of these species in Bmab 1000 showed they are present at low levels in a Bmab 1000 DS lot ([redacted]%) and DS reference standard ([redacted]%). Biological activity of the acidic species with enriched deamidated species was comparable to that of the unfractionated material. In addition, lower levels of deamidation in Bmab 1000 do not preclude a demonstration of highly similar. • The basic peaks in both products are enriched with proline amidation species. Proline amidation is a common post-translational modification to the C-terminus of the mAb that is known to not impact biological activity. Bmab1000 samples with enriched proline amidation showed comparable biological activity to the unfractionated material. In addition, the difference between Bmab-1000 P/X and US-Prolia/Xgeva in % prolyl amidation is small (<1.1%) and is not expected to impact safety. Therefore, the observed differences in proline amidation do not preclude a demonstration of highly similar. Overall, the data support that the differences in charge variants are not expected to have a clinically meaningful impact and therefore do not preclude a demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.
Size variants	Reduced CE-SDS: Purity (HC+LC) of all Bmab 1000 lots trends higher with an overall lower NGHC impurity (<1%) level than US-Prolia and US-Xgeva. Lower NGHC impurities in Bmab 1000 do not preclude a demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.
Post-translational modifications (PTMs)	The MAM analysis shows higher C-terminal proline amidation levels in Bmab 1000 (min-max: 0.76-1.31%) compared to US-Prolia/Xgeva (QR mean±3SD: 0.00-0.71%). However, higher levels of C-terminal proline

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	amidation did not impact functional activity as demonstrated by the potency evaluation of the B2 peak enriched basic variant that contains high level of proline amidation. In addition, proline amidation is a common post-translational modification to the C-terminus of the mAb that has no impact on antigen binding and Fc effector functions based on its location, and is known to have no impact on safety, efficacy, or immunogenicity. Therefore, the differences in C-terminal proline amidation do not preclude a demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.
Disulfide variants (IgG2 isoforms)	The RP-HPLC analysis shows higher levels of B-isoform (min-max: 60.71 – 76.59%), AB-isoform (min-max: 17.82 – 23.17%), and lower mixed isoforms species (min-max: 5.04 – 6.98%) for Bmab-1000 compared to US-Prolia/Xgeva which contains B2 isoform (QR: 60.12-65.03%), AB-isoform (QR: 17.16-20.76%), and mixed isoform species (QR: 7.00-9.14%). Literature[1] indicates that different IgG2 isoforms show potency differences only when targeting cell surface receptors, whereas no difference occurs when directed against non-membrane bound receptors like RANKL. The available functional testing data confirmed no potency/binding differences between the different enriched isoforms in both Bmab 1000P/X and US-Prolia/Xgeva. IgG2 disulfide isoforms are known to readily interconvert in the reducing blood environment where the predominant form becomes the IgG2-B isoform and maintain equivalent FcRn binding for similar half-lives. Overall, the minor differences in disulfide isoform species are not expected to have a clinically meaningful impact and therefore do not preclude a demonstration of highly similar.
Hydrophobic Variants (HIC-HPLC Pre-peak)	The hydrophobic interaction chromatography (HIC-HPLC) analysis shows lower pre-peak levels (min-max: 3.07% - 6.61%) and a higher main peak levels (min-max: 93.25 – 96.69%) in Bmab 1000 as compared to QR of 6.05% - 13.05% and 86.64% - 93.80%, respectively, established based on US-Prolia/Xgeva. Up to 50% of Bmab 1000 lots fall outside the quality range. These results are attributed to lower oxidation levels and higher basic variants in Bmab 1000 as determined by MAM of PTMs. Hydrophobic variant analysis by HIC-HPLC is considered orthogonal to PTM analysis by MAM. The oxidation sites contributing to hydrophobic variants are not located in CDR regions, and lysine variants are common PTMs that do not affect biological activity or PK. In addition, results from all functional assays that reflect the mechanism of action (RANKL binding, NF-κB signaling, and osteoclast differentiation inhibition) were similar with 100% of Bmab-1000 lots within the QRs, confirming that the hydrophobic variant differences do not impact biological activity.

[1] Dillon TM et al. Structural and functional characterization of disulfide isoforms of the human IgG2 subclass. J Biol Chem. 2008 Jun 6;283(23)

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	Overall, the minor differences in hydrophobic variants are not expected to have a clinically meaningful impact and therefore do not preclude a demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.
Total afucosylation	The afucosylation levels in all 10 Bmab 1000 lots (3.71-4.49%) are lower and outside the QR of both US-Prolia/Xgeva (QR: 5.02-9.19%). Afucosylated species are considered a low-risk attribute as denosumab is not known to have effector function and the Applicant provided data showing that both the proposed biosimilar and US-Prolia/Xgeva lack effector function. Therefore, differences in attributes that can impact Fc-mediated functions are not expected to be meaningful. Given the foregoing, the noted differences are not expected to have a clinically meaningful impact. The observed differences in afucosylation do not preclude the demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.
Total mannosylation and total sialyation	N-glycosylation analysis shows that although 90% of the Bmab 1000 lots are within the QR of mean±3SD for mannosylation and sialylation, overall mannosylation and sialylation levels trend lower than those observed in US-Prolia/Xgeva. However, the difference in mannosylation is <5% and the overall levels of sialylation are less than 1% in both products. It is known that high mannose glycans of therapeutic monoclonal antibodies increase serum clearance in human. Scientific literature also indicates that up to 5% difference in high mannose glycan levels does not significantly impact clearance of monoclonal antibodies [Goetze A.M. et al. Glycobiology, 21(7), 949–959; Welch J. et al. Clinical Pharmacology & Therapeutics, 2022, 113(5), 1003-1010]. In addition, both Bmab 1000 and Prolia/Xgeva do not have Fc effector function as discussed above. The observed minor differences should not impact biological activities. Overall, the minor differences in mannosylation and sialyation levels are not expected to have a meaningful clinical impact and therefore do not preclude the demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.

E. Same Strength(s)

Bmab1000 has the same dosage form and route of administration as US-licensed Prolia and US- Xgeva. Biocon is seeking approval of Bmab 1000 60 mg/ mL in a single-dose prefilled syringe (PFS) for the subcutaneous route of administration, and Bmab 1000 120 mg/ 1.7 mL (70 mg/mL) in a single-dose vial for the subcutaneous route of administration as interchangeable biosimilars to US-Prolia and US-Xgeva, respectively. US-Prolia[2] injection and US-Xgeva[3] injection are available in these

[2] US Prescribing Information, US-licensed Prolia. Accessed in September 2025 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125320s219lbl.pdf
[3] US Prescribing Information, US-licensed Xgeva. Accessed in September 2025 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125320s222lbl.pdf

strengths and in these presentations for subcutaneous use. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed (b) (4) Based on the comparative analytical assessment and manufacturing data, the proposed strengths of Bmab 1000 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-Prolia and US-Xgeva. The strength of Bmab 1000 60 mg/1.0 mL in the PFS is the same as that of US-Prolia. The strength of 120 mg/1.7 mL in the single dose vial is the same as that of US-Xgeva.

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