CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761444Orig1s000
761444Orig2s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 04/23/2025

1. Application/Product Information

BLA number	761444
Submission Type	Original Submission
Regulatory Pathway	351(k)
Associated IND/BLA	PIND 153872 Refer to meeting minutes dated Feb 18, 2021, Mar 16, 2023, Jun 12, 2024, and Jun 14, 2024, for BPD Type 2 and 4 meetings held between the applicant and the Agency.
Review Designation	Standard
Applicant	Shanghai Henlius Biotech, Inc.
Indication	All indications currently approved for US-licensed Prolia and US-licensed Xgeva
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** BILDYOS and BILPREVDA (Proposed)
	Non-proprietary Name/Code Name: Denosumab-nxxp
	OBP Naming: MAB HUMAN (IGG2) ANTI O14788 (TNF11_HUMAN) [HLX14]
Drug Product Description	HLX14 is a human monoclonal immunoglobulin G2 antibody (IgG2) produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology. HLX14 targets and binds to receptor activator of nuclear factor kappa-B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts, leading to decrease bone resorption in

	cortical and trabecular bone. HLX14 drug product (DP) is a clear, colorless to slightly yellow, sterile, and preservative-free solution for injection that is presented as single-use vials and a pre-filled syringe (PFS). • Each single dose prefilled syringe (PFS) contains 60 mg/1.0mL denosumab-nxxp, acetic acid, glacial (1.02 mg), sorbitol (47.0 mg), polysorbate 20 (0.1 mg), Water for Injection (USP), and sodium hydroxide to a pH of 5.2. • Each single dose vial syringe contains 60 mg/1.0mL denosumab-nxxp, acetic acid, glacial (1.02 mg), sorbitol (47.0 mg), polysorbate 20 (0.1 mg), Water for Injection (USP), and sodium hydroxide to a pH of 5.2. • Each single dose vial contains 120 mg denosumab-nxxp, acetic acid, glacial (1.84 mg), sorbitol (78.2 mg), polysorbate 20 (0.17 mg), Water for Injection (USP), and sodium hydroxide to a pH of 5.2.		
Dosage Form	Injection (solution)		
Strength	60 mg/mL (PFS); 60mg/1.0 mL (Vial), 120 mg/1.7 mL (Vial)		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	Vial: (b) (4) glass vial (2mL), a 13 mm rubber stopper and 13 mm aluminum flip-off cap. PFS: glass syringe with staked needle, rigid needle shield, and a plunger stopper.		
Device Information	Needle safety device (UltraSafe PlusTM) assembled with PFS		
Co-packaged Product Information	N/A		
	Discipline	**Primary**	**Secondary**

OPQ Review Team	Drug substance	Gunther Boekhoudt	
	Drug product		
	Immunogenicity Assay		
	Facility	Ekaterina Allen	Zhong Li
	Microbiology	Liqun Zhao	Maxwell Van Tassell
	RBPM	Kristine Leahy	
	ATL	Gunther Boekhoudt	
OPQ Issued Consults	CDRH consult ICCR# 01023443		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 76444 for HLX14 manufactured by Shanghai Henlius Biologics Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of HLX14 is well-controlled and leads to a product that is safe, pure, and potent. The comparative analytical data support a demonstration that HLX14 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. It is recommended that these products be approved for human use under conditions specified in the representative package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:**
  Shanghai Henlius Biologics Co., Ltd. (FEI 3023420030)
  (b) (4) Wenjun Road, Songjiang District, Shanghai, 201600, China

- **Drug Product:**
  PFS and Vial: Shanghai Henlius Biologics Co., Ltd. (FEI 3031798286)
  (b) (4) Wenjun Road, Songjiang District, Shanghai

201616, China

b. Fill size and dosage form:

- Single dose vial: supplied as a 120 mg/1.7 mL solution in a single dose vial.
- PFS: supplied as a 60 mg/mL solution in a single dose prefilled syringe assembled with a needle safety device.
- Single dose vial: supplied as a 60 mg/1.0 mL solution in a single dose vial.

c. Dating Period:

- **Drug Product:**
  - Vial (60mg and 120mg): 24 months when stored at 5 ± 3°C protected from light.
  - PFS (60mg): 36 months when stored at 5 ± 3°C protected from light.

- **Drug Substance:** (b) (4) months when stored at (b) (4) (b) (4)

- **Stability Option:**
  - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process performance qualification lots.
  - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance (DS) and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes, HLX14 is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable: None

4. Basis for Recommendation

a. Summary:

HLX14 PFS and vial (denosumab-nxxp) are developed as a proposed interchangeable biosimilar to US Prolia and US Xgeva (denosumab), respectively, for the same strength, dosage form, indications, and routes of administration as for the 60 mg/mL solution PFS/vial (US Prolia) and 120 mg/1.7 mL solution single use vial (US Xgeva). HLX14 is a recombinant

human monoclonal antibody IgG2 that binds with high affinity and specificity, to the transmembrane or soluble protein receptor activator of nuclear factor-κB-ligand (RANKL). The binding to RANKL inhibits downstream signaling and prevents activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. RANKL is essential for the formation, function and survival of osteoclasts which are responsible for bone resorption. Therefore, prevention of the RANKL/RANK interaction is proposed to inhibit osteoclast formation, function, and survival, thereby decreasing bone resorption and cancer-induced bone destruction. Potency of HLX14 is controlled using two bioassays: 1) cell-based RANKL neutralization assay to measure its blockade activity, and 2) an ELISA method to measure its binding activity to RANKL.

The comparative analytical assessment (CAA) supports that HLX14 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components. The analytical component of the scientific bridge was established to support the use of EU-Prolia as a comparator in clinical studies supporting this application. Further discussion on the CAA summary is provided in the Appendix.

HLX14 DS is manufactured by Shanghai Henlius Biologics Co., Ltd. (b) (4)

The overall HLX14 control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for HLX14 as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The

assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the proposed DS manufacturing (Shanghai Henlius Biologics Co., Ltd, (b) (4) FEI# 3023420030), DP (PFS and vial) manufacturing (Shanghai Henlius Biologics Co., Ltd. (b) (4) FEI# 3023420030). Pre-licensure inspections (PLI) were conducted for both of these DS and DP manufacturing facilities. The inspections covered Quality, Production, Materials, Facilities and Equipment, Laboratory Controls, and Packaging and Labeling System. At the conclusion of the inspection, a Form FDA 483 was issued to the firm for both the DS and DP manufacturing facilities. The firm's response to the observations were found to be satisfactory by the compliance reviewer and approval was recommended by OPMA. Individual assessments for each discipline are in separate documents in Panorama. In addition, CDRH recommends approval for the device constituent parts of the combination product (see Cassandra O'Donnell's review in Panorama).

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for HLX14 PFS and vial DP (i.e., there is no specific test method described in regulation for HLX14 that establishes an official standard of potency). Per 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 HLX14 for purposes of § 610.61(r) because HLX14 lot to lot variability is not a concern as the manufacturing process is 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. Stability/requalification protocol for cell bank(s)
   2. (b) (4)
   3. Stability/requalification protocol for reference materials
   4. Post-approval stability commitment
   5. Long-term Leachable stability study

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
   - Post-approval stability commitment

ii. Residual risk: None

iii. Future inspection points to consider: None

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

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

Henlius proposed HLX14, provided in a single-dose PFS (60 mg/mL), a single-dose vial (60 mg/mL), and a single-dose vial (120 mg/1.7 mL) presentations, as an interchangeable biosimilar to the US-Prolia and US-Xgeva (denosumab) reference products, respectively. HLX14 has the same strength, dosage form and route of administration to US-Prolia and US-Xgeva. To demonstrate that HLX14 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components, and to support the relevance of clinical data generated using EU Prolia to the assessment of biosimilarity, Henlius submitted the comparative analytical assessment (CAA) that includes similarity assessment between HLX14, US-Prolia, US-Xgeva, and EU-Prolia. Quality bridging studies were incorporated in the CAA design to address the comparability between HLX14 PFS and HLX14 vial presentations, between US-Prolia and US-Xgeva, and the absence of clinical studies between HLX14 vial and US-Xgeva. Henlius study design was in accordance with the

recommendations of FDA and ICH guidance documents, and from feedback provided during formal Biological Product Development (BPD) meetings Type 2 and Type 4 which were incorporated in the development. The CAA was performed based on quality attributes (QAs) ranked on their potential impact on activity, PK/PD, safety, and immunogenicity, using risk assessment principles set forth in the FDA Guidance for Industry. Similarity is established when at least 90% of data fall within the quality range defined as mean of the reference product lots ± X×SD, where X is the standard deviation (SD) multiplier. The multiplier X = 3 was used for the high- and moderate-risk quality attributes. For the lowest risk quality attributes, raw data/graphical comparison was employed.

The CAA included comparison of physicochemical and functional quality attributes of HLX14, US-Prolia, US-Xgeva, and EU-Prolia. A total of 29 US-reference product consisting of 18 US-Prolia and 11 US-Xgeva lots. For the EU-Prolia, a total of 22 lots were used for comparator. For HLX14, a total of 17 lots manufactured from 11 independent HLX14 drug substance (DS) was used consisting of 5 lots of 60mg vial, 6 lots of 60 mg PFS, and six lots of 120 mg/vial HLX14 were included in the CAA. The number of lots tested and the data analysis approaches were appropriate to allow for a meaningful evaluation of the results. All EU-Prolia lots used in the clinical studies were included in the CAA. All reference product and comparator lots had expiry dates between September 2020 and May 2025, allowing the impact of DP age to be a component of the CAA. The CAA included the pooling of data from 60mg PFS, 60mg vial, and the 120 mg vial HLX14 presentations. Comparability and justification for pooling the data from all the HLX14 presentations was provided and was acceptable. When necessary, results are reported relative to a reference standard. Throughout the CAA, only one primary reference standard (b) (4) (b) (4) was used, and data were provided to adequately qualify the reference standard.

The CAA also included comparative stability studies, which evaluated the stability profile (i.e., degradation pathways and rates) between HLX14 (60mg PFS, 60mg vial, and the 120 mg vial), US Prolia, US-Xgeva, and EU-Prolia under stress conditions (heat, basic, acidic, oxidative, mechanical stress, freeze-thaw cycles, and photo-stress) using orthogonal stability-indicating methods. The quality attributes and stress conditions were supported by development studies and risk assessments. The comparative stability studies demonstrate that HLX14 (60mg PFS, 60mg vial, and the 120 mg vial presentations) have similar degradation profiles to that of US-Prolia and US-Xgeva or EU-Prolia.

Our assessment of the HLX14, US-Prolia, and US-Xgeva data supports the determination that HLX14 is highly similar to US-Prolia and US-Xgeva. HLX14 has the same strengths, dosage forms, and routes of administration as US-Prolia, and US-Xgeva. The comprehensive set of analytical methods used Henlius were suitable to evaluate the critical quality attributes of HLX14, US-Prolia, and US-Xgeva to support the demonstration that the products are highly similar. Although some differences are observed in a limited number of quality attributes, the totality of analytical testing results (discussed below), show that the differences do not preclude a demonstration that HLX14 is highly similar to US-Prolia and US-Xgeva.

In addition, Henlius used three-way pairwise comparisons of HLX14, US-Prolia/US-Xgeva, and EU-Prolia to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU-Prolia as the comparator in the biosimilarity assessment. Henlius used the same methods and statistical approaches used to evaluate that HLX14 is highly similar to US-Prolia/US-Xgeva to establish the analytical component of the scientific bridge between HLX14, US-Prolia/US-Xgeva, and EU-Prolia. The results, supports the relevance of the data generated from clinical studies using EU-Prolia as the comparator for the assessment of biosimilarity.

B. Results of the Comparative Analytical Assessment

The results from the CAA are summarized below in Table 1.

Table 1. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed		Test Method	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure and post-translational modifications	Amino acid sequence		Reduced UPLC-UV/MS/MS	Yes	Yes
	Molecular weight		LC-UV/MS	Yes	Yes
	peptide mapping			Yes	Yes
	N-terminal sequence			Yes	Yes
	C-terminal sequence			Yes	Yes
	Oxidation			Yes	Yes
	Deamidation			Yes	Yes
Glycation & Glycosylation	N-linked glycosylation site		LC-UV/MS/MS	Yes	Yes
	N-linked glycan identification		UPLC-FLD	Yes	Yes
	N-Glycan profile	High Mannose		Yes	Yes
		Afucosylation		Yes	Yes
		Galactosylation		Yes	Yes
		Sialyation		Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed		Test Method	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
		Sialic acid	HPLC-FLD	Yes	Yes
Purity and product-related variants	Size heterogeneity	Monomer	SEC-HPLC	Yes	Yes
		HMWS Species		Yes	Yes
		Monomer	SEC-MALS	Yes	Yes
		HMWS Species		Yes	Yes
		Monomer	AUC-SV	Yes	Yes
		HMWS Species		Yes	Yes
		HC+LC	CE-SDS (Reduced)	Yes	Yes
		NGHC		Yes	Yes
		IgG	CE-SDS (Non-Reduced)	Yes	Yes
		HHL		Yes	Yes
	Charge heterogeneity	Main species	icIEF/CZE	Yes	Yes
		Acidic species		Yes	Yes
		Basic species		Yes	Yes
		Isoelectric point	icIEF	Yes	Yes
Higher order structure and biophysical properties	Disulfide linkage		LCUV/MS/MS	Yes	Yes
	IgG2 disulfide isoforms		RP-UPLC	Yes	Yes
	Free thiols		Thiol fluorescence labelling	Yes	Yes
	Secondary and tertiary structure Thermal stability, and aggregate characterization		DSC	Yes	Yes
			CD (Far- and Near-UV)	Yes	Yes
			FLR	Yes	Yes
			FTIR	Yes	Yes
Quantity	Protein concentration		UV spectrophotometer280nm	Yes	Yes
Immunochemical properties	FcγRIa		SPR	Yes	Yes
	FcγRIIa-R			Yes	Yes
	FcγRIIa-H			Yes	Yes
	FcγRIIb			Yes	Yes
	FcγRIIIa-V			Yes	Yes
	FcγRIIIa-F			Yes	Yes
	FcγRIIIb			Yes	Yes
	FcRn			Yes	Yes
	C1q		ELISA	Yes	Yes
Bioactivity		Soluble RANKL binding	ELISA/SPR	Yes	Yes
		Neutralization activity	Cell-based assay	Yes	Yes
		Inhibition of osteoclast differentiation	Cell-based assay	Yes	Yes
		ADCC-NK	Cell-based assay	Yes	Yes
		CDC	Cell-based assay	Yes	Yes
Forced degradation study			High temperature (50±2ºC)	Yes	Yes
			Light exposure (4500±500 lux at 25±2ºC)	Yes	Yes
			Acidity (0.5 N HCl, pH 3.5, at 25ºC)	Yes	Yes
			Alkalinity (0.5 N NaOH, pH 9.0, at 25ºC)	Yes	Yes
			Oxidation (0.5% tert-butyl hydroperoxide, at 5 ± 3ºC)	Yes	Yes
			Shaking (150 rpm at 25ºC)	Yes	Yes
			Freeze-thaw (≤ -60ºC to RT)	Yes	Yes
Accelerated stability study			25±2°C/60±5% RH	Yes	Yes

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

The clinical development program to support HLX14 as a biosimilar to US-Prolia and US-Xgeva included the following clinical studies:

- Study HLX14-001 Part I: An open-label, randomized, parallel-controlled, single-dose, pilot study to compare the PK, PD, safety, tolerability, and immunogenicity of HLX14 and EU-Prolia via subcutaneous injection in healthy adult male subjects.
- Study HLX14-001 Part II: A double-blind, randomized, four-arm, parallel-controlled, single-dose study to compare the PK, PD, safety, tolerability, and immunogenicity of HLX14 and US, EU, or CN-sourced Prolia via subcutaneous injection in healthy adult male subjects.
- Study HLX14-002-PMOP301: a randomized, double-blind, international multicenter, parallel-controlled comparative clinical study to compare the efficacy, PD, safety, PK, and immunogenicity of HLX14 versus Prolia® (EU-sourced) injection in postmenopausal women with osteoporosis at high risk of fracture.

To justify the relevance of the clinical data generated using EU- Prolia as the comparator product, comparative structural, physicochemical, and biological studies data was provided to support pairwise analytical similarity between HLX14, US-Prolia, and EU-Prolia to support the scientific bridge between the pairs. For the CAA studies, the same analytical methods were used for all the paired assessments. The differences observed in a subset of quality attributes in the CAA (Section D) do not preclude a demonstration that the analytical component of the scientific bridge is established.

D. Assessment of Analytical Study Results

From the extensive quality attributes listed in Table 1, some physicochemical test results did not meet the pre-determined similarity acceptance criteria for the attribute (i.e., at least 90% of HLX14 lots must be within the quality range) or showed differences in qualitative assessments results presented in Section 3.2.R.4 in eCTD Module 3. However, adequate justification was provided to support that the differences observed do not preclude a demonstration that HLX14 is highly similar to US-Prolia and US-Xgeva, or the establishment of the analytical component of the scientific bridge. These differences are discussed below:

Molecular weight and post translational modification (PTM): The analysis of intact (glycosylated) and deglycosylated HLX14, US and EU Prolia by LC-UV/MS showed slight difference in molecular weight (MX) of the glycosylated forms between HLX14 and US-Prolia/US-Xgeva. HLX14 had low abundance MWs of G0F/G0F, -K (missing one C-terminal lysine) compared to US-Prolia/US-Xgeva. In addition, US-Prolia/US-Xgeva had low abundance MWs of G1F/G1F, -2K compared to HLX14. These differences were attributed to low levels of truncated C-terminal

Lysine in HLX14 (66.9–76.9%) compared to US-Prolia/US-Xgeva (98.2-99.3%) and to low levels of galactosydation in HLX14 (<0.5%) compared to US-Prolia/US-Xgeva (0.5-2.2%). Similar small differences in hydroxylation (HLX: <0.5% vs US-Prolia/US-Xgeva: 2.9–5.3%) and in N-terminal glutamate cyclization (HLX: 0.8 – 1.4% vs US-Prolia/US-Xgeva: 0.8 – 1.4%). C-terminal lysine has been widely reported that C-terminal lysine variants do not generally have an impact on safety and efficacy as they are rapidly cleaved off by carboxypeptidase present in the bloodstream. The differences in galactosylation, hydroxylation, and glutamate cyclization have not been specifically associated with adverse safety or efficacy outcomes. These differences in intact molecular weight and post translation modifications had no impact on the biological function showing that HLX14 had similar potency as US-Prolia/US-Xgeva, and EU-Prolia (Table 2). Overall, these differences are considered clinically insignificant and does not preclude a demonstration that HLX14 is highly similar to US-Prolia/US-Xgeva, or the establishment of the analytical component of the scientific bridge.

Table 2. Biological Activities HLX14, US-RPs and EU-Prolia

Product	Relative RANKL binding activity by ELISA (%)	Relative RANKL binding activity by SPR (%)	Relative neutralization activity (%)	Relative differentiation inhibition activity (%)
HLX14	90-104	95-108	90-116	91-109
US-RPs	84-115	89-109	87-119	88-111
EU-Prolia	90-115	82-105	83-119	89-114

IgG2 disulfide isoforms: The purity of HLX14, US-Prolia/US-Xgeva, and EU Prolia were comparatively assessed using non-reduced CE-SDS electropherograms and RP-UPLC chromatograms profiles. Similar peaks and main peak areas were observed between HLX14, US-Prolia/US-Xgeva, and EU Prolia. However, differences were observed in the peak shapes between samples that the applicant attributed to IgG2 isoforms distribution within HLX14, US-Prolia/US-Xgeva, and EU Prolia. IgG2 molecule is well known in the literature to exist as three variants, IgG2-A, IgG2-B and IgG2-A/B.

HLX14 contain less IgG2-B variant (45.9-60.3%) compared to that in US-Prolia/US-Xgeva (63.6-65.9%), EU-Prolia (62.0-65.1%). For IgG2-A/B variant, HLX14 contain higher levels (20.0-28.7%) compared to US Prolia/US-Xgeva (16.3-17.8%), and EU Prolia (16.0-18.1%). For IgG2-A variant, HLX14 also contain higher levels (19.7-25.5%) compared to US Prolia/US-Xgeva (17.0-19.4%), and EU Prolia (17.7-19.9%). The impact to the biosimilarity conclusion was extensively characterized using fractionated samples enriched for each IgG2 variants in HLX 14, US Prolia/US-Xgeva, and EU Prolia. Each fraction was subjected to analysis using LC-MS/MS, SEC-

HPLC, CE-SDS, RANKL binding, and neutralization activity. Each fraction contained similar post translational modifications, similar size variants, and similar biological activity between HLX 14, US Prolia/US-Xgeva, and EU Prolia. Overall, the extensive characterization data suggests that the observed differences in IgG2 variants between HLX 14, US Prolia/US-Xgeva, and EU Prolia should not have any significant clinically impact or preclude a demonstration that HLX14 is highly similar to US Prolia/US-Xgeva, and EU Prolia, or the establishment of the analytical component of the scientific bridge.

Charge Heterogeneity: Comparative assessment was performed on HLX 14, US-Prolia/US-Xgeva, and EU-Prolia samples treated with or without carboxypeptidase B (CpB) enzyme using icIEF and capillary zone electrophoresis (CZE). Differences in the relative levels of the main, acidic, and basic peaks were observed comparing HLX14, US-Prolia/US-Xgeva, and EU-Prolia. Charge variants differences were more pronounced in samples without enzymatic treatment where all 17 HLX14 lots had charge variants levels outside the similarity quality ranges. Specifically, the data from icIEF shows that HLX14 had significantly lower contents of acidic (11.4-15.2%) and main variants (47–54.2%), while higher contents of the basic variant (30.6–40.9%) compared to US-Prolia/US-Xgeva (acidic: 27.5–34.3%, main: 60.1–67.5%, and basic: 4.4–6.2%) and EU-Prolia (acidic: 28.1–35.4%, main 59.4–66.6%, and basic: 4.6–6.2%). Similar results were also obtained using CZE. The sponsor attributed these differences in charge heterogeneity to the differences observed in the C-terminal lysine discussed above. Results from samples treated with CpB enzyme to remove C-terminal lysine did show a less dramatic difference in the charge variants levels. By icIEF, the results after CpB digestion shows HLX14 with slightly lower acidic levels (20.2-24.1%) and slightly higher main peak (72.2-76.7%) compared to US-Prolia/US-Xgeva (acidic: 26.7-34.2%, main: 61.2-69.7%) and EU-Prolia (acidic: 26.1-35.3%, main: 61.2-69.7%). Even though, both the acidic and main peak variants of all 17 HLX14 lots were still outside the CCA quality ranges of both US-Prolia/US-Xgeva (acidic: 24.7-36.5%, main: 58.6-71.8%) and EU-Prolia (acidic: 22.8-38.8%, main: 55.9-73.7%), the differences were less compared to those in non-CpB treated samples. For the basic peak, all 17 HLX14 lots (2.7-3.7%) were within the US-Prolia/US-Xgeva (2.7-5.6%) while only 2 out of 17 HLX14 lots (2.7%) were slightly below the lower limit of the EU- Prolia (3.0%) CAA quality ranges.

The impact of these charge heterogeneity was further investigated by collecting fractionated individual charge variant from CpB-treated HLX14, US-Prolia/US-Xgeva, and EU-Prolia. Structural and functional analysis were performed using peptide mapping (LC-MS), SEC-HPLC, CE-SDS (reduced and non-reduced), HILIC UPLC-FLD (glycan distribution), FcRn binding, and biological assays (RANKL-binding ELISA and neutralization cell-based assay) of individual fractions. The results revealed that sialic acid, deamidation, N-terminal glutamine cyclisation, are the major causes of the remaining charge differences between the proposed biosimilar and US-Prolia/US-

Xgeva and EU-Prolia. No differences were observed in biological activities (RANKL-binding ELISA and neutralization cell-based assay) and in FcRn binding activity comparing the acidic, main, and basic fractions of HLX14, US-Prolia/US-Xgeva, and EU-Prolia. Overall, the totality of the data confirms that the difference in relative contents of acidic or basic variants between HLX14, US-Prolia/US-Xgeva, and EU-Prolia is unlikely to have clinically meaningful impact and thus do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge. This is also consistent with the results of the comparative PK study, in which PK similarity is demonstrated between HLX14, US-Prolia/US-Xgeva, and EU-Prolia (see the BMER).

Glycan profiles: Glycosylation profile of HLX14, US-Prolia/US-Xgeva, and EU-Prolia was assessed using LC-UV/MS and the results revealed some qualitative and quantitative differences between lots. Further investigation using HILIC-UPLC analysis was performed on the four N-glycan groups including galactosylation, afucosylation, high mannose, and sialylated glycans. Based on a denosumab risk impact assessment, high mannose was analyzed using quality ranges due to its potential to impact clearance, ADCC, and FcγRIIIa binding. Qualitative analyses were used for the other glycan groups. Minor differences were observed between HLX14, US-Prolia/US-Xgeva, and EU-Prolia lots in the individual glycan profiles. For high mannose, HLX14 slightly higher levels (8.3-11.4%) compared to US-Prolia/US-Xgeva (6.9-9.2%) and EU-Prolia (6.7-8.9%). In addition, 3 out of 17 HLX14 lots had levels (9.9-11.4%) slightly above the upper limits of US-Prolia/US-Xgeva quality range (9.5%), while 7 out of 17 HLX14 lots had levels (9.4-11.4%) above the EU-Prolia quality range (9.3%). These small differences in high mannose are unlikely to have clinically meaningful impact which was consistent with the results with the comparative PK study demonstrating PK similarity is demonstrated between HLX14, US-Prolia, and EU-Prolia (see BMER). For afucosylation, galactosylation, and sialylation, HLX14 had levels that were slightly below those of US-Prolia/US-Xgeva, and EU-Prolia. Specifically, for afucosylation, HLX14 levels (2.5-2.7%) were lower compared to US-Prolia/US-Xgeva (6.6-8.2%) and EU-Prolia (6.3-8.5). For galactosylation, HLX14 slightly lower levels (11.3-15.2%) compared to US- US-Prolia/US-Xgeva (16.9-25.7%) and EU-Prolia (14.7-26.3%). For Sialylation, HLX14 slightly lower levels (0.5-0.7%) compared to US- US-Prolia/US-Xgeva (0.7-1.1%) and EU-Prolia (0.6-1.3%). Afucosylation, galactosylation, and sialylation could potentially impact FcγRIIIa binding/ADCC, CDC, clearance/ADCC, respectively. However, there was no observed difference in Fc-mediated effective function (ADCC/CDC), FcγRs binding, and C1q binding between HLX14, US-Prolia/US-Xgeva, and EU-Prolia. Overall, there were qualitative and quantitative differences in the N-glycan profiles between HLX14, US-Prolia/US-Xgeva, and EU-Prolia, however the differences did not affect functional activity and are unlikely to present safety and efficacy risk for HLX14. In addition, this is consistent with the results of the comparative PK study, in which PK similarity is demonstrated between HLX14, US-

Prolia, and EU-Prolia (see BMER). Overall, the totality of the data confirms that the difference in the glycan profiles between HLX14, US-Prolia/US-Xgeva, and EU-Prolia is unlikely to have clinically meaningful impact and thus do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

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

- HLX14 is highly similar to US-Prolia/US-Xgeva, notwithstanding minor differences in clinically inactive components.
- Some differences were observed between HLX14, US-Prolia/US-Xgeva, and EU-Prolia. These differences were adequately explored, and residual uncertainties were assessed. The assessment suggests that the differences observed in HLX14 are not expected to have any clinically meaningful impact on safety, PK, and efficacy (see BMER). Overall, the totality of the analytical data supports that the function, activity, and stability profiles of HLX14 and US-Prolia/US-Xgeva are similar and the observed differences between them do not preclude a determination of highly similar or establishment of the analytical component of the scientific bridge.

E. Same Strength

HLX14 in a PFS and a vial presentation has the same dosage form and route of administration as US-Prolia and a second vial presentation that has the same dosage form and route of administration as US-Xgeva. Henlius is seeking licensure of the HLX14 60 mg/mL in a single dose vial and in a single dose PFS assembled with a needle safety device as an interchangeable biosimilar to US-Prolia. They are also seeking licensure of HLX14 120 mg/1.7 mL (70 mg/mL) in a single dose vial as an interchangeable biosimilar to US-Xgeva. The comparative protein concentration (mg/mL) was assessed as part of the CAA comparing the 60 mg and 120 mg HLX14 presentations to US-Prolia and US-Xgeva, respectively. The deliverable volume (PFS), extractable volume (vial), and fill weight data were assessed as part of manufacturing process controls. Based on both the comparative protein concentration data and manufacturing data, the proposed HLX14 presentations are considered to have same total content of drug substance in units of mass in the respective containers and the same concentration of drug substance in unit of mass per unit volume as US-Prolia (60 mg/mL) and US-Xgeva (120 mg/1.7 mL). Overall, the strength of HLX14 60 mg/mL PFS assembled with needle safety device and vial are the same as those of US-Prolia and HLX14 120 mg/1.7 mL vial is the same strength as that of US-Xgeva.

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/s/

GUNTHER H BOEKHOUDT
08/22/2025 01:12:45 PM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 22, 2025
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Gunther Boekhoudt, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761444
Applicant:	Shanghai Henlius Biotech, Inc.
Submission Date:	August 30, 2024
Product:	BILDYOS (denosumab-nxxp) and BILPREVDA (denosumab-nxxp)
Dosage form(s):	Injection
Strength and Container-Closure:	BILDYOS: 60 mg/mL solution in a single-dose prefilled syringe 60 mg/mL solution in a single-dose vial BILPREVDA: 120 mg/1.7 mL (70 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to propose biosimilar and interchangeability to US-licensed Prolia and US-licensed Xgeva.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are acceptable from an OPQA III Labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information, medication guide, and carton labeling submitted on July 31, and 2025 and the container labels submitted on July 18, 2025 were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on August 30, 2024)
  BILDYOS: \\CDSESUB1\EVSPROD\bla761444\0002\m1\us\114-labeling\draft\labeling\drafted-uspi-bildyos.docx

- Prescribing Information (submitted on August 30, 2024)
  BILPREVDA: \\CDSESUB1\EVSPROD\bla761444\0002\m1\us\114-labeling\draft\labeling\drafted-uspi-bilprevda.docx

- Container Labels (submitted on August 30, 2024)

(b) (4)

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

Container[4] Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(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:

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), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Revise (b) (4) to "Mfd by:". Consider removing bolding "Mfd by" to allow for prominence of other critical information on the PCP.

For Bildyos:

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

For the 60 mg/mL PFS, consider revising the abbreviated [redacted] (b) (4) to "U.S. License No.". If spacing is an issue, consider removing [redacted] (b) (4) is not required and can be deleted.

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.

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:

For Bildyos:

On the 60 mg/mL Bildyos PFS, consider relocating the product strength to appear beneath the dosage form as follows:

BILDYOS
(denosumab-xxxx)
Injection
60 mg/mL
For Subcutaneous Use Only

On the 60 m/mL single-dose vial, consider relocating the product strength to appear beneath the proper name and dosage form as follows:

BILDYOS
(denosumab-xxxx) Injection
60 mg/mL
For Subcutaneous Use Only

For Bilprevda:

For single-dose drug products with containers that supply a volume of drug greater than 1 mL, the product should be labeled with a concentration of mg/mL. Revise the product strength to include 70 mg/mL so that the product strength reads appears as: 120 mg/1.7 mL (70 mg/mL).

On the 120 mg/1.7 mL single-dose vial, consider relocating the product strength to appear beneath the proper name and dosage form as follows:

BILPREVDA
(denosumab-xxxx) injection
120 mg/1.7 mL (70 mg/mL)
For Subcutaneous Use Only

The Applicant revised as recommended. (b) (4) (b) (4)

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

Comment/Recommendation:

Statement: "Rx only" (container label)	**Acceptable**

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

Comment/Recommendation:
For the single-dose vials considering removing any bolding or large prominence of Rx Only to allow for prominence of other critical information on the PDP.

The Applicant revised as recommended.

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.

Applicant's response: We have confirmed there is no text on the ferrule cap and 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.

Applicant's response: A 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

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

Comment/Recommendation:
For the single-dose vials, remove the bolding for the route of administration to allow for prominence of other critical information on the PCP.

For Bildyos:
On the 60 mg/mL Bildyos PFS, the route of administration should appear prominently under the strength statement as follows:

BILDYOS
(denosumab-xxxx)
Injection
60 mg/mL
For Subcutaneous Use Only

On the 60 m/mL single-dose vial, the route of administration should appear prominently under the strength statement as follows:

BILDYOS
(denosumab-xxxx) Injection
60 mg/mL

For Subcutaneous Use Only

<u>For Bilprevda:</u>

On the 120 mg/1.7 mL single-dose vial, the route of administration should appear prominently under the strength statement:

BILPREVDA
(denosumab-xxxx) injection
120 mg/1.7 mL (70 mg/mL)
For Subcutaneous Use Only

The Applicant revised as recommended. (b) (4)

(b) (4)

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

Comment/Recommendation:
Add the NDC numbers if they are available. If the NDC numbers are not available at the time of approval, consider stating "NDCs pending" instead of "XXXXX-XXX-XX".

The Applicant revised as recommended.

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

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

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

Comment/Recommendation:
For the single-dose vials, relocate [redacted] (b) (4) It can appear under the route of administration.

Add the statement "Discard unused portion." [redacted] (b) (4) [redacted] (b) (4) If spacing is an issue, consider removing [redacted] (b) (4) [redacted] (b) (4) is not required and can be deleted.

The [redacted] (b) (4) was removed due to spacing issues. The label is small and could be considered a partial label. Thus, the [redacted] (b) (4) is not required.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

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

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes

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

Comment/Recommendation:

Ensure the linear bar code appears on the container label and surrounded by enough white space to facilitate proper scanning.

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: 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.

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: The label is small and could be considered a partial label. Thus, storage requirements are not required.

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

Comment/Recommendation:

Package[6] Labeling Evaluation

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

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

Comment/Recommendation:
For the 60 mg/mL and 120 mg/1.7 mL single-dose vial, the dosage form should appear to the right of or below the proper name as follows:

BILDYOS
(denosumab-xxxx)
Injection

The Applicant revised as recommended.

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

Comment/Recommendation:
Consider adding "Shanghai" to the manufacturer's address and relocating the address to its own line under the name of the manufacturer's as follows:
Manufactured by: Shanghai Henlius Biotech, Inc.
Shanghai, China

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.

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
For Bilprevda:
For single-dose drug products with containers that supply a volume of drug greater than 1 mL, the product should be labeled with a concentration of mg/mL. Revise the product strength to include 70 mg/mL so that the product strength reads appears as: 120 mg/1.7 mL (70 mg/mL).

The Applicant revised as recommended.

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Consider revising the storage instructions to remain consistent with the language in the USPI so that it says, "Refrigerate at 2° to 8°C (36° to 46°) in the original carton."

OPQA III Labeling sent a comment to the Applicant recommending adding a space to write the date the carton was removed from the refrigerator. The Applicant revised as recommended. But in future labeling negotiations, DMEPA recommended that the Applicant remove the space to write the date.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
Consider removing bolding for the dosage form and route of administration to allow for prominence of other critical information on the principal display panel.

The Applicant revised as recommended.

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:
To ensure that all FDA approved labeling fulfils the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles should appear as follows and in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients: "glacial acetic acid, polysorbate 20, sorbitol, Water for Injection, USP, and sodium hydroxide to adjust pH to 5.2".

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:
Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no

U.S. standard of potency has been prescribed for denosumab products (i.e., there is no specific test method described in regulation for denosumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Bildyos and Bilprevda because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

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

The Applicant revised as recommended.

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

Comment/Recommendation:
For the single-dose vials, considering removing any bolding or large prominence of Rx Only to allow for prominence of other critical information on the Principal Display Panel.

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
Add in NDC when available. If the NDC numbers are not available at the time of approval, consider stating "NDCs pending" instead of "XXXXX-XXX-XX".

The Applicant revised as recommended.

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

Comment/Recommendation:

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling*	✓ Yes ☐ No

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*	☐ N/A

Comment/Recommendation:
Currently for the 60 mg/mL PFS, the statement "Discard unused portion" is located after the Statement of Dosage. Relocate "Discard unused portion" so it appears after the package type term.

For the single-dose vials, add the statement "Discard unused portion." to appear after the package type term "single-dose vial".

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

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

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

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

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

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

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

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

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

Comment/Recommendation:
For the single-dose vials, revise the net quantity to appear as: "One 1.7 mL single-dose vial" and "One 1 mL single-dose vial".

The Applicant revised as recommended.

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

Comment/Recommendation:
The Statement of Dosage currently says, (b) (4) (b) (4) Revise the Statement of Dosage to read "Dosage: See prescribing information." to be in alignment with PLR labeling format.

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation: Revise the medication guide statement to read as follows: "ATTENTION: Dispense the enclosed Medication Guide to each patient". *The Applicant revised as recommended.*

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

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

Comment/Recommendation:

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

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation: For Bilprevda:

We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv).

(b) (4)

The Applicant revised as recommended.

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

Comment/Recommendation:

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:
To ensure that all FDA approved labeling fulfils the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles: glacial acetic acid, sorbitol, and polysorbate 20.

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

(b) (4)

The Applicant revised as recommended.

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

Comment/Recommendation:

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

Comment/Recommendation:
Add the NDC numbers when available.

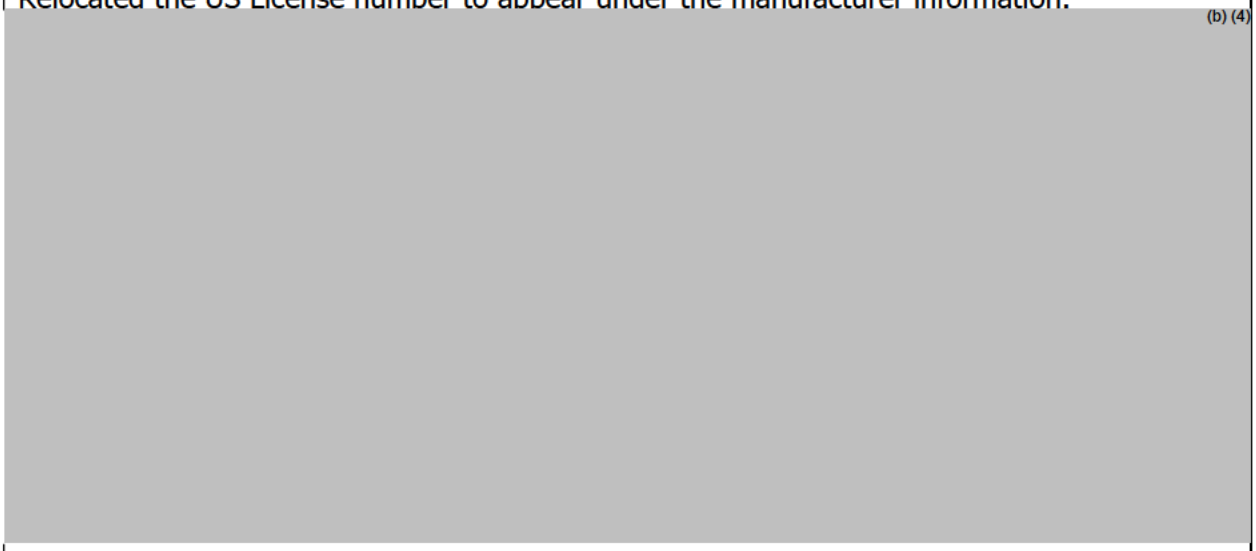
The Applicant revised as recommended.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**

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

Comment/Recommendation:
Relocated the US License number to appear under the manufacturer information.

(b) (4)



The Applicant revised as recommended.

Medication Guide Evaluation

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
To ensure that all FDA approved labeling fulfils the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles: glacial acetic acid, sorbitol, and polysorbate 20.

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

(b) (4)

The Applicant revised as recommended.

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

Comment/Recommendation:
Relocated the US License number to appear under the manufacturer information.

(b) (4)

The Applicant revised as recommended.

APPENDIX C. Acceptable Labels and Labeling

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

- Prescribing Information and Medication Guide (submitted on August 18, 2025)
  BILDYOS: \\CDSESUB1\EVSPROD\bla761444\0033\m1\us\114-labeling\draft\labeling\drafted-uspi-bildyos.docx

- Prescribing Information (submitted on August 18, 2025)
  BILPREVDA: \\CDSESUB1\EVSPROD\bla761444\0033\m1\us\114-labeling\draft\labeling\drafted-uspi-bilprevda.docx

- Container Labels (submitted on July 18, 2025)

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Diana Pei

Digitally signed by Diana Pei
Date: 8/22/2025 10:53:02AM
GUID: 6352da2c009ad0777a2c3b47ec094b9a

Gunther Boekhoudt

Digitally signed by Gunther Boekhoudt
Date: 8/22/2025 11:14:09AM
GUID: 508da6d7000262c4c5e3578cc0a15fbf