

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761364Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary

Assessment Date:

1. Application/Product Information

BLA number	761364
Submission Type	Original Submission
Regulatory Pathway	Biosimilar 351(k)
Associated IND/BLA	IND 141843
Review Designation	Standard Review
Applicant	Accord BioPharma Inc.
Indication	Moderate to severe plaque psoriasis in adult patients and pediatric patients 6 years of age and older, who are candidates for phototherapy or systemic therapy Active psoriatic arthritis in adult patients and pediatric patients 6 years of age and older Moderately to severely active Crohn's disease in adults Moderately to severely active ulcerative colitis in adults
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Imuldosa
	Non-proprietary Name/Code Name: ustekinumab-srlf/DMB-3115
	OBP Naming: MAB HUMAN (IGG1) ANTIP29460 (IL12B_HUMAN) [DMB3115]
Drug Product Description	DMB-3115 is a human immunoglobulin G1 (IgG1 κ) mAb that neutralizes the p40 subunit of IL-12 and IL-23, preventing the cytokines from binding to the IL-12R β 1 receptor protein expressed on the surface of natural

	killer (NK) or T cells, thereby neutralizing cytokine responses. DMB-3115 is supplied as a solution for subcutaneous injection (45mg/0.5 mL and 90 mg/1.0 mL), formulated at 90 mg/mL ustekinumab in sucrose (51.8 mg/mL), (b) (4) histidine- (4.46 mg/mL), L-histidine (b) (4) hydrochloride monohydrate (8.28 mg/mL), and polysorbate 80 (0.04 mg/mL) at pH 5.7-6.3 in a pre-filled syringe (PFS). DMB-3115 is also supplied as a solution for intravenous infusion formulated at 5 mg/mL (130 mg/26 mL) in EDTA disodium (b) (4) histidine (b) (4), L-histidine hydrochloride monohydrate (b) (4) methionine (b) (4), polysorbate 80 (b) (4), and sucrose (b) (4) at pH 5.7-6.3, in a vial.		
Dosage Form	Liquid		
Strength	90 mg/mL (as 45mg/0.5 mL and 90 mg/1.0 mL PFS) and 5 mg/mL (130 mg/26 mL vial)		
Route of Administration	Subcutaneous injection and intravenous infusion		
Primary Container Closure System	Single use 1 mL pre-filled syringe and 30 mL Type I glass vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
	Discipline	Primary	Secondary
	Drug substance	Chringma Sherpa	Anshu Rastogi
	Drug product		

OPQ Review Team	Immunogenicity Assay		
	Comparative Analytical Assessment (CAA)		
	Facility	Melissa Ray (DS) Jeanne Fringer (DP)	Zhong Li
	Microbiology	Melissa Ray (DS) Jeanne Fringer (DP)	Maxwell Van Tassell
	RBPM	Andrew Shiber	
	ATL	Anshu Rastogi	
OPQ Issued Consults	N/A		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761364 for Imuldosa manufactured by Accord BioPharma, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Imuldosa is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Imuldosa is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** (b) (4)

- **Drug Product:**
Pre-filled syringe - (b) (4)
(b) (4)
Vial - (b) (4)
- b. Fill size and dosage form:** 90 mg/mL (supplied as 45mg/0.5 mL and 90 mg/1.0 mL) pre-filled syringe; 5 mg/mL (supplied as 130 mg/26 mL) in a single dose glass vial.
- c. Dating Period:**
 - **Drug Product:** PFS – 36 months at 5°C ± 3°C, protected from light
Vial – 24 months at 5°C ± 3°C, protected from light
 - **Drug Substance:** (b) (4) months at (b) (4)
 - **Stability Option:**
 - For stability protocols:
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- d. Exempt from lot release:**
 - Yes
 - Rationale, if exempted: Imuldosa 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**
 - Perform real-world shipping study(ies) to support the commercial shipping conditions of the commercial pre-filled syringe drug product from Accord Biopharma Inc., UK to the distribution center(s) in the US. The shipping study(ies) should cover worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final packaged pre-filled syringe drug product in the proposed container closure system to ensure there is no impact to product quality and sterility of the drug product (i.e., comparison of pre-shipment to post-shipment data, assessed against pre-defined acceptance criteria).
 - Perform real-world shipping study(ies) to support the commercial shipping conditions of the commercial Vial drug product from the manufacturing and packaging site (b) (4) to the distribution center(s) in the US. The study should cover worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final packaged drug product in the proposed

container closure system to ensure there is no impact to product quality and sterility of the drug product (i.e., comparison of pre-shipment to post-shipment data, assessed against pre-defined acceptance criteria).

- Perform a study using the worst-case headspace size to confirm that stopper placement height specifications would not result in stopper movement that would exceed the sterile boundary under low-pressure conditions.

4. Basis for Recommendation

a. Summary:

DMB-3115 is for the treatment of moderate to severe plaque psoriasis in adult and pediatric [6 years and older] patients, active psoriatic arthritis in adult and pediatric [6 years and older] patients, moderately to severely active Crohn's disease in adult patients, and moderately to severely active ulcerative colitis in adult patients. DMB-3115 is a fully human immunoglobulin G1 (IgG1κ) monoclonal antibody (mAb) produced in a murine cell line (Sp2/0-Ag14). It binds specifically to the p40 subunit of IL-12 and IL-23 cytokines blocking the binding of these cytokines to the IL-12Rβ1 receptor protein expressed on the surface of natural killer (NK) or T cells and subsequently inhibiting IL-12 and IL-23 mediated signaling events. The drug product is supplied as a sterile liquid formulation in single-dose PFS containing 45 mg/0.5 mL or 90 mg/1 mL product for subcutaneous injection and in single-dose vial containing 130 mg/26 mL (5 mg/mL) product for intravenous infusion. The PFS DP is filled into a 1 mL syringe composed of a (b) (4) glass barrel assembled with 29-gauge fixed 1/2 inch needle, a plunger stopper, and a (b) (4) plastic rigid needle shield; the syringe is fitted with a passive safety guard. The vial DP is filled into a sterilized and de-pyrogenated (b) (4) glass vial, stoppered with a sterilized (b) (4) rubber stopper and sealed with a (b) (4) cap.

The potency of DMB-3115 is evaluated through a cell-based assay using a human cell line engineered to express the IL-12R and a luciferase reporter gene driven by a response element. When IL-12 binds, the IL-12R transduces intracellular signals resulting in luminescence. The bioluminescent signal is detected and quantified using (b) (4) Luciferase Assay System and a standard luminometer. In the presence of DMB-3115, IL-12 binding is inhibited resulting in no signal; the luciferase signal is inversely proportional to the concentration of DMB-3115.

The totality of the comparative analytical evidence supports that DMB-3115 is highly similar to US-licensed Stelara, notwithstanding minor differences in clinically inactive components. The strength of 45mg/0.5 mL and 90 mg/1.0 mL single dose prefilled syringes and 130 mg/26 mL single dose vial of DMB-3115

demonstrated the same strength as that of US-licensed Stelara (each presentation). Refer to the Appendix for a detailed summary of the comparative analytical assessment.

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

(b) (4)

(b) (4) The drug product is manufactured at a batch size of (b) (4) for the 45 mg/0.5 mL PFS presentation, a batch size of (b) (4) for the 90 mg/1.0 mL PFS presentation, and a batch size of (b) (4) for the 5 mg/mL (130 mg/26 mL) vial presentation. The DP manufacturing process includes (b) (4)

(b) (4)

The overall manufacturing control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the mab, drug substance and drug product. The manufacturing processes and overall control strategies for DMB-3115 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 assessment of anti-drug antibodies in the clinical studies are adequately validated. The BLA is recommended for approval from a product quality perspective.

The descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the DS and PFS DP manufacturing facility, (b) (4)

(b) (4), the vial DP manufacturing facility, (b) (4)

(b) (4). A pre-licensure inspection (PLI) of the DS/PFS DP manufacturing facility was conducted from from (b) (4)

(b) (4), by Jeanne Fringer (OPMA), Yiwei Li (OPMA), Kathryn King (OPQAI), and Chringma Sherpa (OPQAI). An 8-item form FDA-483, Inspectional Observations, was issued to (b) (4) at the end of the inspection, and the initial field recommendation of the inspection was 'withhold'. The firm responded to the observations, and they were found satisfactory. The firm was recommended for approval by OPMA. A PLI of the manufacturing site

(b) (4) of the vial

presentation of the drug product was waived based on the site's previous inspection history and the current acceptable compliance status.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate with PMCs/PMRs
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate with PMCs/PMRs

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

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

1. DMB-3115 (b) (4) Lifetime Study Protocol
2. DMB-3115 (b) (4) Lifetime Study Protocol
3. DMB-3115 Working Cell Bank (WCB) Stability program
4. DMB-3115 Primary Reference Standard (PRS) Stability test protocol
5. DMB-3115 Working Reference Standard (WRS) Stability test protocol
6. DMB-3115 DS Screening Leachables Study Protocol
7. DMB-3115 DS Stability Testing Protocol

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

- i. Protocols approved:
 - 1. DMB-3115 PFS DP Screening Leachables Study Protocol
 - 2. DMB-3115 PFS DP Stability Testing Protocol
 - 3. DMB-3115 Vial DP Screening Leachables Study Protocol
 - 4. DMB-3115 Vial DP Stability Testing Protocol
- 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. Overview and Conclusions

Accord BioPharma Inc. (Accord) is seeking licensure for DMB-3115 as a biosimilar to US-licensed Stelara for the 45mg/0.5 mL and 90 mg/1.0 mL strengths, and 130 mg/26 mL (5 mg/mL) strength in single dose prefilled syringe and vial presentations, respectively. To support a demonstration that DMB-3115 is highly similar to US-licensed Stelara (hereafter referred to as US-Stelara), Accord performed a comparative analytical assessment using 31 lots of US-Stelara (10 lots of 45 mg PFS, 11 lots of 90 mg PFS, and 10 lots of 130 mg vial) and 34 EU-Stelara lots (13 lots of 45 mg PFS, 11 lots of 90 mg PFS, and 10 lots of 130 mg vial with age ranging from 7 to 35 months. Sixteen (16) independent lots of DMB-3115 DP (5 lots of 45 mg PFS, 5 lots of 90 mg PFS, and 6 lots of 130 mg vial) with age ranging from 1-22 months (PFS: 2-22 months; Vial: 1-12 months). The ages at the time of testing span the shelf-life of US-Stelara (i.e., 36 months) and were adequate to capture potential reference product differences over time. The DMB-3115 lots include engineering lots, clinical lots from the PK similarity study and the comparative clinical study, PPQ lots, and post-PPQ (commercial) lots.

The comparability of the lots manufactured by late-development and pre-commercial processes to DMB-3115 manufactured by the commercial manufacturing process was assessed and found to be established for both previous processes based on data submitted to this BLA. Small improvements were made in the pre-commercial and commercial manufacturing processes; however, these changes would not preclude the ability to leverage the clinical studies that were performed with late development lots of DMB-3115 as they were found to be comparable with lots manufactured by the proposed commercial process.

The comparative analytical assessment was comprised of extensive comparative physicochemical and functional assessment of the quality attributes of DMB-3115 and US-Stelara and included a comparative assessment of their degradation profiles under several relevant forced degradation conditions including thermal stress (25°C ± 2°C, 60% ± 5% RH up to 6 months and 40°C ± 2°C, 75% ± 5% RH up to 3 months), oxidative stress (0.0005% - 0.0015 % H₂O₂ up to 18 hours) base stress (pH 8.0 at 37°C for up to 21 days), acidic stress (pH 3 for PFS and pH 4.5 for vial at 37°C for up to 21 days), mechanical stress (rotation and agitation [79 rpm] up to 3 week), freeze/thaw (5 cycles of freeze at -70°C±10°C for over 4 hours, thaw at 25°C ± 5°C for over 4 hours) and photostress (VIS: 168 klxh; UV: 2 Wh/m² for PFS and VIS: 1200 klxh; UV: 200 Wh/m² for vial).

Accord assessed quality attributes using an approach based on risk and criticality for statistical evaluation of analytical results. The analysis tier was classified into Tier 1, Tier 2, and Tier 3. Tier 1 and Tier 2 analysis involved quantitative comparison of quality

attributes with high or moderate risk ranking using the quality range (QR) approach (QR = Mean of reference product $\pm$ X standard deviation of reference product). The multiplier ("X" in the QR equation) is 2.5 for Tier 1 and 3 for Tier 2 analysis. Tier 1 analysis was performed for high risk ranking quality attributes measured using assays with either low (%RSD: <15%) or high (%RSD: $\geq$ 15%) assay variability and for moderate risk ranking attributes measured using assays with high assay variability. Tier 2 analysis was performed for moderate risk attributes measured using assays with high assay variability. Tier 3 analysis was performed using side-by-side test and involved comparison of raw quantitative data or graphical data of quality attributes with low risk ranking and comparison of qualitative data of quality attributes with moderate to high risk ranking.

Our assessment of the DMB-3115 and US-Stelara data supports that DMB-3115 has been demonstrated to be highly similar to US-Stelara, notwithstanding minor differences in clinically inactive components. DMB-3115 has the same strength, dosage form, and route of administration as US-Stelara. Accord used a comprehensive selection of analytical methods that were suitable to evaluate the critical quality attributes of DMB-3115 and US-Stelara to support the demonstration that the products are highly similar. The numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While some differences were observed in a subset of quality attributes, these differences were determined not to preclude a demonstration that DMB-3115 and US-Stelara are highly similar.

B. Comparative Analytical Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge?
Primary Structure	Molecular weight	Yes	Yes
	Amino acid sequence	Yes	Yes
	Amino acid analysis	Yes	Yes
	Peptide mapping	Yes	Yes
Post-translational Modifications/Glycan Profiles	Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	Isomerization	Yes	Yes
	N-terminal pyroglutamination	Yes	Yes
	C-terminal lysine truncation	Yes	Yes
	C-terminal proline amidation	Yes	Yes
	Glycation at HC and LC	Yes	Yes

	N-glycosylation site	Yes	Yes
	% Afucosylation	Yes	Yes
	% Galactosylation	Yes	Yes
	% Total α -Gal	Yes	Yes
	%Total NGNA	Yes	Yes
	Total NGNA and NANA	Yes	Yes
	Monosaccharide	Yes	Yes
Higher Order Structure/ Hydrophobicity	Secondary structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Disulfide bonds	Yes	Yes
	Thermal stability	Yes	Yes
	Subvisible particles (MFI)	Yes	Yes
	Subvisible particles (DLS)	Yes	Yes
Purity and Product-related Variants or Impurities	Size variants (SEC-HPLC)	Yes	Yes
	Size variants (SEC-MALS)	Yes	Yes
	Size variants (SV-AUC)	Yes	Yes
	NR CE-SDS	Yes	Yes
	R CE-SDS	Yes	Yes
	Charge heterogeneity	Yes	Yes
	pI	Yes	Yes
Biological Properties	IL-12 binding	Yes	Yes
	IL-23 binding	Yes	Yes
	IL-12 neutralizing activity	Yes	Yes
	IL-23 neutralizing activity	Yes	Yes
	FcRn binding	Yes	Yes
	ADCC	Yes	Yes
	CDC	Yes	Yes
	Fc γ RI binding	Yes	Yes
	Fc γ RIIa binding	Yes	Yes
	Fc γ RIIb binding	Yes	Yes
	Fc γ RIIIa-V176 binding	Yes	Yes
	C1q binding	Yes	Yes
Drug Product Attributes	Protein Concentration	Yes	Yes
	Extractable Volume	Yes	Yes

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

The clinical development of DMB-3115 included two clinical studies:

- **Study DMB-3115-1 (PK Similarity Study):** A randomized, double-blind, parallel-group, active-controlled, three-way pairwise similarity study between DMB-3115, US-Stelara, and EU-Stelara to compare the pharmacokinetics, safety, tolerability, immunogenicity, and pharmacodynamics of between the 3 products in healthy subjects.
- **Study DMB-3115-2 (Comparative Clinical Study):** A randomized, double-blind, parallel-group, active-controlled study to compare the efficacy, safety, pharmacokinetics, and immunogenicity study between DMB-3115 and EU-Stelara in subjects with moderate- to- severe chronic plaque psoriasis.

The comparative clinical study (DMB-3115-2) supporting this application used DMB-3115 and EU-Stelara. To support the relevance of the comparative clinical data generated using EU-Stelara as a comparator product to the assessment of biosimilarity, Accord performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way, pairwise PK similarity study. To support the establishment of the analytical component of the scientific bridge, Accord included comparison of DMB-3115 to US-Stelara, DMB-3115 to EU-Stelara, and EU-Stelara to US-Stelara. The same analytical methods used for supporting a demonstration that DMB-3115 is highly similar to US-Stelara were used for the pairwise analytical comparisons with EU-Stelara. The differences observed in the comparative analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See Section D below. The results support the establishment of the analytical component of the scientific bridge.

D. Assessment of Comparative Analytical Study Results

Quantitative Assessment of Analytical Study Results

All quality attributes evaluated against the 2.5SD and 3SD quality range met the comparative analytical acceptance criteria, except for the quality attributes described in Table B below. Refer to the subsequent sections below for justification for how the observed differences in quality attributes do not preclude the demonstration that DMB-3115 is highly similar to US-Stelara, or the establishment of the analytical component of the scientific bridge.

Table B. DMB-3115 Quality Attributes that Exceeded the Comparative Analytical Assessment Acceptance Criteria

Quality Attribute Assessed	Analytical Method	Observed DMB-3115 Results	US-Stelara/ EU-Stelara QR	Percent of DMB-3115 Lots within QR
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Protein concentration (vial)	UV spec	5.0-5.1 mg/mL	US and EU: 4.7-5.0 mg/mL (3SD)	83% (5 out of 6 lots) within US/EU QR
Oxidation	HIC-HPLC	45 mg PFS: 4.3-6.2% 90 mg PFS: 4.3-6.6%	US: 1.7-4.6% (45 mg) and 1.8-4.8% (90 mg) EU: 1.8-4.8% (45 mg) and 1.9-4.5% (90 mg)	67% (4 out of 6 lots [45 mg]) and 83% (5 out of 6 lots [90 mg]) within US QR 67% (4 out of 6 lots [45 mg]) and 83% (5 out of 6 lots [90 mg]) within EU QR
Glycosylation (Sialic acid)	2-AB NP-UPLC	Total α -Gal 4.3-5.1% Total NGNA 17.6-19.9%	Total α -Gal US: 4.4-7.4% (3SD) EU: 4.4-7.5% (3SD) Total NGNA US: 20.4-29.1% EU: 20.1-30.4%	Total α -Gal 89% (8 out of 9 lots) within US/EU QR Total NGNA 0% (0 out of 9 lots) within US/EU QR
Low Molecular Weight Species	SEC-HPLC	PFS: 0-0.1% Vial: 0-0.1%	US: 0.1-0.1% EU: 0-0.2% (PFS and Vial)	58% (7 out of 12 PFS lots) are within the US QR 50% (3 out of 6 Vial lots) are within the US QR
Purity/Fragments	NR CE-SDS	Intact IgG: 91-94.7% 2HL: 3.7-5.5% Total fragments: 5.3-9%	US: Intact IgG: 95.3-97.4% 2HL: 1.4-3.3% Total fragments: 2.6-4.7% EU: Intact IgG: 95.2-97.4% 2HL: 1.4-3.3%	0% (0 out of 6 lots) are within the US/EU QR for each assessment

			Total fragments: 2.6-4.8%	
Basic Peaks	IEC-HPLC	3.8-4.2%	US and EU: 1.3-1.9%	0% (0 out of 10 lots) are within the US/EU QR

Protein Concentration: Among the 6 lots of DMB-3115 vials, 1 lot had a protein concentration of 5.1 mg/mL, which exceeded the quality range of EU- and US- Stelara (4.7 - 5.0 mg/mL). However, this is within the method variability, the result is within the specification for protein concentration, the difference is very minor, and there is no impact on the clinical efficacy. Therefore, the protein concentration in the vial of DMB-3115 can be considered similar to US-Stelara.

Oxidation: The % oxidation in the PFS presentations was about 1-2% higher in DMB-3115 lots compared to US- and EU-Stelara. However, when measured by LC-MS in both PFS and vial formulations, oxidation in DMB-3115 was only 0.4 % higher compared to Stelara. Only 1 or 2 lots out of 6 were outside of the QRs. In the forced oxidation studies, no significant changes were observed in Fab-related IL-12 or IL-23 neutralizing activity or Fc-related FcRn binding affinity, therefore, the levels of oxidation do not significantly affect efficacy and remain within specifications on stability. Therefore, oxidation can be considered similar between DMB-3115 and US-Stelara.

Total α -Gal and NGNA: DMB-3115 lots had a lower total NGNA level by ~7 % and a lower total α -Gal level by approximately 1.3 % compared to US- and EU-Stelara and fell outside the QR for each. However, the difference in the total NGNA and total α -Gal did not affect Fab or Fc-related biological activity. Therefore, the difference does not preclude the determination of highly similar between DMB-3115 and US-Stelara.

Low Molecular Weight Species (LMWS): DMB-3115 and US-Stelara had the same LMWS average at 0.1 %. However, US-Stelara data ranged from 0.1%-0.1%, therefore, a QR could not be calculated. Hence DMB-3115 lots did not meet the QR. Since the difference is only 0.1%, and the average is the same, LMWS can be considered similar between DMB-3115 and US-Stelara.

Purity/fragments: DMB-3115 lots had ~3% higher total fragments (and ~3% lower intact IgG) compared to US- and EU-Stelara. The higher level of total fragments was mainly due to the higher amount of 2HL (~3%) in DMB-3115. The 2HL form is expected to affect Fab-related activity, but at the current level, IL-12 and IL-23 neutralizing activities were found to be similar between DMB-3115, EU-Stelara, and US-Stelara. Therefore, this difference was found to be clinically insignificant in terms of

efficacy and safety. The level is also within specifications on stability, therefore, levels of fragments/intact IgG can be considered similar between DMB-3115 and US-Stelara.

Basic Peaks: Basic variants did not meet the QR of EU- and US- Stelara. Basic variants are mostly C-terminal lysine variants, which are commonly observed in mammalian cell-produced antibody drugs, and they are naturally removed during the metabolic process in the human body. It has been reported that the removal of C-terminal lysine variants does not affect the structure, thermal stability, antigen binding and affinity, FcRn binding and PK. There was no difference in Fab or Fc related biological activities of DMB-3115, US-, and EU-Stelara observed according to the level of lysine variants, and biological activity and purity of DMB-3115 were maintained during long-term storage. Therefore, the difference in basic peaks/lysine truncation does not impact the clinical efficacy and safety of DMB-3115, and it can be considered similar to US-Stelara.

E. Same Strength(s)

DMB-3115 has the same dosage form and route of administration as US-Stelara. Accord is seeking licensure of 45mg/0.5 mL and 90 mg/1.0 ml single dose prefilled syringes and 130 mg/26 mL of DMB-3115 in a single-use vial. US-Stelara is available as in a single-use vial. Accord is seeking approval of DMB-3115 for the same strength as US-Stelara. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed as part of manufacturing process controls. The proposed strengths of 45mg/0.5 mL and 90 mg/1.0 ml prefilled syringes and 130 mg/26 mL vial of DMB-3115 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-Stelara. The strength of DMB-3115 single dose PFS and single-use vial is the same as that of US-Stelara.

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/s/

ANSHU RASTOGI
10/08/2024 10:13:25 AM

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BLA 761364

Product: DMB-3115 (Ustekinumab-srlf)
Manufacturer: Accord BioPharma Inc.

Chringma Sherpa, Ph.D., Primary Reviewer
Anshu Rastogi, Ph.D., Application Technical Lead

Division of Product Quality Assessment XIII
Office of Product Quality Assessment III
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP Product Quality Assessment Data Sheet

1. BLA: 761364

2. Assessment Date: October 7, 2024

3. Primary Assessment Team:

Clinical: Sangeeta Jain and Snezana Trajkovic (TL)

Clinical Pharmacology: Hyewon Kim and Chinmay Shukla (TL)

Nonclinical: Xinguang (Cindy) Li and Barbara Hill (TL)

Product Quality Team: Chringma Sherpa and Anshu Rastogi (ATL)

Microbiology: Melissa Ray (DS), Jeanne Fringer (DP), and Maxwell Van Tassell (TL)

Facilities: Melissa Ray (DS), Jeanne Fringer (DP), and Zhong Li (TL)

Statistics: Juan Vivar, Guoxing Soon (TL), Thamban Valappil (TL), Solomon Chefo

CDRH Consult: Michael Lancina and Shruti Mistry (TL)

OBP Labeling: Diana Pei

OPRO RBPM: Andrew Shiber

Clinical RPM: Sascha Randolph

4. Major GRMP Deadlines:

Filing Meeting: November 21, 2023

Mid-cycle meeting (internal): March 25, 2024

Late-cycle meeting (internal): June 10, 2024

Wrap meeting: August 21, 2024

Integrated Review: August 23, 2024

BSAUFa action date: Oct 10, 2024

5. Communications with Applicant and OND:

Communication/Document:	Date Sent:
Information Request 1	April 26, 2024
Information Request 2	May 17, 2024
Information Request 3	August 13, 2024
Information Request 4	August 26, 2024
Information Request 5	September 22, 2024

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (Yes or No)
761364/0002 Original Submission	October 10, 2023	Yes
761364/0010 Response to IR 1	May 06, 2024	Yes
761364/0013 Response to IR 2	May 28, 2024	Yes
761364/0022 Response to IR 3	August 23, 2024	Yes
761364/0024 Response to IR 4	August 30, 2024	Yes
761364/0028 Response to IR 5	September 26, 2024	Yes

7. Drug Product Name/Code/Type:

Proprietary Name: Imuldosa
Non-Proprietary Name (USAN/INN): Ustekinumab
CAS Name: 815610-63-0
Common Name: DMB-3115
Compendial name: Not applicable
OBP systematic name: MAB HUMAN (IGG1) ANTI P29460 (IL12B_HUMAN) [DMB-3115]

8. Pharmacological Category: Dermatological Agent; DMB-3115 is an anti-interleukin 23 (IL-23) and interleukin-12 (IL-12) binding recombinant human monoclonal IgG1 antibody

9. Dosage Form:

- a. single dose prefilled syringe (PFS) containing 45 mg/0.5 mL
- b. single-dose PFS containing 90 mg/1.0 mL
- c. single-dose vial containing 130 mg/26 mL

10. Strength/Potency: 90 mg/mL solution in PFS and 5 mg/mL solution in vial

11. Route of Administration: Subcutaneous injection for PFS and intravenous infusion for vial

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	Not Reviewed. Sufficient information was provided in the BLA from OPQA III's perspective.
			Yes	
			Yes	
			Yes	
			Yes	

(b) (4)	Yes	Deferred to OPMA
	Yes	
	Yes	
	Yes	

13. Inspectional Activities:

An on-site pre-license inspection (PLI) of the drug substance and the drug product (PFS presentation only) manufacturing site (b) (4) was conducted because the site has not been subjected to prior inspectional activities by the FDA. The on-site inspection was conducted from (b) (4), by Jeanne Fringer (CDER/OPQ/OPMA), Yiwei Li (CDER/OPQ/OPMA), Kathryn King (CDER/OPQ/OPQA III), and Chringma Sherpa (CDER/OPQ/OPQA III). An 8-item Form FDA 483 Inspectional Observations was issued to the applicant and the initial field recommendation of the inspection was 'withhold'. The firm responded to the observations, and they were found satisfactory. The firm was recommended for approval by OPMA. Refer to the OPMA review in CDER Informatics platform, as well as the Action Letter, for more information. A PLI of the vial DP manufacturing site (b) (4) was waived based on the site's current acceptable compliance status.

An inspection of the testing site for immunogenicity assays was performed by Kara Scheibner (CDER/OTS/OSIS). An 8-item Form FDA 483 was issued at the inspection close-out. However, after reviewing the inspectional findings, exhibits provided in the EIR, and the firm's response to Form FDA 483, there are no concerns regarding the reliability of the data for inspected study DMB-3115-1.

14. Consults Requested by OBP:

CDRH (refer to ICCR# 00957557 in Salesforce)

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology

	Expanded Change Protocol
--	--------------------------

16. Administrative:

Name and Title	Signature and Date
Chringma Sherpa Primary Reviewer Division of Product Quality Assessment XIII Office of Product Quality Assessment III	See CDER Informatics Platform
Anshu Rastogi, Ph.D. Application Technical Lead Division of Product Quality Assessment XIII Office of Product Quality Assessment III	See CDER Informatics Platform

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

The data and information submitted in this Biologics License Application (STN 761364) support the conclusion that the manufacture of 45 mg/0.5 mL and 90 mg/mL PFS and 130 mg/26 mL Vial DMB-3115 is well controlled and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents, sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. Therefore, the Office of Product Quality Assessment recommends approval of BLA 761364 for DMB-3115 from a product quality perspective.

The assessment of the microbiology and facility related data and information for DMB-3115 drug substance and drug product as well the acceptability of the PLI is deferred to OPMA assessors.

II. List of Deficiencies to be Communicated

N/A

III. List of Post-Marketing Commitments/Requirements

The applicant agreed to perform real-time shipping studies to support the commercial shipping conditions of the commercial pre-filled syringe drug product from Accord Biopharma Inc., UK to the distribution center(s) in the US and the commercial shipping conditions of the commercial vial drug product from (b) (4) to the distribution center(s) in the US as post marketing commitments ([Information request# 5; sent on 9/22/2024; response received on 9/26/2024](#)). These shipping studies will cover worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) on the final packaged drug product in the proposed container closure system to ensure there is no impact to product quality and sterility of the drug product (i.e., comparison of pre-shipment to post-shipment data, assessed against pre-defined acceptance criteria). It is estimated that these studies will be completed by May 2026.

IV. List of protocols approved with this BLA

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.5	DMB-3115 (b) (4) Lifetime Study Protocol	Lifetime verification of (b) (4) downstream process for DMB-3115 PPQ batches and commercial manufacturing	Annual report
3.2.S.2.5	DMB-3115 (b) (4) Lifetime Study Protocol	Lifetime verification of (b) (4) in downstream process for DMB-3115 PPQ batches and commercial manufacturing	Annual report
3.2.S.2.3	DMB-3115 working cell bank (WCB) Stability program	This report is intended to confirm that the DMB-3115 manufacturing cell bank (WCB) vial stored at all WCB storage sites maintains continuous productivity and growth during the storage period and is suitable for use in the production process.	Annual report
3.2.S.5	DMB-3115 Primary Reference Standard (PRS) Stability test protocol	Re-test protocol of PRS for extension of shelf-life	Annual report
3.2.S.5	DMB-3115 Working Reference Standard (WRS) Stability test protocol	Re-test protocol of WRS for extension of shelf-life	Annual report
3.2.S.6	DMB-3115 DS Screening Leachables Study Protocol	Screening leachable amounts of compounds present in a drug substance after storage in DS bag	Annual report
3.2.S.7.3	DMB-3115 DS Stability Test Protocol (Long-term testing)	Primary stability test protocol for DS shelf-life claim	Annual report

3.2.P.2.4 (Drug Product - PFS)	DMB-3115 PFS DP Screening Leachables Study Protocol	A protocol for screening leachable amounts of compounds present in drug products after storage in container closure systems (prefilled syringe)	Annual report
3.2.P.8.3 (Drug Product - PFS)	DMB-3115 PFS DP Stability Test Protocol (Long-term testing)	Stability test protocol for PFS shelf-life claim	Annual report
3.2.P.2.4 (Drug Product - Vial)	DMB-3115 Vial DP Screening Leachables Study Protocol	A protocol for screening leachable amounts of compounds present in drug product after storage in container closure systems(vial).	Annual Report
3.2.P.8.3 (Drug Product - Vial)	DMB-3115 Vial DP Stability Test Protocol (Testing at long-term, accelerated, and stressed conditions)	Stability test protocol for PFS shelf-life claim	Annual report

V. Assessment of Common Technical Document- Quality Module 1

Environmental Assessment of Claim of Categorical Exclusion

In Section 1.12.14, Accord BioPharma Inc. requested categorical exclusion from the environmental assessment requirement under 21 CFR 25.15(d) and 21 CFR 25.31. These claims of categorical exclusions are acceptable for BLA 761364.

VI. Primary Container Labeling Assessment

The OPQA review of drug product labeling was performed by Diana Pei (see review in CDER Informatics Platform).

VII. Assessment of Common Technical Document- Quality Module 3

This document.

VIII. Assessment of Immunogenicity Assays- Module 5.3.1.4

This document.

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DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	9/16/2024		
To:	Andrew Shiber		
Requesting Center/Office	CDER/OPQ	Clinical Review Division	Other
From	Michael Lancina OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA 761364, Imuldosa ICC2301057 ICCR00957557		
Recommendation	Final Recommendation: ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
Recommendation	Comments to Review Team: The combination product uses a glass syringe with a staked needle. CDRH review is limited only to the needle safety device. PMC/PMR or CR Deficiencies: None. The needle safety device is acceptable. CDRH has no approvability concerns at this time.		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)
Michael G. Lancina -S Digitally signed by Michael G. Lancina -S Date: 2024.09.16 13:54:16 -04'00'	Shruti N. Mistry -S	2024.09.16 14:24:50 -04'00'

1. PURPOSE

This review provides an assessment of the needle safety device constituent part¹ of the prefilled syringe product.

This review will cover the following review areas:

☒ Needle safety device constituent performance ¹

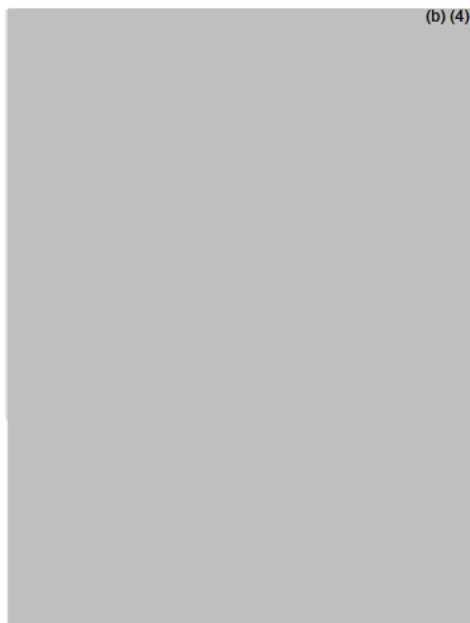
CDRH Quality Systems Assessment / Facilities consult not required per internal MAP 5017.7

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential²) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

DMB-3115 (Ustekinumab 45 mg and 90 mg) solution for injection is supplied in a 1 ml syringe composed of a (b) (4) glass barrel assembled with fixed ½ inch needle with a (b) (4) plastic rigid needle shield. It also contains a plunger stopper. The syringe is fitted with a passive safety guard. These components together form the pre-filled syringe (PFS) or the delivery system.

Figure P.7-2 (b) (4) Needle Guard with Plunger Rod and Extended Finger
Flange



The submission states that the (b) (4) passive needle safety system will be used. Several 510k cleared devices use the device name (b) (4) but no 510k number is referenced in this submission. The sponsor has clarified that the device used in this BLA does not have an active 510(k) clearance but is instead described in master file (b) (4).

¹ The scope of this review will be limited to the device constituent performance in accordance with ISO 23908:2011 Sharps Injury Protection and FDA guidance Medical Devices with Sharps Injury Prevention Features. Therefore, for a PFS with a needle safety device constituent the review will be limited to needle safety performance requirements and will not cover functions of the primary container (container content, breakloose force, glide force, needle shield removal force, etc.,).

² Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

(b) (4) is an expansive master file with nine different amendments and three supplements. The information provided is not sufficient to determine which specific sections of (b) (4) are applicable to the subject BLA. Section 1.4.1 contains the following description of the relevant files in (b) (4)



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Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	The intended patient population is children, adults and elderly patients for parenteral routes of administration. It is intended to be used by health care professionals, adult/elderly patients and caregivers. The EFF is an optional accessory that can be added (b) (4) (u) (4)
Needle connection (e.g. luer, slip tip, staked)	staked
Needle safety type (active or passive)	passive

3. FILING REVIEW (optional)

Checklist	Present		
Item	Yes	No	N/A
Device Description			x
Letters of Authorization			x
Design Verification Summary and reports for needle safety attributes			x

CDRH was not consulted prior to the filing date, so no filing review was performed.

4. DEVICE PERFORMANCE REVIEW

8.2 Test Plan

The test plan is divided into 4 parts:

- Part 1: Main functions are tested at nominal conditions and without EFF
- Part 2: Main functions are tested again after ageing, cycling temperature and transport conditions. With cut flange syringes
- Part 3: Main functions are tested at nominal conditions with EFF
- Part 4: Main functions are tested again after ageing, cycling temperature and transport conditions with EFF

An overall view is presented in Table 9.

Table 9 - Test plans A and B according to conditions and (b) (4) version tested

	(b) (4) 1ml long staked cut flange syringe	(b) (4) 1ml long Extended Finger Flange
Test Plan Level A: without ageing without cycling hot/cold temperature without transport conditions	DVP part 1	DVP part 3
Test Plan Level B: with ageing with cycling hot/cold temperature with transport conditions	DVP part 2	DVP part 4

Table 10 - Tests summary

Test protocol reference (b) (4)	Test name according to dFMEA	Method description
(b) (4) D1- TESTP039	Drop test on safety device without syringe (b) (4)	According to ISO 11608-1, §6.4 and §10.5d1
D1- TESTP016	Syringe loading force test	Tensile testing machine
D1- TESTP040	Drop test. Safety device with syringe 1 ml long, before use.	According to ISO 11608-1, §6.4 and §10.5d1
D1- TESTP050	The user must be able to perform an injection	Tensile testing machine
D1- TESTP154	Spring back force before final locking ("margin force")	Tensile testing machine
D1- TESTP042	Drop test on activated safety device with syringe and Plunger	According to ISO 11608-1, §6.4 and §10.5d1
D1- TESTP007	Device must be Chemical resistance	Tested with (b) (4)
D1- TESTP008	The activation of the device must be independent of the injection orientation	Device is manually activated in 3 orientations : Vertical needle downwards, Vertical needle downwards, horizontal
D1- TESTP084	The device allows full volume delivery	The residual volume is measured with a scale (accuracy $\pm$ (b) (4))
D1- TESTP030	Transport test	According to ASTM D41692
D1- TESTP020	High force needed to reactivate/override the safety feature, to prevent re-use	Tensile testing machine
D1- TESTP018	Syringe unloading force test	Tensile testing machine
D1- TESTP021	High force needed to pull the sleeve out of the body, to prevent re-use	Tensile testing machine
D1- TESTP015	Body and cone disassembly force	Tensile testing machine
E1- TESTP001	Drop test of extended finger flange + (b) (4) not activated, without syringe	According to ISO 11608-1, §6.4 and §10.5d1
E1- TESTP002	Drop test of extended finger flange + (b) (4) with syringe, before use	According to ISO 11608-1, §6.4 and §10.5d1

Test protocol reference (b) (4)	Test name according to dFMEA	Method description
(b) (4) E1- TESTP003	Drop test of extended finger flange + activated (b) (4), with syringe, after use	According to ISO 11608-1, §6.4 and §10.5d1
E1- TESTP004	Transport test	According to ASTM D4169
E1- TESTP005	Extended finger flange disassembly load (b) (4)	Tensile testing machine
E1- TESTP006	Chemical resistance	Tested with isopropyl alcohol and ethyl alcohol
E1- TESTP007	Activation in different orientations	Device is manually activated in 3 orientations : Vertical needle downwards, Vertical needle downwards, horizontal

4.1. Performance Data

Performance Requirement	Specification	Confidence / Reliability	Verification Data Acceptable (Y/N)
Needle Safety Activation force	(b) (4)	☒ 95% / 99.99%	N= 288 total Variable All groups met acceptance criteria
Override Pull Force	(b) (4)	☒ 95% / 99.99%	N= 288 total Variable All groups met acceptance criteria
Needle Safety Pre-activation – using drop test	NMT (b) (4) activations when dropped	☒ 95% / 99.99%	N=216 Attribute All groups met acceptance criteria
Needle safety Access in safe mode	Not tested in device validation	N/A	Verification of this EPR is not needed. Tolerance analysis and simulated clinical testing are used. This approach is acceptable.
Simulated Clinical Use Testing	No needle-stick injury Complete activation	☒ 95% / 99%	N = 1000 total, 675 w/ HCP, 325 w/ patients No injuries were reported Two incomplete activations reported with patient group, both on first attempt

Sample sizes for each test group were calculated based on 95% confidence/ 99.99% reliability, resulting in a k factor of 3.62 and group sample size of 72 for each group. Larger sample sizes represent the pooling of groups with different pre-conditioning (hot or cold environmental temperature, shipping, accelerated aging, etc),

Reviewer Comments:

Testing exceeds the requirements of ISO 23908:2011 Sharps Injury Protection. Simulated use testing was performed on the base model and the extended finger-flange (EFF) version of the device. Evaluators were both healthcare professionals and non-healthcare professionals, which included 7 prospective patients with multiple sclerosis or rheumatoid arthritis. While there were no needle-stick injuries reported, two non-healthcare professional users failed to completely activate the needle safety feature on their first attempts.

Information Request #1		(b) (4)
Sponsor Response		
Reviewer Comments	This response is inadequate. MAF (b) (4) is expansive, including three supplements and nine amendments. The sponsor should identify specific files in MAF (b) (4) to facilitate the review.	
Response Adequate:	☐ Yes ☒ No, See IR #2	

Information Request #2		(b) (4)
Sponsor Response		
Reviewer Comments	Exact model is specified in images included in the response.	
Response Adequate:	☒ Yes ☐ No, See IR	

Reviewer Comments:
n/a

<<END OF REVIEW>>

APPEARS THIS WAY ON ORIGINAL



Anshu
Rastogi

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Chringma
Sherpa

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LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 30, 2024
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Chringma Sherpa, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIII
Application:	BLA 761364
Applicant:	Accord BioPharma Inc.
Submission Date:	October 10, 2023
Product:	IMULDOSA (ustekinumab-srlf)
Dosage form(s):	Injection
Strength and Container-Closure:	45 mg/0.5 mL solution in a single-dose prefilled syringe 90 mg/mL solution in a single-dose prefilled syringe 130 mg/26 mL (5 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the proposed biosimilar product, ustekinumab injection 45 mg/0.5 mL and 90 mg/mL prefilled syringes, and 130 mg/26 mL vial.
Recommendations:	The prescribing information, medication guide, instructions for use, container labels, carton labeling, and blister 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, patient labeling, instructions for use, container labels, and carton labeling submitted on August 20, 2024 and September 30, 2024 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 October 10, 2023)

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Instructions for Use (submitted on October 10, 2023)

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Container Labels (submitted on October 10, 2023)



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Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

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

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the manufacturer name and address appear exactly as intended for the US license holder including punctuation. The container label has a period after "Inc." while there is no period after the "Inc" in the form FDA 356h. If necessary, correct this on your form FDA 356h.

Accord's response: Accord would like to clarify that the manufacturer name and address is appearing exactly as intended for the US license holder in the container label. However,

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."

punctuation mark was inadvertently missed out after "Inc" in form FDA 356h. Accord is now submitting the updated form FDA 356h which is aligned with manufacturer name in container label.

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

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: Add "Rx only" statement to the 130 mg/26 mL vial container label. *The Applicant revised as requested*

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

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

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

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *Accord's response:*

(b) (4)

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.
Accord's response: Accord confirms that after the label is affixed to the container, a sufficient area of the container remains uncovered, allowing visual inspection.

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
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ 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

<i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☐ Yes ☐ No ☒ N/A
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Package type term (container label)	Acceptable
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the appropriate package type term to the 130 mg/26 mL vial container label. *Accord's response: Accord has updated its package type term statement and discard statement to read "Single-Dose vial" and "Discard unused portion" to the 130 mg/26 mL vial container label.*

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

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

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

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

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No

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

Comment/Recommendation: Ensure the linear bar code appears on the container labels and surrounded by enough white space to facilitate proper scanning. *Accord's response: Accord has positioned the barcode vertically on the prefilled syringe and vial container label to enhance its scannability. Accord would also like to inform the Agency that the prefilled syringe label has been rotated 90 degrees counter clockwise to enhance its readability based on the direction of unwinding.*

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

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

Comment/Recommendation: Add the dosage statement to the vial container label. *Accord's response: Accord has updated its dosage statement to read (b) (4) Dosage: see Prescribing Information" to the 130 mg/26 mL vial container label.*

The prefilled syringe labels are 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
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation: Add the storage requirements to the 130 mg/26 mL vial label. *Accord's response: In compliance with USP General Chapter <7>, the storage conditions statement on 130 mg/26 mL vial container label has been added as "Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not shake. Do not freeze. Keep out of reach of children".*

Note that the 45 mg/0.5 mL and the 90 mg/mL prefilled syringe have the storage information on the container label and are acceptable.

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

Package⁶ Labeling Evaluation

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

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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the manufacturer name and address appear exactly as intended for the US license holder including punctuation. The labeling has a period after "Inc." while there is no period after the "Inc" in the form FDA 356h. If necessary, correct this on your form FDA 356h. *Accord's response: Accord would like to clarify that the manufacturer name and address is appearing exactly as intended for the US license holder in the container label. However, punctuation mark was inadvertently missed out after "Inc" in form FDA 356h. Accord is now submitting the updated form FDA 356h which is aligned with manufacturer name in container label.*

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: On the 45 mg/0.5 mL and 90 mg/mL prefilled syringe carton labeling, indicate the location of the lot number. *Accord's response: Accord has added place holder for the lot number on the prefilled syringe carton label, in compliance with 21 CFR 201.10(i)(1).*

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

Comment/Recommendation: On the 45 mg/0.5 mL and 90 mg/mL prefilled syringe carton labeling, indicate the location of the expiration date. *Accord's response: As recommended in USP General Chapter <7>, Accord has updated the format for the expiration date as a numerical character which include a 4-digit year, month and day in YYYY-MM-DD format on the prefilled syringe carton. Additionally, a placeholder has been added for the expiration date.*

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

Comment/Recommendation: Consider adding a statement about the number of containers for the 130 mg/26 mL carton label similar to how the prefilled syringes have one. Such as: "Contains one 130 mg/26 mL vial". <i>Accord has updated a net quantity statement on the principle display panel of prefilled syringe blister labeling to read "Contains one 45 mg/0.5 mL syringe" and "Contains one 90 mg/mL syringe". Also the vial carton labeling has been updated to read "Contains one vial".</i>

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

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

Comment/Recommendation: We recommend revising the room temperature storage information for the prefilled syringes from 30° C to 25° C (77° F). There is data for storage at
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room temperature for 25° C and 40° C but no data for 30° C. (b) (4)
 (b) (4) we recommend revising the room temperature storage temperature to 25° C (77° F) to err on the side of caution.

Accord's response: Accord would like to clarify that information about room temperature storage is based on in-use stability data from a temperature excursion study conducted with the DMB-3115 PFS. Details are described in sections 3.2.P.8.1.8 and 3.2.P.8.3.4. The product quality assessor determined that Accord's response is adequate, the storage information remains as proposed.

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

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

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ 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 drug 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
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list for the prefilled syringes 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, histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and sucrose. *Accord's response: Accord would like to inform the Agency that the name of the inactive ingredient have been updated by using the established names for drugs on the prefilled syringe carton label.*

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list for the 130 mg/26 mL vial 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, edetate disodium, histidine, L-histidine hydrochloride monohydrate, methionine, polysorbate 80, and sucrose. *Accord's response: Accord would like to inform the Agency that the name of the inactive ingredient have been updated by using the established names for drugs on the vial carton label.*

Add the four letter suffix to the proper name in the ingredient list on all carton labeling.
The Applicant revised as recommended.

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

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

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for ustekinumab products (i.e., there is no specific test method described in regulation for ustekinumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for

IMULDOSA 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. The applicant did not propose to include a "No U.S. standard of potency" statement on the carton. Thus, no comment will be sent to the applicant.

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

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

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

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (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
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Package type term (package labeling)	Acceptable
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ 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

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

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

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

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ 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. <i>Accord's response: Accord has updated its dosage statement on its vial and prefilled syringe carton label to read "Dosage: see Prescribing Information".</i>	
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Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

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

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
<u>PRODUCT TITLE</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

Highlights of Prescribing Information	
<u>DOSAGE FORMS AND STRENGTHS</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
<u>2 DOSAGE AND ADMINISTRATION</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(3)(iv) <i>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:</i>	☒ Yes ☐ No ☐ N/A

"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."	
<i>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</i> Draft Guidance <i>Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry</i> (January 2023)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: 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). <i>The Applicant revised similarly as requested per RP labeling</i> Please include the material of construction information for the infusion bags. <i>The Applicant revised similarly as requested per RP labeling.</i> Please include the material of construction information for the filter and the infusion set. <i>The Applicant revised similarly as requested per RP labeling.</i> We revised this to read as "Each vial is for one-time use in only one patient." for clarity and to mitigate confusion with the package type term no longer used in FDA labeling, "single use", which in the past was used to describe a container that allowed for multiple doses in a single patient. <i>Applicant revised as recommended.</i>

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>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</i> (October 2018) <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
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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
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list for the prefilled syringes 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, histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and sucrose. *The Applicant revised as requested*

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list for the 130 mg/26 mL vial 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, edetate disodium, histidine, L-histidine hydrochloride monohydrate, methionine, polysorbate 80, and sucrose. *The Applicant revised as requested*

Confirm (b) (4) the definition of edetate disodium, USP monograph. (b) (4)

(b) (4). Confirm the provided calculation and provide an updated Description and Composition Table in section 3.2.P.1 (b) (4)

(b) (4). Ensure all inactive ingredients with a USP monograph are provided as such.

The Applicant revised the molecular weight (b) (4). Product quality team recommended that the molecular weight be revised to 148 kDa as provided in Section 3.2.S.1.3. Per OTBB, generally OTBB recommends not changing MW to avoid suggesting differences in measurement reflects differences between 351(k) and RP and revised the MW to align with RP prescribing information. *The Applicant accepted revised MW as RP.*

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

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

Comment/Recommendation: In-use stability data to support the storage of the PFS drug product at 30° C for up to 30 days was provided in Table P.8.3-69, Section 3.2.P.8.3. According to the product quality assessor, at this storage condition, a 3% increase in acidic peaks accompanied by a 4.7% decrease in mean peak by IEC were observed with no appreciable changes in all other product quality attributes. Because the observed changes in charge variants are not very significant and within the release and stability specifications for PFS drug product, the product quality assessor determined that the in-use storage condition of PFS drug product is supported by the provided in-use stability data.
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Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product
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and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, for biologic products, the applicant as listed in field 2 Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Ensure that the manufacturer name and address appears exactly as intended for the US license holder including punctuation. The form FDA 356h does not include a period after "Inc", however the labeling includes a period after "Inc.". If necessary, correct this on your form FDA 356h.

The licensed manufacturer should appear as:

Manufactured by:

Applicant name as listed in field 2 of Form FDA 356h

Address as listed on line 5 of form FDA 356h

Added a placeholder for the US License number.

The Applicant revised as requested and corrected form FDA 356h

Medication Guide Evaluation

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

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

Comment/Recommendation: In-use stability data to support the storage of the PFS drug product at 30° C for up to 30 days was provided in Table P.8.3-69, Section 3.2.P.8.3. According to the product quality assessor, at this storage condition, a 3% increase in acidic peaks accompanied by a 4.7% decrease in mean peak by IEC were observed with no appreciable changes in all other product quality attributes. Because the observed changes in charge variants are not very significant and within the release and stability specifications for PFS drug product, the product quality assessor determined that the in-use storage condition of PFS drug product is supported by the provided in-use stability data.

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

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list for the prefilled syringes 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, histidine, L-histidine hydrochloride monohydrate, polysorbate 80, and sucrose.

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) revise the inactive ingredient list for the 130 mg/26 mL vial 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, edetate disodium, histidine, L-histidine hydrochloride monohydrate, methionine, polysorbate 80, and sucrose.

(b) (4)

Applicant revised as recommended.

MEDICATION GUIDE	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>

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: FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, for biologic products, the applicant as listed in field 2 Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Ensure that the manufacturer name and address appears exactly as intended for the US license holder including punctuation. The form FDA 356h does not include a period after "Inc", however the labeling includes a period after "Inc.". If necessary, correct this on your form FDA 356h.

The licensed manufacturer should appear as:

Manufactured by: Applicant name as listed in field 2 of Form FDA 356h
Address as listed on line 5 of form FDA 356h

Added a placeholder for the US License number.

(b) (4)

Applicant revised as recommended.

Instructions for Use Evaluation

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

Comment/Recommendation: Change the parenthesis around the pronunciation spelling to brackets as per Instructions for Use – Patient Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry (July 2022).

(b) (4)

Applicant revised as recommended.

INSTRUCTIONS FOR USE

STORAGE AND HANDLING

Acceptable

Recommended labeling practices for IFU: Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)

☒ Yes
☐ No
☐ N/A

Comment/Recommendation: In-use stability data to support the storage of the PFS drug product at 30° C for up to 30 days was provided in Table P.8.3-69, Section 3.2.P.8.3. According to the product quality assessor, at this storage condition, a 3% increase in acidic peaks accompanied by a 4.7% decrease in mean peak by IEC were observed with no appreciable changes in all other product quality attributes. Because the observed changes in charge variants are not very significant and within the release and stability specifications for PFS drug product, the product quality assessor determined that the in-use storage condition of PFS drug product is supported by the provided in-use stability data.

INSTRUCTIONS FOR USE

INGREDIENTS

Acceptable

Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)

☐ Yes
☐ No
☒ N/A

INSTRUCTIONS FOR USE

MANUFACTURER INFORMATION

Acceptable

21 CFR 201.1, 19 CFR 134.11

☒ Yes
☐ No
☐ N/A

Guidance for Industry <i>Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format</i> (July 2022). 21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☒ Yes ☐ No ☐ N/A
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Comment/Recommendation: FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, for biologic products, the applicant as listed in field 2 Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Ensure that the manufacturer name and address appears exactly as intended for the US license holder including punctuation. The form FDA 356h does not include a period after "Inc", however the labeling includes a period after "Inc.". If necessary, correct this on your form FDA 356h.

The licensed manufacturer should appear as:

Manufactured by: Applicant name as listed in field 2 of Form FDA 356h
Address as listed on line 5 of form FDA 356h

Added a placeholder for the US License number.

The phrase (b) (4) before "Manufactured by" was deleted. The zip code for the address was added.



Applicant revised as recommended.

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on August 20, 2024)

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Medication Guide (submitted on August 20, 2024)

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



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Pei

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Chringma
Sherpa

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**PRODUCT QUALITY MICROBIOLOGY/FACILITY
ASSESSMENT****Memorandum of Review to the File**

Application ID	BLA 761364
Submission Type	Original BLA
Drug Product Name	ustekinumab
Strengths	PFS - 45 mg, 90 mg & Vial - 130 mg
Dosage Form	Pre-Filled Syringe (PFS) and Vial
Administration Route	PFS - Subcutaneous & Vial - Intravenous
Indication	Moderate to severe plaque psoriasis (Ps) (both adult and pediatric), active psoriatic arthritis (both adult and pediatric), moderately to severely active Crohn's disease, moderately to severely active ulcerative colitis.
Applicant Name	Accord BioPharma Inc.
US License Number	2105
Application Type	351 (k)
Primary Reviewer	Jeanne Fringer, CDER/OPQ/OPMA/DPMVA
Secondary Reviewer	Maxwell Van Tassell (micro), CDER/OPQ/OPMA/DPMVA Zhong Li (facilities), CDER/OPQ/OPMA/DPMVA
Goal Date	09Oct2024

Recommendation for Approvability:

- This BLA was reviewed from a sterility assurance perspective and is recommended for Approval with the following post-marketing commitment(s):
 1. Perform a study using the worst-case headspace size to confirm that stopper placement height specifications would not result in stopper movement that would exceed the sterile boundary under low-pressure conditions.
- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized using a validated (b) (4)

(b) (4)

(b) (4). Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the	(b) (4)	

		container closure integrity	(b) (4)	
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
BLA-761364-ORIG-1 (SN# 0002)	10/10/2023
IR #1 response (SN# 0008)	4/29/2024
IR #2 response (SN# 0023)	9/3/2024
IR #3 response (SN# 0027)	9/24/2024
IR #4 response (SN# 0030)	9/30/2024

List of DMFs Assessed (Table):

DMF #	Item Referenced	Date Reviewed	Finding	Document Reference
(b) (4)	Amendment (SN 0038)	7/18/2024	Adequate	(b) (4) M03R01
	Multiple submissions (SN 0031)	7/15/2024	Adequate	(b) (4) M02R01
	Multiple submissions	7/15/2024	Adequate	(b) (4) M02R01
	New/Annual Report	7/15/2024	Adequate	(b) (4) M01R03

Application Submission Background

Accord BioPharma Inc. is submitting this BLA for Ustekinumab (Imuldosa) in a single dose 45 mg/0.5 mL pre-filled syringe (PFS); single dose 90 mg/1 mL PFS; and 130 mg/26 mL vial presentation. Ustekinumab (Project Code: DMB-3115) is an anti-(human interleukin 12 p40 subunit) (human monoclonal CNTO 1275 γ 1-chain)-immunoglobulin G1. It is a proposed biosimilar to US-licensed Stelara®, licensed under BLA 761044 by Janssen Biotech Inc., indicated for moderate to severe plaque psoriasis (both adult and pediatric), active psoriatic arthritis (both adult and pediatric), moderately to severely active Crohn's disease, and moderately to severely active ulcerative colitis. Ustekinumab drug substance is a formulated liquid solution containing the same excipients as Stelara®, however, some of them are at a different concentration.

The PFS presentation is supplied with a (b) (4) passive needle safety guard and is considered as drug-device combination product. Manufacture of the PFS is at (b) (4). A pre license inspection of (b) (4) was performed, and the facility was approved. The vial presentation is manufactured at (b) (4). An inspection waiver was granted for (b) (4) and it was approved. Refer to facilities section of this memo for additional information on facilities.

Reviewer's Comment: For Information

PFS presentations micro and facility review

MODULE 1

1.14 LABELING

Reconstitution and Dilution Instructions

The PFS are single dose and have no in use storage conditions.

Reviewer's Comment: For Information

MODULE 3.2.P

Module 3.2.P Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

P.1 Description and Composition of the Drug Product

The DP is 45mg/0.5 mL and 90 mg/1.0 mL in a pre-filled syringe. The PFS consists of a sterile 1mL (b) (4) glass syringe with a fixed half-inch needle with a (b) (4) stopper equipped with a plunger rod with needle guard system. The composition of the DP is shown in Table 3.2.P.1-1:

Table 3.2.P.1-1. Qualitative and quantitative composition of DMB-3115 Pre-Filled Syringe Drug Product

Name of Ingredient	Quantity (mg) per 0.5 mL (PFS)	Quantity (mg) per 1.0 mL (PFS)	Function	Reference to Quality Standard
Ustekinumab	45	90	Active pharmaceutical ingredient	In-house
Sucrose	25.9	51.8	(b) (4)	NF/USP
(b) (4) histidine	2.23	4.46		USP
L-histidine hydrochloride monohydrate	4.14	8.28		Ph. Eur
Polysorbate 80	0.02	0.04		NF/USP
(b) (4)				USP, Ph. Eur, KP, JP

Reviewer's Comment: For Information

P.2 Pharmaceutical Development

(b) (4)



Maxwell
Van Tassell

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Thuy Thanh
Nguyen

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Jeanne
Fringer

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**PRODUCT QUALITY MICROBIOLOGY/FACILITY
ASSESSMENT****Memorandum of Review to the File**

Application ID	BLA 761364-ORIG-1
Submission Type	Original BLA
Drug Product Name	ustekinumab
Strengths	PFS - 45 mg, 90 mg & Vial - 130 mg
Dosage Form	Pre-Filled Syringe (PFS) and Vial
Administration Route	PFS - Subcutaneous & Vial - Intravenous
Indication	Moderate to severe plaque psoriasis (Ps) (both adult and pediatric), active psoriatic arthritis (both adult and pediatric), moderately to severely active Crohn's disease, moderately to severely active ulcerative colitis.
Applicant Name	Accord BioPharma Inc
US License Number	2105
Application Type	351 (k)
Primary Reviewer	Melissa Ray, PhD, Microbiologist, CDER/OPQ/OPMA/DPMVA
Secondary Reviewer (Microbiology)	Maxwell Van Tassell, PhD, SPQA, CDER/OPQ/OPMA/DPMVA
Secondary Reviewer (Facility)	Zhong Li, PhD, SPQA, CDER/OPQ/OPMA/DPMVAI
Goal Date	10/09/2024

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and is recommended for Approval.
- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OPQAIII.

Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) at each critical step. Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at DS release. Microbial control (b) (4) is monitored throughout (b) (4). Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for DMB-3115 (ustekinumab) DS manufacture. All proposed manufacturing and

testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin	Safety, Purity	Raw materials, manufacturing process	(b) (4)	N/A
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process		N/A

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
ORIG-1 (Sequence # 0002)	10/10/2023
Response to IR1 (Sequence # 0021)	8/23/2024

Application Submission Background

Reviewer's Comment: For Information

Accord BioPharma Inc. is submitting this BLA under the section 351(k) of the Public Health Service Act for approval to market ustekinumab (Imuldosa) in 45 mg/0.5 mL PFS; 90 mg/mL PFS; and 130 mg/26 mL vial presentations. Ustekinumab (Project Code: DMB-3115) is a proposed biosimilar to US-licensed Stelara by Janssen Biotech Inc. BLA 761044.

MODULE 3.2.S

Module 3.2.S Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

S.1 General Information

DMB-3115 (ustekinumab) is a human IgG1 monoclonal antibody against IL-23 and IL-12 cytokines, disrupting the IL-23 and IL-12 mediated signaling and cytokine cascades. Ustekinumab has two heavy chains with 449 amino acids and two light chains with 214 amino acids which includes N-linked glycosylation at the Asp 299 residue of each heavy chain. Ustekinumab is produced as a glycosylated protein with a molecular weight of approximately 148 kDa. It is expressed in an Sp2/0-Ag14 cell line. Sp2/0-Ag14 is a non-Ig-secreting or synthesizing line derived from a cell line created by fusing a BALB/c mouse spleen cell and the mouse myeloma P3X63Ag8.

Reviewer's Comment: For Information



Melissa
Ray

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Zhong
Li

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Maxwell
Van Tassell

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