CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761398Orig1s000
761398Orig2s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	March 24, 2025
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Li Lu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761398
Applicant:	Fresenius Kabi USA, LLC
Submission Date:	March 25, 2024
Product:	Conexxence (denosumab-bnht) Bomyntra (denosumab-bnht)
Dosage form(s):	Injection
Strength and Container-Closure:	60 mg/mL solution in single-dose prefilled syringe 120 mg/1.7 mL (70 mg/mL) solution in single-dose vial 120 mg/1.7 mL (70 mg/mL) solution in single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application for a proposed denosumab interchangeable biosimilar to the RP US licensed Prolia and Xgeva with the same therapeutic indications and dosing regimen. In addition, the applicant has proposed an additional prefilled syringe presentation for the 120 mg/1.7 mL strength, which is not available presentation for US Xgeva. The application has also submitted unbranded label and labeling for evaluation.
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).

We compared the proposed unbranded labeling to the acceptable branded labeling for removal of the branded name and consistent presentation of information from a product quality-related

labeling perspective. For biologics, the proper name does not include the dosage form.[1] We assessed the placement of the dosage form on the container label and carton labeling to ensure it appears beneath the proper name, rather than adjacent to it. We assessed the writing style of the proper name in product quality related sections of labeling[2] to ensure that when describing the drug substance that either sentence case or lower case is used and that when describing the drug product that the first letter of each word in the proper name is capitalized with the adjacent dosage form appearing in lower case.

CONCLUSION

The prescribing information (submitted on March 24, 2025), medication guide (submitted on March 24, 2025), container labels and carton labeling (submitted on March 19, 2025) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling (submitted on March 25, 2024)

- 60 mg PFS branded Prescribing Information and Medication Guide
  \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-60-mg-pfs.docx
  60 mg PFS unbranded Prescribing Information and Medication Guide
  \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-med-guide-60mg-pfs-unbranded.docx
  120 mg vial and PFS branded Prescribing Information
  \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-120-mg-vial-and-pfs.docx
  120 mg vial and PFS unbranded Prescribing Information
  \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-120-mg-vial-and-pfs-unbranded.docx
- Container Labels
  60 mg branded and unbranded PFS
  \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-container-labeling-primary-pfs-1ml.pdf
  \\CDSESUB1\EVSPROD\bla761398\0001\m1\us\114-labeling\114a-draft-label\draft-container-labeling-primary-pfs-1ml-non-branded.pdf

[1] 21 CFR 600.3(k)

[2] Product quality related sections of labeling include Product Title, Highlights Dosage Forms and Strengths, FPI Dosage Forms and Strengths, FPI Description, FPI How Supplied/Storage and Handling. Other labeling components assessed include Patient Information Labeling, Medication Guide, and Instructions for Use.

6 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[3,4] and Labeling[5] Standards

Container[6] 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(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

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(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

[3] 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.
[4] 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.
[5] 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.
[6] 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 (U.S license number for container bearing a partial label[7])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: for both 120 mg branded and unbranded vial label:
Revise the US license number placeholder to the active US license number "2146".

For both 60 mg and 120 mg PFS branded and unbranded container label:
Recommended adding the active US license number "2146" if enough space on the container label, because the US license number is considered to be important manufacturer information.

The applicant has revised as requested.

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(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

[7] 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."

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: for 60 mg PFS branded and unbranded labels:
Revise the product strength to read as "60 mg/mL".

The applicant has revised as requested.

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

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 has confirmed that there is no information on the ferrule and cap overseal of the vials.

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 has confirmed 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. See image below for representation to provide clarity on the sufficient space:

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

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

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: for all container labels: Confirm and ensure the Bar Code as indicated on all container labels are linear bar code which will be surrounded by enough white space to facilitate proper scanning. *The applicant has confirmed that Bar Code as indicated on all container labels are linear bar code which will be surrounded by enough white space to facilitate proper scanning.*

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

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: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

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. See carton labeling comments.

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

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

Package[8] 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

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 the US license number placeholder to the active U.S. License number "2146" to all cartons. *The applicant has revised as requested.*

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

[8] 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.

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 product strength to read as "60 mg/mL" to both 60 mg PFS branded and unbranded cartons.

The applicant has revised as requested.

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

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

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: For both 60 mg PFS branded and unbranded cartons, revise the Inactive ingredients list to read "glacial acetic acid (0.23 mg), polysorbate 20 (0.1 mg), sodium acetate (1.07 mg), sorbitol (47 mg), and Water for Injection, USP. Sodium hydroxide may be added to adjust pH to 5.2".

For 120 mg PFS and vial branded and unbranded cartons, revise the Inactive ingredients list to read "glacial acetic acid (0.39 mg), polysorbate 20 (0.17 mg), sodium acetate (1.83 mg), sorbitol (79.9 mg), and Water for Injection, USP. Sodium hydroxide may be added to adjust pH to 5.2".

The applicant has revised as requested.

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 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 **Bomyntra and Connexxence** 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.

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

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

Comment/Recommendation: Confirm and ensure the Bar Code as indicated on all cartons are linear bar code which will be surrounded by enough white space to facilitate proper scanning.

The applicant has confirmed that Bar Code as indicated on all carton labeling are linear bar code which will be surrounded by enough white space to facilitate proper scanning.

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

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

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)	✓ Yes ☐ No ☐ N/A

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).*	

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

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

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:
For 60 mg PFS unbranded USPI:
Revised the dosage form to appear in all lowercase letters according to Guidance for Industry: *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).

The applicant has revised as requested.

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 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

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: All USPI:
Revised to the following verbatim statement for parenterals per 21 CFR 201.57(c)(3)(iv).

The product quality team confirmed that the drug product should not contain particles per specification in the submission and recommended the following wording "…contains (b) (4) particles…" to be deleted from the label. To Applicant comment: We revised this statement because your product does not contain visible particles per specification."

For 120 mg vial and PFS unbranded USPI in subsection 2 IFU:

Revised to "a clear, colorless to pale yellow solution" to be consistent throughout the prescribing information.

The applicant has revised as requested. Note that OND ADL has revised the visual inspection statement to read as:" Do not use if the solution is discolored or cloudy or if the solution contains particles or foreign particulate matter."

Revised to read as "Discard vial after single entry." to avoid using package type term "single-dose" in Dosing and Administration section, which is intended to describe the container. Ensure to update the wording in the unbranded labeling to be consistent.

Instructions for Bomyntra Vial
Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial.
Discard vial after single (b) (4) entry.

The applicant has revised as requested.

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: For 60 mg/mL PFS branded and unbranded USPI:
Recommend removing the proper name as it is not required in this section.

Injection: 1 mL of a 60 mg/mL clear, colorless to pale yellow (b) (4) solution in a single-dose prefilled syringe.

For 120 mg branded and unbranded USPI:
Revised to include the description of the identifying characteristics of the dosage forms per 21 CFR 201.57(c)(4)(ii).

3 DOSAGE FORMS AND STRENGTHS

- Injection: 120 mg/1.7 mL (70 mg/mL) (b) (4) solution in a single-dose vial.
- Injection: 120 mg/1.7 mL (70 mg/mL) (b) (4) solution in a single-dose prefilled syringe.

The applicant has revised as requested.

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: For 60 mg PFS and 120 mg branded USPI:
Removed [redacted]

For 60 mg/mL PFS unbranded USPI:
Revised to include the type of dosage form per 21 CFR 201.57(c)(12)(i)(B).

For 120 mg branded and unbranded USPI:
Revised to include the type of dosage form and the route of administration to which the labeling applies in section 11. See 21 CFR 201.57(c)(12)(i)(B).

The applicant has revised as requested.

For 60 mg PFS branded and unbranded USPI:
We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on March 25, 2024. We are evaluating the submission to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and excipients). Per your 3.2.P.1, glacial acetic acid and sodium acetate [redacted] are both excipients used in the [redacted] formulation which is proposed to be labeled as "acetate". 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 for all excipients to their compendial names (when available) and individual amounts based on USP monograph definition. The USP monograph for sodium acetate states sodium acetate amount is calculated on the dried basis. Thus, the name and quantity of sodium acetate [redacted] should be presented as sodium acetate (1.07 mg). **Confirm** the calculated amount of sodium acetate [redacted] Submit an updated Description and Composition [redacted] The footnote should serve as a link between the names and quantities presented in section 3.2.P.1 to the names and quantities presented in the USPI and carton labeling.

Each 1 mL single-dose prefilled syringe of PROPRIETARY NAME contains 60 mg denosumab-xxxx (60 mg/mL solution), glacial acetic acid (0.23 mg), polysorbate 20 (0.1 mg), sodium acetate [redacted] 1.07 [redacted] mg), [redacted] sorbitol (47 mg), [redacted] and Water

Inactive ingredients names have been revised to appear in alphabetical order as recommended in USP General Chapters <1091> Labeling of Inactive Ingredients. We've also revised the presentation of the inactive ingredients to have the quantitative amounts of the

active ingredients appear in front of the name and the quantitative amounts of the inactive ingredients appear after the name in parenthesis to differentiate the actives from inactives.

For 120 mg vial and PFS branded and unbranded USPI:
We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on March 25, 2024. We are evaluating the submission to ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and excipients). Per your 3.2.P.1, glacial acetic acid and sodium acetate (b) (4) are both excipients used in the (b) (4) formulation which is proposed to be labeled as "acetate". 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 for all excipients to their compendial names (when available) and individual amounts based on USP monograph definition. The USP monograph for sodium acetate states sodium acetate amount is calculated on the dried basis. Thus, the name and quantity of sodium acetate (b) (4) should be presented as sodium acetate (1.83 mg). **Confirm** the calculated amount of sodium acetate (b) (4) (b) (4) per the monograph definition. Submit an updated Description and Composition (b) (4) (b) (4) The footnote should serve as a link between the names and quantities presented in section 3.2.P.1 to the names and quantities presented in the USPI and carton labeling.

contains 120 mg denosumab-xxxx (70 mg/mL solution), glacial acetic acid (0.39 mg), polysorbate 20 (0.17 mg), sodium acetate (b) (4) 1.83 mg), (b) (4) sorbitol (b) (4) 79.9 mg), and Water for Injection (USP) with a pH of 5.2. (b) (4)

Inactive ingredients names have been revised to appear in alphabetical order as recommended in USP General Chapters <1091> Labeling of Inactive Ingredients. We've also revised the presentation of the inactive ingredients to have the quantitative amounts of the active ingredients appear in front of the name and the quantitative amounts of the inactive ingredients appear after the name in parenthesis to differentiate the actives from inactives.

The applicant has revised as requested. However, during last labeling communication (the day before goal) to the applicant, the division has recommended the applicant to revise the ingredients list to show amount before inactive ingredient and the applicant has accepted division's suggestion. Therefore, the final ingredient list in all 4 USPI is shown with amount listed before inactive ingredient.

(b) (4)

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15:	☐ Yes ☐ No ☒ N/A

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]	

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: For 120 mg vial and PFS branded and unbranded USPI:
Revised to include the dosage form and description of identifying characteristics of the dosage form per 21 CFR 201.57(c)(17).

Revised the product strength to read "120 mg/1.7 mL (70 mg/mL)" to include strength/mL for single-dose injectable drug products with containers that supply a volume of drug greater than 1 mL according to *USP General Chapter <7> Labeling*.

For 60 mg PFS branded and unbranded USPI:
Revised the product strength to read "60 mg/mL".

We refer to your labeling IR responses submitted on February 10, 2025. Please revise the NDC numbers for sellable units in Section 16 of USPI. Ensure NDC numbers are consistent among the prescribing information and cartons.

The applicant has revised as requested. Noted that the applicant has decided to revise the total alternative room temperature storage of the supplied DP time frame from "30 days" to "14 days" so that it aligns between Module 3 and the carton mockups. OPQA III labeling previously consulted product quality CMC team that it is acceptable for the 14 days duration because data actually support up to 30 days.

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	✓ Yes ☐ No ☐ N/A

(Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	

Comment/Recommendation: We replaced the US license No. placeholder with the active US license No."2146".

The applicant has revised as requested.

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

Comment/Recommendation: Revised the alternative RT up to 77°F (25°C) duration to "14 days" in the unbranded 60 mg to be consistent with the branded labeling.

The applicant has revised as requested.

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: For both 60 mg PFS branded and unbranded MG:
Added 4-letter suffix placeholder 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) by using established names for drugs (i.e., drug products and ingredients), the established names for inactive ingredients in your products are revised according to the USP/NF monographs titles. Also, inactive ingredients names have been revised to appear in alphabetical order as recommended in *USP General Chapters <1091> Labeling of Inactive Ingredients* and to be consistent with USPI section 11.

The applicant has revised as requested.

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: For both 60 mg PFS branded and unbranded MG:
Recommend adding the US license number for consistency with the carton labeling.

The applicant has revised as requested.

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.

- 60 mg PFS branded Prescribing Information and Medication Guide (submitted on March 24, 2025)
  \\CDSESUB1\EVSPROD\bla761398\0037\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-60-mg-pfs.docx
  60 mg PFS unbranded Prescribing Information and Medication Guide (submitted on March 24, 2025)
  \\CDSESUB1\EVSPROD\bla761398\0037\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide-1ml-unbrand-1.docx
  120 mg vial and PFS branded Prescribing Information (submitted on March 24, 2025)
  \\CDSESUB1\EVSPROD\bla761398\0037\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-120-mg-vial-and-pfs.docx
  120 mg vial and PFS unbranded Prescribing Information (submitted on March 24, 2025)
  \\CDSESUB1\EVSPROD\bla761398\0037\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-medication-guide-1-7-ml-unbrand-1.docx
- Container Labels (submitted on March 19, 2025)
  60 mg branded and unbranded PFS
  \\CDSESUB1\EVSPROD\bla761398\0036\m1\us\114-labeling\114a-draft-label\draft-container-labeling-primary-pfs-1ml.pdf
  \\CDSESUB1\EVSPROD\bla761398\0036\m1\us\114-labeling\114a-draft-label\draft-container-labeling-primary-pfs-1ml-non-branded.pdf

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

Liming Lu

Digitally signed by Liming Lu
Date: 3/24/2025 08:55:37AM
GUID: 633d82d0001fb9cd8535e78c71271f3d

Li Lu

Digitally signed by Li Lu
Date: 3/24/2025 10:10:06AM
GUID: 508da7420002bb597e464bbaed29484f

BLA Executive Summary
Assessment Date: March 14, 2025

1. Application/Product Information

BLA number	761398
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351 (k)
Associated IND	IND 145897
Review Designation	Standard review
Applicant	Fresenius Kabi USA, LLC
Indication	The same indications for FKS518 as those are approved for US-Prolia and US-Xgeva
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: CONEXXENCE (as an interchangeable biosimilar for US-Prolia) BOMYNTRA (as an interchangeable biosimilar for US-Xgeva)
	Non-proprietary Name/Code Name: denosumab-bnht/FKS518
	OPQAIII Naming: MAB HUMAN (IGG2) ANTI O14788 (TNF11_HUMAN) [FKS518]
Drug Product Description	Conexxence/Bomyntra (denosumab-bnht) injection is a sterile, preservative-free, clear, colorless to pale yellow solution for subcutaneous use. Each 1 mL single-dose prefilled syringe (PFS) of Conexxence contains 60 mg denosumab-bnht (60 mg/mL solution), glacial acetic acid (0.23 mg), polysorbate 20 (0.1 mg), sodium acetate (1.07 mg), sorbitol (47 mg), and Water for Injection (USP) with a pH of 5.2. Sodium hydroxide may be added to adjust pH. Each ready-to-use, single-dose PFS and single-dose vial of Bomyntra contains 120 mg denosumab-bnht (70 mg/mL

	solution), glacial acetic acid (0.39 mg), polysorbate 20 (0.17 mg), sodium acetate (1.83 mg), sorbitol (79.9 mg), and Water for Injection (USP) with a pH of 5.2. Sodium hydroxide may be added to adjust pH.		
Dosage Form	Injection, solution		
Strength	Conexxence: 60 mg/1 mL (60 mg/mL) Bomyntra: 120 mg/1.7 mL (70 mg/mL)		
Route of Administration	Subcutaneous (SC) injection		
Primary Container Closure System	Single-dose PFS Single-dose vial		
Device Information	PFS for Conexxence and Bomyntra		
Co-packaged Product Information	Not applicable		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance (DS), Drug product (DP), and Immunogenicity Assay	Li Lu	Bazarragchaa Damdinsuren
	DS microbiology/facility	Lindsey Brown	Maxwell Van Tassell, Zhong Li
	DP microbiology/facility	Chani Broner	
	RBPM	Anita Brown	
	ATL	Bazarragchaa Damdinsuren	
OPQ Issued Consults	CDRH consult (ICC2400383)		

2. Recommendation and Conclusion on Approvability
   Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761398 for Conexxence and Bomyntra manufactured by Fresenius Kabi USA, LLC. The data submitted in this application are adequate to support the conclusion that the manufactures of Conexxence and Bomyntra are well-controlled and lead to products that are pure and potent. The comparative analytical data support a demonstration that Conexxence and Bomyntra are highly similar to US-licensed Prolia and Xgeva, notwithstanding minor differences in clinically inactive components. It is recommended that these products be approved for human use under conditions specified in the respective package insert.

3. CMC Information for Action Letter
   a. Manufacturing Location:
      - Drug Substance:
        (b) (4)
      - Drug Product:
        (b) (4)
      - Labeling and secondary packaging:
        Fresenius Kabi Austria GmbH (FK-Werndorf) (FEI: 3003708554)
        Am Gewerbepark 6
        8402 Werndorf, Austria

   b. Fill sizes and dosage forms:
      Conexxence: 60 mg/1 mL (60 mg/mL) single-dose PFS, injection, for subcutaneous use
      Bomyntra: 120 mg/1.7 mL (70 mg/mL) single-dose vial and single-dose PFS, injection, for subcutaneous use

   c. Dating Period:
      - Drug Products: 30 months when stored at 5 ± 3°C
      - Drug Substance: (b) (4) months when stored at (b) (4) ± (b) (4) °C
      - For packaged products: Not packaged
      - 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: Conexxence and Bomyntra are exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

Conexxence (denosumab-bnht, FKS518) is a proposed interchangeable biosimilar to US-licensed Prolia (US-Prolia) that is intended to be delivered by the same route of administration (SC) for the same indications as the US-Prolia reference product. Bomyntra (denosumab-bnht, FKS518) is a proposed interchangeable biosimilar to US-licensed Xgeva (US-Xgeva) that is intended to be delivered by the same route of administration (SC) for the same indications as the US-Xgeva reference product. The comparative analytical assessment (CAA) data submitted support the demonstration that Conexxence and Bomyntra are highly similar to US-Prolia and US-Xgeva, respectively, notwithstanding minor differences in clinically inactive components.

Denosumab-bnht is a recombinant, human IgG2 monoclonal antibody against human receptor activator of nuclear factor κB ligand (RANKL). Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Denosumab binding to RANKL prevents its interaction with RANK on the surface of osteoclasts and other cells, which inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength. Denosumab-bnht has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. The biological activity of denosumab-bnht is evaluated on its ability to bind to RANKL and prevent the RANKL/RANK interaction, thereby inhibiting the RANK signaling and IκB degradation in a dose-dependent manner.

The drug substance (DS) manufacturing process consists of (b) (4) (b) (4)

(b) (4)

The Conexxence and Bomyntra DP PFS manufacturing includes (b) (4)
(b) (4)

The Bomyntra DP vial manufacturing includes (b) (4)
(b) (4)

An on-site pre-license inspection for the drug substance and drug product manufacturing facilities at (b) (4) was conducted on (b) (4) and a 2-item Form FDA 483 was issued to the firm at the end of the inspection. The responses to 483 items were reviewed and found satisfactory. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional activity.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of sterile products.

The immunogenicity assays to detect, and confirm the amounts and neutralizing capacity of anti-drug antibodies against denosumab in the clinical studies to support this BLA were adequately validated and suitable for their intended purpose.

b. Subdiscipline Recommendation:

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

Individual assessments for each discipline are located in separate documents in Panorama.

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 Conexxence and Bomyntra (i.e., there is no specific test method described in regulation for Conexxence and Bomyntra that establishes an official standard of potency). We next considered whether potency is a factor for Conexxence and Bomyntra 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 Conexxence and Bomyntra for purposes of § 610.61(r) because lot variability is not a concern for Conexxence and Bomyntra, as Conexxence's and Bomyntra's manufacturing processes are appropriately controlled to ensure the consistency and quality of the final products.

5. Life-Cycle Considerations
   a. Established Conditions based on ICH Q12 principles: No

   b. Drug Substance:
      i. Protocols approved:

(b) (4)

(b) (4)

ii. Residual risk: No
iii. Future inspection points to consider: None

c. Drug Product:
   i. Protocols approved:
      1. On-going stability studies for DP PFS and DP vial (3.2.P.8.1 – PFS, 3.2.P.8.1 – Vial)
      2. Post-approval annual stability and commitments for DP PFS and DP vial (3.2.P.8.2 – PFS, 3.2.P.8.2 – Vial)
   ii. Residual risk: No
   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

A. Analytical Assessment Overview and Conclusions

To demonstrate that FKS518 is highly similar to US-licensed Prolia and US-licensed Xgeva, and to support the assessment of biosimilarity and interchangeability, the Applicant performed a comparative analytical assessment (CAA) between FKS518 drug product (DP) and combined US-Prolia and US-Xgeva (hereafter referred to as US-Prolia/Xgeva). Analytical results were analyzed with Prolia and Xgeva batches separately between the two originator presentations to support pooling them to calculate the similarity ranges. All FKS518 batches (prefilled syringe and vial) are comparable and combined in the CAA assessment. In this review, “FKS518 DPs” or “US-Prolia/Xgeva” indicates that pooled data are being discussed.

The CAA included comparisons of 10 batches of FKS518 60 mg/1 mL in prefilled syringe (PFS) (60 mg-PFS) and 8 batches of FKS518 120 mg/1.7 mL in vial (120 mg-vial), manufactured respectively in March 2020 – September 2022 and in August 2020 – June 2022), and 19 and 15 batches of US-Prolia and US-Xgeva (with respective expiry dates August 2018 – May 2024 and January 2018 – February 2024). The FKS518 DP batches used in each CAA were derived from independent DS batches and included the process validation batches (i.e., 3 batches each for 60 mg-PFS and 120 mg-vial). In addition, the CAA included all FKS518 DP and US-Prolia batches used in the comparative clinical studies included in the BLA.

The Applicant used a comprehensive array of analytical methods that were suitable to comparatively evaluate the critical quality attributes (CQAs) of each product. Results from method validation, qualification and verification studies were provided and adequately support the suitability of each method for its intended use in the CAA. The same analytical methods were used across all products.

The CAA was comprised of extensive comparative physiochemical and functional assessment of the quality attributes of FKS518 DPs and US-Prolia/Xgeva. The Applicant used an acceptable risk-based approach for statistical evaluation of analytical results. The CQAs and attributes linked to CQAs that were tested using quantitative assays were evaluated using quality ranges (QRs) obtained from US-Prolia/Xgeva to account for manufacturing variability and assay variability. In addition, the most sensitive assays for detecting product differences were selected for statistical evaluation using QRs. The selective high risk-ranked quality attributes directly reflecting mechanism of action (MOA) and protein concentration were evaluated against the QR determined by US-Prolia/Xgeva [mean ± x*standard deviation] with multiplier (x) of 2.58. High and moderate risk-ranked quality attributes that are not directly reflecting MOA and tested using quantitative assays were evaluated against the QR determined by US-Prolia/Xgeva [mean ± x*SD] with multiplier of 3. Attributes tested using quantitative assays not amenable to statistical analysis and qualitative assays were evaluated using visual comparisons (referred as descriptive assessment). The Applicant also provided a comparison of stability under forced degradation conditions of thermal (high temperature), light stress, high and low pH stress, oxidative stress, and mechanical stress.

Based on the OPQAIII assessment, the FKS518 and US-Prolia/Xgeva data support a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components. FKS518 has the same strength, dosage form, and route of administration as US-Prolia and US-Xgeva. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of FKS518 and US-Prolia and US-Xgeva to support the demonstration that the products are highly similar. Numbers and type of batches tested were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While

differences were observed in a limited number of attributes, these differences do not preclude a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva (see section D below).

The Applicant is also seeking approval of FKS518 120 mg/1.7 mL in PFS, which is supported through a demonstration of comparability between FKS518 120 mg-PFS and FKS518 120 mg-vial.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that FKS518 is highly similar to US-Prolia/Xgeva and the results are summarized in Table A below.

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)		Supports a Demonstration of Highly Similar
Primary Structure	Amino acid sequence (LC-MS/MS)		Yes
	Molecular mass (LC-MS)		Yes
	N-terminal sequence (Edman chemistry)		Yes
Post-Translational Modifications	Deamidation and isomerization (peptide mapping by LC-ESI-MS)		Yes
	Oxidation (peptide mapping by LC-ESI-MS)		Yes
	Glycation (peptide mapping by LC-MS/MS)		Yes
	N-glyco site occupancy (peptide mapping by LC-ESI-MS)		Yes
	N- and C-terminal variants (peptide mapping by LC-ESI-MS)		Yes
Higher Order Structure	Free Thiol content (Ellman's test)		Yes
	Secondary structure	(FTIR)	Yes
	Secondary and Tertiary structure	(CD, near and far UV)	Yes
	Tertiary structure	(Fluorescence spectroscopy)	Yes
	Disulfide linkage (non-reduced peptide mapping by LC-ESI-MS)		Yes
	Disulfide isoforms (non-reduced RP-UPLC)		Yes
	Thermal stability (DSC)		Yes
Size purity/impurity	Size variants (including HMW species)	(SEC-HPLC)	Yes
		(AUC)	Yes
	Monomer and dimer	(SEC-MALS)	Yes
	HC + LC	(reduced CE-SDS)	Yes

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)		Supports a Demonstration of Highly Similar
	NGHC	(reduced CE-SDS)	Yes
	Intact IgG	(non-reduced CE-SDS)	Yes
	LMW species	(non-reduced CE-SDS)	Yes
Charge Variants	Main Peak, Acidic and Basic Species	(AEX-HPLC)	Yes
		(icIEF)	Yes
Glycosylation	Sialylated glycans (DMB-UPLC, 2-AB UPLC-FL glycan mapping)		Yes
	Galactosylated glycans (2-AB UPLC-FL glycan mapping)		Yes
	Afucosylated glycans (2-AB UPLC-FL glycan mapping)		Yes
	High mannose (2-AB UPLC-FL glycan mapping)		Yes
Content	Protein Concentration (UV280)		Yes
	Extractable volume (Gravimetric volume determination)		Yes
Fab binding and Biological activity	Inhibition of sRANKL-induced IκB degradation (in vitro bioassay)		Yes
	Affinity to sRANKL (SPR)		Yes
	Inhibition of sRANKL-induced osteoclastogenesis (in vitro bioassay)		Yes
	Binding to tmRANKL (Flow cytometry)		Yes
Fc binding	FcRn binding affinity (SPR)		Yes
	FcγRIIa (H131, R131) binding affinity (SPR)		Yes
	FcγRIIb binding affinity (SPR)		Yes
Comparative in vitro activities (not part of the MOA of denosumab)*	Antibody-dependent cellular cytotoxicity (ADCC-induced cell viability reduction by luminescence)		Yes
	Complement-dependent cytotoxicity (CDC-induced cell viability reduction by luminescence)		Yes
	FcγRIIIa (F158, V158) binding affinity (SPR)		Yes
	FcγRIIIb binding affinity (SPR)		Yes
	FcγRI binding affinity (SPR)		Yes
	C1q binding (ELISA)		Yes
Degradation profiles*	High Temperature (55°C, 14 days)#		Yes
	Light stress (5 klux, 6 weeks)#		Yes
	Chemical Oxidation (H_2O_2 0.1%, 8 hours)#		Yes
	Low and high pH (pH 4.0 and 9.0, 7 days)#		Yes
	Mechanical stress (shaking at 300 rpm, 4 weeks)#		Yes

* - Additional characterization studies performed with 3-10 lots of each product

- Conditions for Forced Degradation Study

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

Not Applicable.

D. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria for the pairwise comparison between FKS518 DPs and US-Prolia/Xgeva were met for all attributes evaluated with the following exceptions:

- High mannose

FKS518 lots contained lower levels of high mannose (min/max: 3.78 – 6.64%) than US-Prolia/Xgeva lots (min/max: 6.73 - 9.54%, QR 5.87 - 10.34%). The high mannose glycans is identified as a moderate criticality attribute. The Applicant justified that a difference in high mannose content of antibodies impact antibody clearance, however, a small difference (up to 6%) in high mannose content is not expected to impact PK in humans in a measurable manner (Goetze, et al. Glycobiology 2011; Welch, et al. Clinical Pharmacology & Therapeutics 2023). Therefore, the observed approximately 3% difference for high mannose content is not expected to be clinically meaningful, and does not preclude a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva.

- Glycation

Levels of glycation of FKS518 lots (min/max: 1.3-3.3%) were found to be higher than US-Prolia/Xgeva (min/max: 0.4-2.7%). Glycation is identified as a low criticality attribute, and the location of the glycation sites is not associated to binding epitopes (i.e., CDR), and the slightly higher level would not be expected to have an adverse effect on safety and efficacy. Therefore, the minor difference observed in the glycation of FKS518 does not preclude a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva.

- Free thiols

Levels of free thiols of FKS518 lots (min/max: 0.56-0.66 mol/mol) were found to be higher than US-Prolia/Xgeva (min/max: 0.37-0.51 mol/mol). Free thiols is identified as a moderate criticality attribute, and existence of free thiols in therapeutic antibodies may have a negative impact on antibody stability, structure and biological function. The slightly higher level free thiols observed in FKS518 is not anticipated to have a significant impact on structure, stability and biological activity and would not have an adverse effect on safety and efficacy. Therefore, the minor difference observed in the free thiols of FKS518 does not preclude a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva.

- Extractable volume

Extractable volume of FKS518 is assessed in the context of [(b) (4)] The Applicant performed extractable volume comparative analytical study. [(b) (4)] volumes were found for FKS518 60 mg-PFS [(b) (4)] than US-Prolia [(b) (4)] [(b) (4)] and for FKS518 120 mg-vial [(b) (4)] than US-Xgeva [(b) (4)] Note that the extractable volume assessment for the PFS presentations (i.e., FKS518 60 mg-PFS vs. US-Prolia) used a QR approach, and a descriptive assessment is used for vial presentations (i.e., FKS518 120 mg-vial vs. US-Xgeva). These approaches are acceptable because the full content of a PFS is directly administered for dosing, while an overfill is applied to a vial to ensure the correct volume can be withdrawn.

The Applicant explained that the engineering and first two FKS518 60 mg-PFS GMP batches had [(b) (4)] extractable volume than the targeted fill. [(b) (4)] [(b) (4)]. All later FKS518 60 mg-PFS batches had extractable volume within the QR of US-Prolia. For the 120 mg-vial comparison, FKS518 120 mg-vial lots met USP <1151> (excess volume) and gross content specifications for DP batch release. Additionally, [(b) (4)] [(b) (4)] would not have an adverse effect on safety and efficacy and does not impact the demonstration of same strength. Therefore, the initial differences observed in the extractable volume do not preclude a demonstration that FKS518 is highly similar to US-Prolia and US-Xgeva. These differences do not preclude a demonstration that FKS518 has the same strength as that of US-Prolia and US-Xgeva.

E. Same Strength

FKS518 has the same dosage forms and route of administration as US-licensed Prolia and US-Xgeva. US-Prolia is available at 60 mg/1 mL in a prefilled syringe for SC administration[1]. US-Xgeva is available at 120 mg/1.7 mL (70 mg/mL) in a vial for SC administration[2]. The Applicant is seeking approval of FKS518 60 mg/1 mL in prefilled syringe in Safe'n'Sound safety device, FKS518 120 mg/1.7 mL vial, and FKS518 120 mg/1.7 mL in prefilled syringe in Safe'n'Sound safety device. Comparative concentration (mg/mL) and extractable volume were assessed as part of the CAA. The extractable volume and fill weight data were also assessed in the context of [(b) (4)] [(b) (4)] Based on the comparative concentration data and manufacturing data, the proposed presentations of FKS518 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

[1] US Prescribing Information, US-licensed Prolia. Accessed in February 2025 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125320s213lbl.pdf

[2] US Prescribing Information, US-licensed Xgeva. Accessed in February 2025 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125320s203lbl.pdf

mass per unit volume as the corresponding strengths of US-Prolia and US-Xgeva. The strength of FKS518 60 mg/mL prefilled syringe is the same as that of US-Prolia. The strength of FKS518 120 mg/1.7 mL vial and prefilled syringe is the same as that of US-Xgeva.

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