CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761439Orig1/Orig2s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: September 14, 2025

1. Application/Product Information

BLA number	761439
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351 (k)
Associated IND	IND 146025
Review Designation	Standard review
Applicant	Hikma Pharmaceuticals USA Inc.
Indication	The same indications for RGB-14 as those are approved for US-licensed Prolia and US-licensed Xgeva
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: ENOBY (as an interchangeable biosimilar for US-Prolia) XTRENBO (as an interchangeable biosimilar for US-Xgeva)
	Non-proprietary Name/Code Name: denosumab-qbde / RGB-14
	OPQAIII Naming: MAB HUMAN (IGG2) ANTI O14788 (TNF11_HUMAN) [RGB14]
Drug Product Description	ENOBY/XTRENBO (denosumab-qbde) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous use. Each 1 mL single-dose prefilled syringe (PFS) of ENOBY contains 60 mg denosumab-qbde (60 mg/mL), glacial acetic acid (1.08 mg), polysorbate 20 (0.1 mg), sorbitol (46.0 mg), and Water for Injection (USP) with a pH of 5.2. Sodium hydroxide may be added to adjust pH. Each (b) (4) single-dose vial of XTRENBO contains 120 mg denosumab-qbde (70 mg/mL), glacial acetic acid (1.08 mg),

	polysorbate 20 (0.1 mg), sorbitol (46.0 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	ENOBY: 60 mg/1 mL (60 mg/mL) XTRENBO: 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 ENOBY		
Co-packaged Product Information	Not applicable		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance (DS)	Hirdesh Kumar	Jacek Cieslak
	Drug product (DP)	Min-Hyung Lee	
	Immunogenicity Assay	Li Lu	
	DS microbiology/facility	Denise Miller	Maxwell Van Tassell, Zhong Li
	DP microbiology/facility	Jeanne Fringer	
	Labeling	Liming Lu	
	RBPM	Anita Brown	
	ATL	Jacek Cieslak	
OPQ Issued Consults	CDRH consult (ICCR: 01031370; ICCR: 2401043)		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761439 for ENOBY and XTRENBO manufactured by Chemical Works of Gedeon Richter Plc. The data submitted in this application are adequate to support the conclusion that the manufactures of ENOBY and XTRENBO are well-controlled and lead to products that are pure and potent. The comparative analytical data support a demonstration that ENOBY and XTRENBO 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 and Drug Product:**
  Chemical Works of Gedeon Richter Plc. (FEI: 3022999632)
  Richter Gedeon utca 20., Debrecen, Hungary
- **Secondary packaging (Xtrenbo):**
  (b) (4) (FEI: (b) (4)
  (b) (4)

b. Fill sizes and dosage forms:

ENOBY: 60 mg/1 mL (60 mg/mL) single-dose PFS, injection, for subcutaneous use
XTRENBO: 120 mg/1.7 mL (70 mg/mL) single-dose vial, injection, for subcutaneous use

c. Dating Period:

- **Drug Products:** 36 months when stored at 5 ± 3°C (PFS and vial)
- **Drug Substance:** (b) (4) months when stored at (b) (4) °C
- **Stability Option:**
  - For stability protocols:
    - We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Enoby and Xtrenbo are exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

Enoby (denosumab-qbde, RGB-14) 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. Xtrenbo (denosumab-qbde, RGB-14) 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 Enoby and Xtrenbo are highly similar to US-Prolia and US-Xgeva, respectively, notwithstanding minor differences in clinically inactive components.

Denosumab-qbde 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-qbde has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. The biological activity of denosumab-qbde 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 production in CHO cell culture and purification of denosumab-qbde using typical antibody manufacturing processes. The cell culture is initiated by (b) (4)

(b) (4)

The Enoby DP PFS manufacturing includes (b) (4) (b) (4) (b) (4) The final DP PFS is stored at 5 ± 3°C for long term storage.

The Xtrenbo DP vial manufacturing includes (b) (4) (b) (4) (b) (4) The final DP vial is stored at 5 ± 3°C for long term storage.

An on-site pre-license inspection of the drug substance and drug product manufacturing facilities at Chemical Works of Gedeon Richter Plc. (FEI: 3022999632) was conducted on March 24 – April 4, 2025, and a 7-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 Enoby and Xtrenbo (i.e., there is no specific test method described in regulation for Enoby and Xtrenbo that establishes an official standard of potency). We next considered whether potency is a factor for Enoby and Xtrenbo 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 Enoby and Xtrenbo for purposes of § 610.61(r) because lot variability is not a concern for Enoby and Xtrenbo, as Enoby's and Xtrenbo'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:
   1. Master and working cell bank stability
   2. Production and qualification of future working cell banks
   3. Manufacturing (b) (4) validation
   4. Production and qualification of future reference standards
   5. Reference standard stability/re-qualification
   6. On-going stability studies
   7. Post-approval annual stability and commitment

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
   2. Post-approval annual stability with shelf-life extension and commitments for DP PFS and DP 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 RGB-14 is highly similar to US-licensed Prolia (US-Prolia) and US-licensed Xgeva (US-Xgeva), and to support the assessment of biosimilarity and interchangeability, the applicant performed comparative analytical assessments (CAA) between RGB-14-P and US-Prolia and RGB-14-X and US-Xgeva, respectively. Analytical results were analyzed with Prolia and Xgeva batches separately between the two originator presentations.

The CAA included comparisons of 8 batches of RGB-14-P 60 mg/1 mL in prefilled syringe (PFS) (60 mg-PFS) and 6 batches of RGB-14-X 120 mg/1.7 mL in vial (120 mg-vial), manufactured respectively in May 2021 – June 2023 and in May 2020 – May 2023), and 34 and 25 batches of US-Prolia and US-Xgeva (with respective expiry dates March 2018 – October 2024 and October 2016 – September 2024). The RGB-14 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 RGB-14 DP and US-Prolia and US-Xgeva batches used in the comparative clinical studies included in the BLA.

The applicant used a comprehensive array of analytical methods 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 RGB-14 DPs and US-Prolia/US-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 and US-Xgeva, respectively, 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/US-Xgeva [mean ± x*standard deviation, SD] with multiplier (x) of 2.00. 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/US-Xgeva [mean ± x*SD] with multipliers ranging from 2.20 to 2.95. 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, and oxidative stress.

Based on the OPQAIII assessment, the RGB-14 and US-Prolia/US-Xgeva data support a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva, respectively, notwithstanding minor differences in clinically inactive components. RGB-14-P and RGB-14-X have the same strength, dosage forms, and route of administration as US-Prolia and US-Xgeva, respectively. The applicant used a comprehensive array of analytical methods that were suitable to evaluate CQAs of RGB-14 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 RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva (see section D below).

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva, respectively, 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
Post-Translational Modifications	Deamidation and isomerization (peptide mapping by LC-MS/MS)		Yes
	Oxidation (RP-HPLC-UV focused peptide mapping)		Yes
	Glycation (peptide mapping by LC-MS)		Yes
	N- and C-terminal variants (peptide mapping by LC-MS-MS)		
Higher Order Structure	Free Thiol content (Colorimetry)		Yes
	Secondary structure	(FTIR)	Yes
	Secondary and Tertiary structure	(CD, far UV)	Yes
	Secondary and Tertiary structure	HDX-MS	Yes
	Secondary and Tertiary structure	2D NMR	Yes

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)		Supports a Demonstration of Highly Similar
	Disulfide bridges (RP-HPLC/ESI-MS)		Yes
	Disulfide isoforms (RP-HPLC)		Yes
	Thermal stability (DSC)		Yes
Size purity/impurity	Size variants (including HMW and LMW species)	(SEC-HPLC)	Yes
		(AUC)	Yes
	Monomer, HMW and LMW and molecular weight	(SEC-MALS)	Yes
	HC + LC	(reduced CE-SDS)	Yes
	NGHC	(reduced CE-SDS)	Yes
	Intact IgG	(non-reduced CE-SDS)	Yes
	LMW species	(non-reduced CE-SDS)	Yes
Charge Variants	Main Peak, Acidic, Basic Species and Isoelectric point	(cIEF)	Yes
	Main Peak, Acidic, Basic Species	(cIEF-CPB digested)	Yes
Glycosylation	G0F, G1F, G1'F, G2F	HILIC-UHPLC-FL	Yes
	Sialic acid		Yes
	Galactosylated glycans		Yes
	Afucosylated glycans		Yes
	High mannose		Yes
	Sialylated glycans	RP-HPLC-FL	Yes
Content	Protein Concentration (UV280)		Yes
Fab binding and Biological activity	Inhibition of RANKL/RANK signaling (RANKL neutralization bioassay)		Yes
	Affinity to RANKL (ELISA)		Yes
	Affinity to RANKL (BLI)		Yes
	Inhibition of osteoclast differentiation (in vitro bioassay)		Yes
Fc binding	FcRn binding affinity (BLI)		Yes
	FcγRIIIa (V158) binding affinity (BLI)		Yes
	FcγRIIa (H131) binding affinity (BLI)		Yes
	FcγRI binding affinity (BLI)		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
	C1q binding (BLI)		Yes
Degradation profiles	High Temperature (60°C, 168 hours)		Yes
	Light stress (5033 Wh/m^2, 168 hours)		Yes
	Chemical Oxidation (H_2O_2 0.2%, 4 hours)		Yes

Physico-chemical/ Functional Characteristics	Quality Attribute Assessed (analytical methods)	Supports a Demonstration of Highly Similar
	Low pH (pH 3.5, 6 hours)	Yes
	High pH (10.0, 2 hours)	Yes

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

Not Applicable.

D. Assessment of Comparative Analytical Study Results

Of the quality attributes listed in Table A above, some physicochemical test results did not meet the pre-determined similarity acceptance criteria for select attributes (i.e., at least 90% of RGB-14-P and RGB-14-X lots must be within the quality range) or showed variable results in qualitative assessments Section 3.2.R.7.2 and 3.2.R.7.7 in eCTD Module 3; however, adequate justifications have been provided that the differences observed do not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva, respectively. These instances are described below:

- Fucosylation and Galactosylation

RGB-14-P and RGB-14-X lots contained slightly higher levels of overall total galactose content (min/max: 25.0 – 30.0) and fucosylated glycan excluding mannose (min/max: 81.7 – 85.0) than US-Prolia/Xgeva lots (galactosylated QR: 10.0 – 29.7%, fucosylated QR: 75.6 – 83.4%)). The main galactosylated and main fucosylated glycans are identified as a low criticality attributes. Differences in galactosylated forms of antibodies are known to affect CDC activity (L. Liu, J Pharm Sci 104, 1866-1884, 2015). CDC activity is induced by binding to C1q, the C1q binding activities of RGB-14 and US-Prolia and US-Xgeva have been shown to be highly similar and no detectable CDC activity was found in either product. In addition, fucosylated forms are known to affect ADCC activity which is mediated via FcγRIIIa (CD16) binding. CD16 binding activities of RGB-14 and US-Prolia and US-Xgeva have been shown to be similar and no detectable ADCC activity was found in either of the products. Therefore, difference in content of the galactosylated and main fucosylated glycans is not expected to be clinically meaningful and does not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva.

- Size variants by AUC

RGB-14-P and RGB-14-X lots contained slightly lower levels of monomer content (min/max: 91.26 – 96.62%) compared to US-Prolia/US-Xgeva lots (QR: 92.05 – 96.85%with mean values of 94.48% and 93.30% for RGB-14-P and RGB-14-X

respectively versus 94.30% and 94.54% for US-Prolia and US-Xgeva. Additionally, marginal differences in sedimentation coefficient were observed, with one RGB-14-P at 5.40 S and RGB-14-X at 5.42 S compared to the quality ranges of 5.37-5.39 S and 5.35-5.41 S for US-Prolia and US-Xgeva, respectively. The molecular weight of monomer species remained consistent across all products (147-152 kDa for RGB-14 vs. 147-153 kDa for US-Prolia/US-Xgeva), confirming structural integrity. The observed differences (≤1.2% for monomer content and ≤0.01 S for sedimentation coefficient) fall within typical analytical method variability for AUC measurements. HMW and LMW species were below the limit of quantitation for RGB-14 and US-Prolia/US-Xgeva, demonstrating comparable purity profiles. The quality ranges were established using stringent statistical multipliers (mean ± 2.20*SD), and the minimal deviations observed represent analytical variability rather than meaningful product differences. Therefore, the observed size variant differences are not expected to be clinically meaningful, and do not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva.

- Size variants by SEC-MALLS

RGB-14-X showed slightly lower monomer content (min/max: 99.2-99.5%) compared to US-Xgeva reference products (QR: 99.3-99.5%), with marginally higher HMW content (min/max: 0.5-0.9%) versus reference products (QR: 0.3-1.1%). RGB-14-P showed slightly higher monomer content (98.9-99.6) compared to US-Prolia reference products (98.5-99.6%), with marginally lower HMW content (min/max: 0.4-0.9%) versus reference products (QR: 0.3-1.1%). The primary purpose of SEC-MALLS is to evaluate molecular weight rather than quantify absolute HMW/LMW levels. Observed differences (0.1% for monomer and HMW content) are marginal and fall within method variability. Molecular weights remained highly similar (RGB-14 min/max: 138.1-141.3 kDa vs. reference products QR: 134.9-144.9 kDa), confirming structural integrity. Quality ranges using mean ± 2.35*SD resulted in very narrow acceptance criteria. In summary, molecular weights of monomer and HMW are analytically similar between RGB-14 and US-Prolia/US-Xgeva, while content differences are partially similar but marginal and have no impact on product quality, and do not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva.

- Size variant by R-CE-SDS (Ng-HC, LC, HC, LC+HC)

RGB-14 showed lower non-glycosylated heavy chain (NgHC) content (min/max: 0.4-0.6%) compared to US-Prolia/US-Xgeva reference products (QR:0.6-1.4%), with correspondingly higher HC+LC content (min/max: 99.5-99.7%) versus (QR: 98.7-99.4%) for US-Prolia/US-Xgeva. Mean NgHC values were 0.4, 0.5% for RGB-14 versus 1.0, 1.1% for US-Prolia/US-Xgeva, representing differences of ~0.5-0.6%. Quality ranges were established using mean ± 2.35SD for NgHC content and mean ± 2.20SD for other parameters. The lower NgHC content in RGB-14 correlates with higher glycosylated HC content, as antibodies with high NgHC levels have significantly reduced Fc-related effector function. Aglycosylation of Asn297 abolishes binding to FcγRIII and

reduces C1q binding affinity, abrogating ADCC and CDC activities. Since ADCC and CDC are not part of denosumab's mechanism of action, NgHC levels are not critical for function. The differences in NgHC content (~0.5-0.6%) between RGB-14 and US-Prolia/US-Xgeva are not considered clinically relevant, as denosumab has no effector function and the observed differences do not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva.

- Charge variants by cIEF

After CPB digestion, RGB-14 showed lower basic variant content (min/max: 2.2-3.7%) compared to US-Prolia/US-Xgeva (QR: 3.3-5.7%), with correspondingly higher main peak content (min/max: 61.3-65.0%) versus (QR: 56.6-64.5%). All RGB-14 batches showed basic variant levels below the lower quality range limits, with differences of 0.4-1.7% for RGB-14-X and 0.1-1.1% for RGB-14-P. Quality ranges were established using mean ± 2.65*SD formula from US-Prolia/US-Xgeva batches. Charge variant enrichment studies revealed that C-terminal lysine and proline amidated forms are enriched in the basic fraction (~70% basic variant level). RGB-14 has higher levels of C-terminal lysine variants, which are reduced more by CPB digestion compared to US-Prolia/US-Xgeva. Additionally, RGB-14 showed ~0.6% lower NgHC levels than US-Prolia/US-Xgeva, and since NgHC is enriched in basic variant species, this contributes to the observed differences in basic variants and correspondingly in main peak levels. Biological activity testing of enriched charge variant fractions showed no significant differences in RANKL and FcRn binding activities. The basic variant fractions demonstrated equivalent antigen binding activity and comparable impurity profiles to release samples. Given the characteristics of charge variants and biological activity results, the lower basic variant content and higher main peak levels in RGB-14 have no impact on safety, efficacy and the observed differences do not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva.

- Sialic acid (NANA)

RGB-14 showed lower NANA content (min/max: 40.3-48.3 ng/mg protein) compared to US-Prolia/US-Xgeva reference products (QR: 56.7 - 110.0ng/mg protein) when measured by RP-HPLC-FL. Mean NANA values were 44.4 ng/mg protein for RGB-14-X and 44.7 ng/mg protein for RGB-14-P versus 83.1 ng/mg protein for US-Xgeva and 83.4 ng/mg protein for US-Prolia. Sialylation is identified as a moderate criticality attributes. Quality ranges were established using mean ± 2.50*SD formula from reference product batches. The absolute value of NANA content is very low in all cases (<0.6% for US-Prolia/US-Xgeva, <0.3% for RGB-14), and NGNA levels were below detection/quantification limits for both products. Total sialic acid content measured by HILIC-UHPLC-FL showed similarity between products. Increased NANA content may affect glycoprotein PK by preventing elimination through asialoglycoprotein receptor binding, but literature reports no PK differences between antibodies with high NANA content (≤40%) (Goetze, et al. Glycobiology 2011 and Welch, et al. Clinical Pharmacology & Therapeutics 2023), and those with enzymatically removed sialic acids,

indicating very high NANA content is required to affect antibody PK. Given the very low absolute NANA content in both products and similar total sialic acid content by orthogonal methods, the observed differences have negligible capacity to impact PK, immunogenicity, or clearance, and the observed differences do not preclude a demonstration that RGB-14-P and RGB-14-X are highly similar to US-Prolia and US-Xgeva.

- Glycation

Analysis of the mono-glycated form revealed two distinct clusters within the reference product lots: batches manufactured before April 2020 had lower glycation levels, while later batches showed higher levels. The glycation levels of the RGB-14 lots were consistently lower than the overall reference product range and align with the earlier, lower-glycation cluster. This difference is not expected to have an adverse effect on safety and efficacy because glycation is identified as a low criticality attribute, the observed glycation sites are not located in the binding epitopes (i.e., CDRs), and the levels of glycation in RGB-14 batches are within the two clusters of reference product batches. Therefore, the minor difference observed in the glycation of RGB-14 does not preclude a demonstration that RGB-14 is highly similar to US-Prolia and US-Xgeva.

- Oxidation

The relative oxidation contents of methionine (M) residues and less frequently at tryptophan (W), histidine (H) residues in RGB-14, US-Prolia, and US-Xgeva were analyzed by peptide mapping RP-HPLC-UV. Seven residues in the heavy chain (HC_M106, HC_M253, HC_H269, HC_M359, HC_M398, HC_M429, HC_W418) were detected as major oxidation sites. Oxidation is identified as a moderate criticality attributes. Methionine at position 253 was observed to be most susceptible to oxidation in both RGB-14, US-Prolia and US-Xgeva. The oxidation level of M253 for RGB-14-X was slightly lower than those for US-Xgeva (min/max: 2.32-3.47 % in RGB-14-X vs. 3.05-4.47% observed in US-Xgeva). Overall, the oxidation level and magnitude of difference is not substantial and there was no statistical difference in RANKL binding activity between RGB-14, US-Prolia, and US-Xgeva. Thus, the slight difference observed in oxidation contents was not considered clinically significant and does not preclude a demonstration that RGB-14 is highly similar to US-Prolia and US-Xgeva.

- Deamidation

Lower values were observed in RGB-14 (min/max: 2.30-2.92%) compared to US-Prolia/US-Xgeva (QR: 2.95-3.89 %). Overall, a slightly higher rate of deamidation was observed in the US-Prolia/US-Xgeva batches, affecting one site (N385) of the heavy chain. This site is not located in the CDR region and the differences are considered to have low impact on safety, PK, efficacy, and immunogenicity. Overall, the observed differences in deamidation results (approx. 1.1%) do not preclude the demonstration that RGB-14 is highly similar to US-Prolia and US-Xgeva.

- Hydroxylation

Hydroxylation of the amino acids proline (K126) and lysine (P194) was observed for RGB-14, US-Prolia, and US-Xgeva affecting these two sites of the heavy chain. Lower values were observed in RGB-14 (K126 0.28-0.38%, P194 0.96-1.05%) compared to US-Prolia/US-Xgeva (K126 3.21-4.63%, P194 2.91-3.35%). These sites are not located in the CDR region and the differences are considered to have low impact on safety, PK, and efficacy. Overall, the observed differences in hydroxylation do not preclude the demonstration that RGB-14 is highly similar to US-Prolia and US-Xgeva.

- Disulfide Isoforms and Disulfide Bridges

Disulfide isoform heterogeneity was observed across RGB-14, US-Prolia, and US-Xgeva due to variable disulfide bridge connectivity patterns. RGB-14 exhibited slightly elevated A1 isoform levels (min/max: 9.5-11.7%) compared to the US-Xgeva quality range upper limit (10.5%), increased A/B variant content (min/max: 20.2-23.6%) relative to both reference products (QR US-Xgeva/US-Prolia: 5.5-28.2%), and reduced B variant levels compared to reference product batches manufactured after April 2020. Non-reduced peptide mapping provided molecular-level confirmation of these differences. RGB-14 lots contained higher levels of A/B isoform-specific peptides: SS12iso levels were 83.0-120.8% (mean 99.1%) for RGB-14-X and 86.2-109.6% (mean 94.3%) for RGB-14-P versus 45.9-76.6% (mean 58.6, 59.6%) for US-Prolia/US-Xgeva. SS14 levels for RGB-14 were 88.6-101.1% (mean 95.4, 95.8%) versus US-Prolia/US-Xgeva at 61.2-73.0% (mean 67.3, 69.6%). RGB-14 also showed elevated B3 subvariant-specific peptides: SS11 levels were 87.2-121.9% (mean 97.5, 102.5%) versus 38.5-52.5% (mean 45.1, 45.5%) for reference products. Peptides characteristic of all other isoforms showed high similarity.

The correlation between manufacturing date and isoform distribution showed that reference product batches manufactured before April 2020 had higher A/B variant ratios than batches with expiry dates after August 2020, with RGB-14 disulfide isoform ratios similar to pre-April 2020 reference product batches. Biological activity testing demonstrated that these structural differences did not affect functional performance. RANKL binding activity by ELISA ranged from 93.7-116.8% (mean 102.4%) for RGB-14-X compared to US-Xgeva range of 85.0-112.9% (mean 99.8%); RANKL neutralization activity measured 86.5-110.7% (mean 100.5%) versus US-Xgeva range of 82.4-108.5% (mean 100.2%); and osteoclast differentiation inhibition ranged from 92.6-103.3% (mean 98.5%) versus US-Xgeva range of 94.3-102.2% (mean 98.8%). Similar results were observed for RGB-14-P and US-Prolia. Controlled enrichment studies confirmed minimal functional impact, showing RANKL binding activity increased to only 127.1% versus control samples. These disulfide isoforms are naturally occurring endogenous protein variants that undergo dynamic interconversion in vivo following the sequence IgG2-A > IgG2-A/B > IgG2-B. Published studies indicate no differences in clearance between disulfide isoforms (Liu et al, Mol. Immunol (2013)), and FcγR and complement factor C1q binding (Zhang et al, Biochemistry (2015)) are not influenced by disulfide isoform structure. Therefore, the observed differences in disulfide isoform distribution

represent acceptable structural heterogeneity within the natural variability of IgG2 antibodies and do not preclude the demonstration that RGB-14 is highly similar to both US-Prolia and US-Xgeva.

E. Same Strength

RGB-14-P in PFS and RGB-14-X in vial have the same dosage forms and route of administration as US-Prolia and US-Xgeva respectively. Gedeon Richter Plc. is seeking licensure of the 60 mg/mL RGB-14-P in a single dose PFS assembled with a needle safety device (b) (4) Needle Guard (b) (4) as an interchangeable biosimilar to US Prolia for SC administration[1]. They are also seeking licensure of the 120 mg/1.7 mL RGB-14-X in a single dose vial as an interchangeable biosimilar to US-licensed Xgeva for SC administration[2]. Comparative protein concentration (mg/mL) was assessed as part of the CAA. The (b) (4) and (b) (4) (b) (4) were assessed as part of manufacturing process controls. Based on the comparative protein concentration data and manufacturing data, RGB-14-P has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in unit of mass per unit volume as US-Prolia (60 mg/mL) and RGB-14-X has the same total content and concentration as US-Xgeva (120 mg/1.7 mL). The strength of RGB-14-P PFS assembled with a Needle Safety Device (NSD) and RGB-14-X vial is the same as that of US-Prolia and US-Xgeva, respectively.

[1] US Prescribing Information, US-licensed Prolia. Accessed in February 2025 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125320s219lbl.pdf

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACEK CIESLAK
09/23/2025 03:39:00 PM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 16, 2025
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Min-Hyung Lee, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761439
Applicant:	Hikma Pharmaceuticals USA Inc.
Submission Date:	September 27, 2024
Product:	Enoby (denosumab-qbde) Xtrenbo (denosumab-qbde)
Dosage form(s):	Injection
Strength and Container-Closure:	60 mg/mL single-dose prefilled syringe 120 mg/1.7 mL (70 mg/mL) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the proposed interchangeable biosimilar to the US licensed Prolia 60 mg/mL single-dose prefilled syringe and US licensed Xgeva 120 mg/1.7 mL (70 mg/mL) single-dose vial.
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).

Note that the applicant has also updated the reminder card for the presentation of proper name and the finished dosage form as recommended.

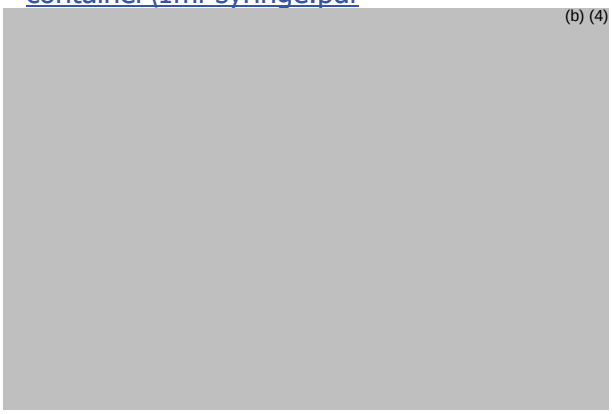
CONCLUSION

The prescribing information and medication guide (submitted on September 10, 2025), container labels (submitted on July 31 and August 29, 2025), and carton labeling (submitted on August 29, 2025) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

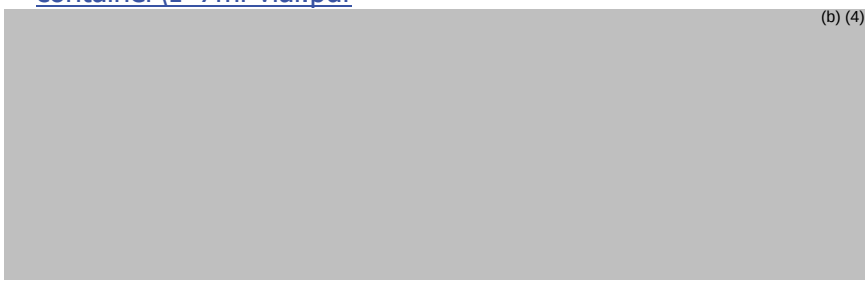
APPENDICES

Appendix A: Proposed Labeling

- 60 mg/mL single-dose prefilled syringe Prescribing Information and Medication Guide (submitted on September 27, 2024)
  \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\labeling\1ml-proposed-insert-word.docx
- 120 mg/1.7 mL (70 mg/mL) single-dose vial Prescribing Information (submitted on September 27, 2024)
  \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\labeling\1_7ml-proposed-insert-word.docx
- Container Labels (submitted on September 27, 2024)
  60 mg/mL single-dose prefilled syringe
  \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\carton-and-container\1ml-syringe.pdf



  120 mg/1.7 mL (70 mg/mL) single-dose vial
  \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\carton-and-container\1_7ml-vial.pdf



- Carton Labeling (submitted on September 27, 2024)
  60 mg/mL single-dose prefilled syringe
  \\CDSESUB1\EVSPROD\bla761439\0001\m1\us\114-labeling\draft\carton-and-container\1-ml-carton-1pk.pdf

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

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(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: Recommend revising on container and carton labeling so that the finished dosage form appears outside of parenthesis and/or below the proper name. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).
For example:

Tradename
(denosumab-xxxx) injection

Or

Trade name
(denosumab-xxxx)
Injection

The applicant has revised as requested.

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
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The name, address, and license number of the manufacturer shall appear on the container label affixed to each container of a product capable of bearing a full label. If the container is capable of bearing a partial label, only the name of the manufacturer is required, per 21 CFR 610.60(c). Refer to 21 CFR 600.3(t) for the

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

definition of "manufacturer". For biologic products, the applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. **Confirm** "Hikma Pharmaceuticals USA Inc." is the manufacturer. Ensure that the manufacturer name appear exactly as intended for the US license holder on the container label. If the label is small and there is space limitation, the qualifying phrase "Manufactured by" or its abbreviation can be omitted from the container label. *The applicant has revised to "Hikma Pharmaceuticals USA Inc." on container labels. Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.*

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
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

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

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 there is no text on the ferrul 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 for Enoby and the container for Xtrenbo 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.

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: Ensure the orientation of the linear bar code appears appropriately on the container label (prefilled syringe and vial) and surrounded by enough white space to facilitate proper scanning.

The applicant has revised as requested.

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

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

Comment/Recommendation: The label is small enough as partial label.

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. Thus, an inactive ingredient statement is not required. See package 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

Comment/Recommendation: Partial label no storage statement to container labels.

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

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
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

[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.

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

Comment/Recommendation: Recommend revising on container and carton labeling so that the finished dosage form appears outside of parenthesis and/or below the proper name. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).
For example:

Tradename
(denosumab-xxxx) injection
Or
Trade name
(denosumab-xxxx)
Injection

The applicant has revised as requested.

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 applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. Revise the licensed manufacturer to appear as:

Manufactured by:
Hikma Pharmaceuticals USA Inc.
Address as listed on box 5 of FORM FDA 356h
US License No. xxxx

Confirm if "Hikma Pharmaceuticals USA Inc." is also the distributer. The applicant may include the distributor information to the carton labeling when there is adequate space, and the licensed manufacturer is on the carton labeling.

Discrepancy b/w the name on cartons "Hikma Pharmaceutical USA Inc." & name on Form 356h "Hikma Pharmaceuticals USA Inc." in Seq#0029 on 7/31/2025. Applicant revised as per 356h as requested.
Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

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

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

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

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

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

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

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

Comment/Recommendation: "Do not freeze." and "Avoid excessive shaking" on carton labeling same as in the USPI.

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: We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on September 27, 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). According to Table 1 in 3.2.P.1, glacial acetic acid and (b) (4) are used in manufacturing (b) (4) and applicants must list the

established name of inactive ingredients in the statement of ingredients in a drug product's labeling when applicable. Additionally, FDA recommends all ingredients should be in the same units of amount where appropriate. Therefore, we have revised the corresponding inactive ingredients list in labeling. **Confirm** you agree with the revision.

Also, we have revised the inactive ingredients in alphabetical order (see *USP General Chapters <1091> Labeling of inactive ingredients*) based on the revision of inactive ingredients.

Revise the inactive ingredients list of the vial presentation to read as:
"Each vial contains: 120 mg denosumab-qbde, glacial acetic acid (1.8375 mg), polysorbate 20 (0.17 mg), sorbitol (78.2 mg), Water for Injection, USP. Sodium hydroxide may be added to adjust pH approximately to 5.2"

Revise the inactive ingredients list of the PFS presentation to read as:
"Each prefilled syringe contains: 60 mg denosumab-qbde, glacial acetic acid (1.0809 mg), polysorbate 20 (0.10 mg), sorbitol (46.0 mg), Water for Injection, USP, and sodium hydroxide 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: Remove the statement "No U.S. standard of potency" from the carton labeling, as our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for your product's carton labeling.

The applicant has revised as requested.
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 **Enoby and Xtrenbo** 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

Comment/Recommendation: The applicant confirms that "Hikma Pharmaceuticals USA Inc." is the distributor but removed it from cartons.

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

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

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

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

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

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

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) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Revise Statement of Dosage to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling format. *the applicant has revised to "Recommended Dosage: See Prescribing Information." Per DMEPA's recommendation.*

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

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	☐ Yes ☐ No ☒ N/A

Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	

Comment/Recommendation: For both USPI:
Revised to the required parenteral verbatim per 21 CFR 201.57(c)(3)(iv).

We revised this statement because your product does not contain visible particles based on the evaluation of the submitted data.

pale yellow solution. Do not use if the solution is discolored or cloudy or if the solution contains (b) (4) particles or foreign particulate matter.

For the vial USPI: The package type term "single-dose" is intended to describe the container and has already been placed as a modifier for the word "vial" as "single-dose vial" in pertinent sections of the labeling. Placement of the modifier "single-dose" in this sentence as an action to be taken for "single-dose" may present ambiguity for the intended action. We revised this wording for clarity.

Discard vial after single (b) (4) entry.

The applicant has revised as requested. In addition, we revised the identifying characteristics ("clear to slightly opalescent") as supported by product data and specifications here and in pertinent sections of labeling.

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 both USPI, Recommend deleting "preservative-free" to reduce redundancy since this information already appears in Section 11.

The applicant has revised as requested. In addition, we revised the identifying characteristics ("clear to slightly opalescent") as supported by product data and specifications here and in pertinent sections of labeling.

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 1.7 mL vial:
We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on September 27, 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). According to Table 1 in 3.2.P.1, glacial acetic acid and (b) (4) used in manufacturing (b) (4) and applicants must list the established name of inactive ingredients in the statement of ingredients in a drug product's labeling when applicable. Additionally, FDA recommends all ingredients should be in the same units of amount where appropriate. Therefore, we have revised the corresponding inactive ingredients list in labeling. **Confirm** you agree with the revision.

Revised to the statement of pH adjuster's effect for sodium hydroxide per 21 CFR 201.100(b)(5)(iii). We've also revised the pH statement based on the evaluation of the data (the specification is a range).

Each single-dose vial (b) (4) contains 120 mg denosumab-xxxx, (b) (4) glacial acetic acid (b) (4) 1.8375 mg), polysorbate 20 (b) (4) 0.17 mg), sorbitol (b) (4) 78.2 mg), Water for Injection (USP) (b) (4) Sodium hydroxide may be added to adjust pH to approximately (b) (4) 5.2

For 1 mL PFS:
We refer to your Description and Composition of the Drug Product submitted to BLA section 3.2.P.1 on September 27, 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). According to Table 1 in 3.2.P.1, glacial acetic acid and (b) (4) are used in manufacturing (b) (4) and applicants must list the established name of inactive ingredients in the statement of ingredients in a drug product's labeling when applicable. Additionally, FDA recommends all ingredients should be in the same units of amount where appropriate. Therefore, we have revised the corresponding inactive ingredients list in labeling. **Confirm** you agree with the revision.

Also, we have revised the inactive ingredients in alphabetical order (see *USP General Chapters <1091> Labeling of inactive ingredients*) based on the revision of inactive ingredients.

Revised to the statement of pH adjuster's effect for sodium hydroxide per 21 CFR 201.100(b)(5)(iii). We've also revised the pH statement based on the evaluation of the data (the specification is a range).

Each 1 mL single-dose prefilled syringe (b) (4) contains 60 mg denosumab-xxxx (60 mg/mL solution) glacial acetic acid (1.0809 mg), (b) (4) polysorbate 20 (0.10 mg), sorbitol (46.0 mg), Water for Injection (USP), (b) (4) Sodium hydroxide may be added to adjust pH to approximately (b) (4) 5.2.

The applicant has revised as requested. In addition, we revised the identifying characteristics ("clear to slightly opalescent") as supported by product data and specifications here and in pertinent sections of labeling.

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

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: for Xtrenbo USPI:
Recommend adding dosage form per 21 CFR 201.57(c)(17) to Section 16 of Xtrenbo USPI.

Recommend deleting (b) (4) fact and (b) (4) to reduce redundancy since it already appears in section 11 of the USPI.

The applicant has revised as requested. In addition, we revised the identifying characteristics ("clear to slightly opalescent") as supported by product data and specifications here and in pertinent sections of labeling.

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: For both USPI:
The applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. See 21CFR 600.3(t) for manufacturer's definition. Ensure that the manufacturer name and address appear exactly as intended for the US license holder, following the appropriate qualifying phrase "Manufactured by". **Confirm** if "Hikma Pharmaceuticals USA Inc." is also the distributer. The applicant may include the distributor information when there is adequate space, and the licensed manufacturer is on the label/labeling.

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

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: The inactive ingredients are revised to be consistent with the prescribing information.

Active ingredient: denosumab-xxxx
Inactive ingredients: glacial acetic acid, polysorbate 20, sorbitol, (b) (4) Water for Injection (USP), and sodium hydroxide is added to adjust pH.

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: The applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder, following the appropriate qualifying phrase "Manufactured by". Add the US license number for consistency. **Confirm** if "Hikma Pharmaceuticals USA Inc." is also the distributer. The applicant may include the distributor information when there is adequate space, and the licensed manufacturer is on the label/labeling.

Manufactured by: Hikma Pharmaceuticals USA Inc. (b) (4)
(b) (4) Address as listed on box 5 of FORM FDA 356h. U.S. License No. xxxx
Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922

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.

- Prescribing Information and Medication Guide (submitted on September 10, 2025)
  \\CDSESUB1\EVSPROD\bla761439\0040\m1\us\114-labeling\draft\labeling\1ml-proposed-insert-word.docx
  \\CDSESUB1\EVSPROD\bla761439\0040\m1\us\114-labeling\draft\labeling\1_7ml-proposed-insert-word.docx
- Container Labels (submitted on July 31 and August 29, 2025)
  \\CDSESUB1\EVSPROD\bla761439\0029\m1\us\114-labeling\draft\carton-and-container\1ml-syringe.pdf

3 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: 9/16/2025 08:51:30AM
GUID: 633d82d0001fb9cd8535e78c71271f3d

Min-Hyung Lee

Digitally signed by Min-Hyung Lee
Date: 9/16/2025 09:09:43AM
GUID: 615da9830029018cf8e9ca1b25776c54