CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761216Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA/NDA Number: 761216
Assessment Number: First round
Assessment Date: September 19, 2021

Drug Name/Dosage Form	YUSIMRY (adalimumab-aqvh) solution for intravenous infusion
Strength/Potency	40 mg/0.8 mL (100 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis
Applicant/Sponsor	Coherus Biosciences
US agent, if applicable	N/A

Product Overview:

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance, Comparative Analytical Assessment, Immunogenicity	Lymarie Maldonado-Baez	OBP/DBRR-I
Drug Product	Chringma Sherpa	OBP/DBRR-I
Method Validation, Reference Materials	Deborah Schmiel	OBP/DBRR-I
Labeling	James Barlow	OBP/IO
Microbiology and Facilities, DS	Lindsey Brown	OPMA/DBM/BMB1
Microbiology and Facilities, DP	Zhong Li	OPMA/DBM/BMB1
Facilities QAL	Thuy Nguyen	OPMA/DBM/BMB1
Microbiology QAL	Maxwell Van Tassell	OPMA/DBM/BMB1
Application Technical Lead	Jennifer Swisher	OBP/DBRR-I
RBPM	Andrew Shiber	OPRO/DRBPMI/RBPMB2

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Elaine Sit	OND/ORO/DROII
Cross-disciplinary Team Lead	Hon-Sum Ko	OND/OII/DDD
Medical Officer	Sandhya Apparaju Suna Seo Juli Tomaino	OND/OII/DG
Pharmacology/Toxicology	Eleni Sariclu; Xiaochun Chen, TL	OND/OII/DPTII
Clinical Pharmacology	Ping Ji; Priya Brunsdon, TL	OTS/OCP/DIIP
Statistics	Mohamed Alosh; Kathy Fritsch, TL	OB/DBIII

1. Names:

   a. Proprietary Name: YUSIMRY
   c. Non-Proprietary Name/USAN: adalimumab-aqvh
   d. CAS Registry Number: 331731-18-1
   e. Company/Laboratory Code: CHS-1420

f. INN Name: adalimumab
h. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [CHS-1420]

Submissions Assessed:

Submission(s) Assessed	Document Date
761216/0003 (Original BLA)	12/18/2020
761216/0003 (OBP IR#1 response)	01/27/2021
761216/0005 (OBP IR#2 response)	02/11/2021
761216/0007 (OPMA IR #1 response)	3/18/2021
761216/0009 (OPMA IR #2 response)	5/18/2021
761216/0010 (OPMA IR #3 response)	6/4/2021
761216/0013 (OBP IR#3 response)	07/15/2021
761216/0016 (OBP IR#4 response)	8/23/2021
761216/0019 (OBP IR#5 response)	9/20/2021
761216/0021 (OPMA IR#4 response)	8/23/2021
761216/0022 (OBP IRs 2 and 3 response)	9/20/2021
761216/0022 (OPMA IR #4 response)	10/15/2021
761216/0022 (OBP IR #6 response)	10/23/2021

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	Type III		(b) (4)	3	Adequate	N/A	None
	Type III			3	Adequate	N/A	None
	Type III			3	Adequate	N/A	None
	Type III			3	Adequate	N/A	None
	Type V			3	Adequate	N/A	None
	Type III			3	Adequate	N/A	None
	Type V			3	Adequate	N/A	None

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under “comments”)
2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

   B. Other documents: none

3. Consults: none

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761216 for YUSIMRY manufactured by Coherus Biosciences. The data submitted in this application are adequate to support the conclusion that the manufacture of YUSIMRY is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    - (b) (4)
  - Drug Product:
    - (b) (4)
- Fill size and dosage form:
  - Prefilled Syringes (PFS): 40 mg/0.8 mL
- Dating period:
  - Drug Product: Either 36 months at 5 ± 3°C or the age of the drug substance batch subtracted from 48 months, whichever is shorter. This dating period may include a single period up to 14 days at a maximum of 25°C with protection from light. The start date of the dating period is the date of manufacture defined as the date of final sterile filtration of the formulated drug product.
  - Drug Substance: (b) (4) months at (b) (4) °C
- Exempt from lot release:
  - Yes, YUSIMRY is a specified product and exempt from lot release. Per FR notice 95-29960 well-characterized therapeutic recombinant DNA-derived and

monoclonal antibody biotechnology products are exempted from 21 CFR 601.2a lot release requirements.

Coherus states that because this BLA is submitted under the 351(k) pathway, it is exempt from the 21 CFR 25.20 requirement to provide an environmental assessment. They request a categorical exclusion under 21 CFR Part 25.31(g): "Establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing".
The grounds for this request are acceptable; the exclusion may be granted.

C. Assessment Summary:

YUSIMRY (adalimumab-aqvh, CHS-1420) is a proposed biosimilar to US-Humira Pfizer seeking licensure for the following indications: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD) in patients 6 years of age and older, Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Juvenile idiopathic arthritis (JIA) in patients 2 years of age and older, for which US-Humira is licensed.

The data submitted support the demonstration that YUSIMRY is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components (refer to Section II of this memo for further details and discussion of the differences observed).

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for drug substance (DS) and drug product (DP) manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product and the OPMA assessors are recommending approval for this BLA from a sterility assurance and microbiology product quality perspective.

The OPMA facilities assessment supports their recommendation of approval for this BLA.

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

II. Comparative Assessment and Evaluation of the Analytical Component of the Scientific Bridge

A. Analytical Assessment Overview and Conclusions

To support a demonstration that CHS-1420 is highly similar to US-licensed Humira (hereafter referred to as US-Humira), Coherus Biosciences performed a comparative analytical assessment using 43 lots of US-Humira (40 mg/0.8 mL) with expiration dates ranging from April 2015 through June 2021 and 16 independent lots of CHS-1420 DP in addition to a single independent lot of DS (all at 40 mg/0.8 mL) with expiration dates ranging from May 2018 to October 2022. The ages at the time of testing span the shelf-life of US-Humira and were adequate to capture potential reference product differences over time for the 40 mg/0.8 mL strength.

There were three process iterations during the commercial development stage of CHS-1420: the late-development (used in comparative clinical studies), pre-commercial, and commercial manufacturing processes. These process iterations had the goal of enhancing process consistency and further improvement of the analytical similarity between CHS-1420 and US-Humira. All late development lots used in comparative clinical studies were included in the comparative analytical assessment. The CHS-1420 lots used in the comparative analytical assessment all represent independent DS lots; their derivation is as follows:

- 6 lots of late-development CHS-1420 DP manufactured at commercial scale (b) (4)
- 5 lots of pre-commercial CHS-1420 DP manufactured at commercial scale
- 5 lots of commercial CHS-1420 DP manufactured at commercial scale
- 1 lot of commercial CHS-1420 DS manufactured at commercial scale

The comparability of the lots manufactured by late-development and pre-commercial processes to CHS-1420 manufactured by the commercial manufacturing process was discussed in a BPD Type 2 meeting held with the Agency on August 1, 2019 and was assessed and found to be established for both previous processes based on data submitted to this BLA. While the small improvements that were made in the pre-commercial and commercial manufacturing processes to (b) (4) with US-Humira strengthened the data to support a demonstration that CHS-1420 is highly similar to US-Humira, these changes would not preclude the ability to leverage the clinical studies that were performed with late-development lots of CHS-1420 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 CHS-1420 and US-Humira and included a comparative assessment of their degradation profiles under several relevant forced degradation conditions including thermal stress (40°C for 3 months), oxidative stress (~0.01% H2O2 at 37°C for 3 hours), base stress (pH 8.0 at 37°C for 10 days), acidic stress (pH 2.2 at 37°C for 2 hours), and photo (light) stress (200 W/m2 UV-A light-hr + 1200 klux-hr visible light).

Coherus assessed quality attributes using an approach based on risk and criticality for statistical evaluation of analytical results. The highest-ranking attributes that were tested using quantitative assays were evaluated using equivalence testing. Attributes that were considered moderate for criticality that were tested using quantitative assays were evaluated using quality ranges that took both manufacturing variability of US-Humira as well as assay variability into account; these ranges were established by multiplying the standard deviation of the US-Humira data by a multiplier of 3. The standard deviation multiplier used to establish each quality range was scientifically justified. The least critical attributes, and those attributes that were tested using qualitative assays, were evaluated using a comparison of visual displays of the data. Results from method validation or qualification studies support the suitability of the methods used in the comparative analytical assessment.

Coherus is seeking licensure of 40 mg/0.8 mL CHS-1420 in a single-dose prefilled syringe. Our assessment of the CHS-1420 and US-Humira data supports that CHS-1420 has been

demonstrated to be highly similar to US-Humira, notwithstanding minor differences in clinically inactive components. CHS-1420 has the same strength, dosage form, and route of administration as US-Humira. Coherus used a comprehensive selection of analytical methods that were suitable to evaluate the critical quality attributes of CHS-1420 and US-Humira to support the demonstration that the products are highly similar. 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 CHS-1420 and US-Humira are highly similar.

B. Results of the Comparative Analytical Assessment

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
Primary Structure	Amino acid sequence	Yes
	Intact, reduced, and reduced and deglycosylated molecular mass	Yes
	Tryptic peptide mapping	Yes
N-linked Glycans	High Mannose	Yes
	Afucosylation	Yes
	Terminal Galactosylation	Yes
	Sialylation	Yes
Amino Acid Modifications	Methionine Oxidation	Yes
	Deamidation	Yes
	N-terminal Variants	Yes
	C-terminal Variants	Yes
	Free Thiol	Yes
Higher Order Structure	Secondary Structure	Yes
	Tertiary Structure	Yes
	Melting Temperature (DSC)	Yes
Product-related variants and impurities	HMW (SE-UPLC)	Yes
	Monomer (SE-UPLC)	Yes
	LMW (SE-UPLC)	Yes
	Purity (HC + LC) (rCE-SDS)	Yes
	NGHC (rCE-SDS)	Yes
	Purity (nrCE-SDS)	Yes
	Main Peak (CEX-HPLC, w/ & w/out CPB)	Yes
	Acidic Species (CEX-HPLC, w/ & w/out CPB)	Yes
	Basic Species (CEX-HPLC, w/ & w/out CPB)	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar
Bioactivity- Fab mediated	sTNFα neutralization activity (inhibition of apoptosis by caspase 3/7 activity in U937 cells)	Yes
	Suppression of cytokine secretion (PBMC derived MLR assay)	Yes
	Reverse Signaling (Apoptosis induced in mTNFα-expressing cells)	Yes
	Reverse Signaling (Suppression of NF-kB activity in LPS activated macrophages)	Yes
	sTNFα binding assay (SPR)	Yes
	sTNFα binding assay (ELISA)	Yes
	Binding to mTNFα (Flow cytometry)	Yes
Bioactivity- Fc mediated	FcRN binding	Yes
	FcγRIa binding	Yes
	FcγRIIa binding	Yes
	FcγRIIb binding	Yes
	FcγRIIIa (158F) binding	Yes
	FcγRIIIa (158V) binding	Yes
	FcγRIIIb binding	Yes
	C1q binding	Yes
	Antibody-dependent cellular cytotoxicity (ADCC)	Yes
	Complement-dependent cytotoxicity (CDC)	Yes
	Induction of regulatory macrophages in an MLR by inhibition of proliferation	Yes
Drug Product Attributes	Protein concentration	Yes
	Deliverable volume	Yes

Soluble TNFα (sTNF Soluble TNFα (sTNFα) binding and neutralization of sTNFα-induced cytotoxicity are generally regarded as the primary mechanisms of action for adalimumab. Three assays were conducted to address these activities and the results were analyzed by equivalence testing (ELISA for sTNFα and inhibition of apoptosis) and by establishing a quality range (SPR for sTNFα). For both the cytotoxicity neutralization assay and the sTNF-α binding assay by ELISA, Coherus provided data from 16 lots of CHS-1420 and 26 lots of US-Humira. OBP reviewed the justification of lots selected and concluded that the lot selection for each product adequately captured the lot-to-lot variability. The data met the equivalence margins for the binding ELISA data for sTNFα and inhibition of apoptosis, and CHS-1420 data fell within the US-Humira Quality Range supporting a demonstration that CHS-1420 is highly similar to US- Humira.

Additional potential mechanisms of action have been described for adalimumab, including antibody dependent cell-mediated cytotoxicity against cells expressing transmembrane TNF-α (tmTNF-α), complement dependent cytotoxicity against tmTNF-α positive cells, “reverse signaling” (signal transduction into cells by activation of tmTNF-α), and induction of regulatory

macrophages. Evidence suggests that the Fc-dependent induction of regulatory macrophages is important in Crohn's Disease and Ulcerative Colitis. Assays that are orthogonal to the sTNFα binding and the neutralization assays, assays that evaluate these additional potential mechanisms of action, and assays that evaluate purity, protein content, and other general properties of adalimumab were assigned for quality range or visual comparison assessment.

The biochemical and biological activity attributes tested in Table A met the pre-defined comparative analytical acceptance criteria in the comparison of CHS-1420 to US-Humira with exceptions discussed in Section D of this memo. The results of comparative stability studies under stressed and accelerated conditions indicate that the degradation pathways and the rate of degradation of CHS-1420 DP and US-Humira are similar and the differences noted do not preclude a demonstration that CHS-1420 is highly similar to US-Humira.

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

Not applicable.

D. Assessment of Analytical Study Results

Comparative analytical acceptance criteria were met for all attributes evaluated with quality ranges with the following exceptions:

- Sialic acid: Sialylated glycans in 4 of 17 CHS-1420 lots (0.1-0.2%) are below the QR of US-Humira (0.2-1.0%). These lots were all manufactured by the late-development process, whereas sialic acid levels for all pre-commercial and commercial lots of CHS-1420 fell within the QR. Sialyation of the conserved Fc glycan may have the potential to impact Fc functions or PK but no correlation to suggest such an impact was found in the biological function and FcR-binding assays, likely due to the fact that there are very low amounts of this modification in either CHS-1420 or US-Humira. Therefore, the differences noted in sialic acid content do not preclude a demonstration that CHS-1420 is highly similar to US-Humira.

- Terminal Galactose: Similar to sialic acid, the levels of terminal galactosylation (tGal) of the N-linked glycan of CHS-1420 were lower than those of US-Humira in 5 of 17 lots with a 6th lot at the lower limit of the QR (4.7 – 15.3%), although all of these lots were manufactured by the late-development process. tGal levels of pre-commercial and commercial lots of CHS-1420 are within the QR for US-Humira (15.3-19.9%). While lower galactosylation can decrease Fc binding to C1q and result in lower CDC activity, no differences were observed for either C1q binding or CDC activity between CHS-1420 and US-Humira. In addition, terminal galactosylation is adequately controlled in CHS-1420 DS release. Therefore, the differences noted in terminal galactose levels do not preclude a demonstration that CHS-1420 is highly similar to US-Humira.

- FcγRIIIa (158V) binding: 2 of 16 lots of CHS-1420 tested showed percent relative binding affinities to the high-affinity variant of FcγRIIIa (158V) that were slightly below the QR for US-Humira (93.7% (CHS-1420 late-development lot) and 95.0% (CHS-1420 commercial lot) compared with US-Humira (QR of 96.7-122.3%), although similar results were not found for the low-affinity variant of FcγRIIIa (158F), FcγRIIIb, or ADCC. Generally, the low-affinity

variant is more sensitive to differences in binding affinity, and these small differences in relative binding affinity by K_D would not be considered impactful and may have been due to experimental variability. Regardless, in consideration of all of the comparative data that support potential FcγRIII-dependent mechanisms of action, as well as the fact that levels of fucosylated glycans and ADCC are adequately controlled in CHS-1420 DS release, the differences noted in FcγRIIIa (158V) binding do not preclude a demonstration that CHS-1420 is highly similar to US-Humira.

- Size Variants (% Main Peak by non-reduced CE-SDS (nrCE-SDS)): 9 of 16 lots of CHS-1420 demonstrated purity by non-reducing CE-SDS that was lower than the QR for US-Humira. However, these differences were attributed to earlier manufacturing processes for CHS-1420; all CHS-1420 DS lots manufactured by the current commercial process demonstrated purity between 97.2-97.7% (QR ≥ 96.3%). Differences were attributable to increased levels of partially reduced species such as light chain and heavy-heavy-light fragments. The cause of these partially reduced species in CHS-1420 is unknown but such fragments can be caused by cellular lysis during harvest steps or poor cell growth conditions. Furthermore, lots with lower purity by nrCE-SDS demonstrate no meaningful differences in terms of potency and Fab- or Fc-dependent binding, as non-covalent interactions are known to maintain antibody integrity as evidenced by the lack of difference observed between CHS-1420 and US-Humira by SE-UPLC. Overall, the difference observed in purity by nrCE-SDS reflects earlier iterations of the manufacturing process and does not preclude a demonstration that CHS-1420 is highly similar to US-Humira. Furthermore, CHS-1420 DS and DP purity by nrCE-SDS is adequately controlled at release and on stability.

- Protein Concentration: While 2 out of 16 lots of CHS-1420 were higher than the QR for protein concentration of US-Humira (51.6 and 51.9%, compared to a QR of 45.3-50.3%), these lots were late development lots and subsequent process modifications have ensured that all lots of pre-commercial and commercial CHS-1420, as well as all lots manufactured by the commercial process, are within an acceptable range. The differences observed in the protein concentration of the late development CHS-1420 lots does not preclude a demonstration that CHS-1430 is highly similar to US-Humira.

In summary, the totality of the comparative analytical assessment supports the following conclusion:

- CHS-1420 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components.

- For attributes where minor differences were observed between CHS-1420 and US-Humira, the totality of the analytical data supports that the function, activity, and in vitro stability of CHS-1420 and US-Humira are similar. Specifically, the differences noted in glycosylation, fragment levels, and FcγRIIIa (158V) binding were not found in the CHS-1420 commercial lots and further, were not reflected in cell-based functional assays such as cytotoxicity, neutralization, ADCC, and CDC assays. Therefore, the analytical differences observed do not preclude a demonstration that CHS-1420 is highly similar to US-Humira.

E. Same Strength

CHS-1420 has the same dosage form and route of administration as US-Humira. Coherus Biosciences is seeking approval of 40 mg/0.8 mL CHS-1420 in a single-dose prefilled syringe. US-Humira is available at this strength in this presentation. Coherus Biosciences is seeking approval of CHS-1420 for the same strength as US-Humira. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. (b) (4) were assessed as part of manufacturing process controls. Based on the similarity and manufacturing data, the 40 mg/0.8 mL CHS-1420 prefilled syringe has 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 the corresponding presentation of US-licensed Humira. The strength of 40mg/0.8mL CHS-1420 in the prefilled syringe is the same as that of US-Humira.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
TNF binding and neutralization (potency)	Efficacy	Intrinsic to the molecule	(b) (4)	
Low molecular weight (LMW) species (product-related impurities)	Potency, Efficacy, PK/PD	Can be introduced during manufacture and storage		Increased upon exposure to heat, high pH stress, and light stress.
High molecular weight (HMW) species /Aggregates (product-related impurities)	Efficacy, PK and immunogenicity	Manufacturing process and storage conditions. Minimal increase is expected on DS stability under controlled conditions.		Aggregates are increased upon exposure to light, heat, and high pH stress.
Glycosylation (product-related variants)	Efficacy, PK	Cell culture; affected by (b) (4)		(b) (4)
Misfolded/denatured species	Efficacy, immunogenicity	(b) (4) manufacturing process and storage conditions		
Deamidation/Isomerization	Efficacy, PK, immunogenicity	(b) (4)		

		manufacturing process and storage conditions	(b) (4)	
Oxidation	Efficacy, safety, immunogenicity	Manufacturing process and during storage		

B. Drug Substance adalimumab-aqvh Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 3: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by microbial contamination)	Raw materials and manufacturing process	(b) (4)	
Bacterial endotoxins (Contaminant)	Safety, purity, immunogenicity	Raw materials and manufacturing process		
Mycoplasma	Safety	Cell culture		
Viral contamination	Safety	Raw materials, cell culture		
Protein concentration	Efficacy	DS manufacturing		
(b) (4)	Safety	DS manufacturing, formulation		
Host cell DNA	Safety and immunogenicity	Cell culture		
Host cell protein	Safety and immunogenicity	Cell culture		Characterization using (b) (4)

			(b) (4)	
(b) (4)	Safety and immunogenicity	(b) (4)		Reduced during (b) (4)
(b) (4)	Safety	Cell culture		
(b) (4)	Safety	Cell culture		
(b) (4)	Safety	Cell culture		Reduced during (b) (4)

- **Description:**
CHS-1420 is a recombinant human IgG1 kappa monoclonal antibody produced in CHO cells consisting of 2 heavy chains and 2 kappa light chains. Each heavy chain contains 451 amino acids and each light chain contains 214 amino acids. The antibody targets human TNF. The heavy chains contain typical N-linked glycans at a consensus glycosylation site on asparagine 301 that are predominantly core fucosylated, complex-type, bi-antennary structures, G0F/G0F (major species), and G0F/G1F, G1F/G1F, with small amounts of G2F. CHS-1420 has a molecular weight of approximately 148 kDa and has a typical IgG1 antibody structure of 16 disulfide bridges including 12 intrachain and 4 interchain. (b) (4)

Mechanism of Action (MoA):
CHS-1420 specifically binds to TNF-α and inhibits its function by blocking its interaction with TNFR-1 and TNFR-2. TNF-α, expressed by immune cells and other cells in response to infection or inflammation, is expressed both as a soluble cytokine (TNFα) and a membrane-bound (mTNF-α) form. CHS-1420 can also induce multiple Fc-dependent effector functions that depend on binding to m TNFα, including induction of regulatory macrophages, antibody mediated reverse signaling, ADCC and CDC. These activities have been suggested to contribute to inflammatory bowel disease indications, although the significance of the contribution of any of these individual mechanisms is not well established (based on literature review).

Potency Assay:
Coherus proposes to use three potency assays for CHS-1420. The first measures its ability to neutralize TNFα binding to cell surface TNFα receptors by assessing the CHS-1420 inhibition of TNFα induced apoptosis in U937 cells, a human monocyte cell line that expresses TNFα receptors.

The ADCC potency assay uses Chinese Hamster Ovary (CHO)-K1 cells that express a membrane-bound tumor necrosis factor alpha (mTNFα CHO-K1) and ADCC effector cells from an engineered Jurkat cell line. ADCC activity is measured as NFAT-driven luciferase activity resulting from binding of effector cells to CHS-1420.

C1q binding by ELISA is used as a surrogate for potential CHS-1420-dependent CDC activity.

- **Reference Materials:**
The primary reference standard (PRS) 1420-DS-111-RS was generated from CHS-1420 material for release and stability testing of CHS-1420 DS and DP. It was prepared from commercial-scale lot CHB1506CA manufactured by the (b) (4)

- **Critical starting materials or intermediates:**
(b) (4)

- **Manufacturing process summary:**
(b) (4)

- **Container closure:**
The DS container closures are (b) (4) that are adequate for storage at (b) (4) °C.

- **Dating period and storage conditions:**

The dating period for the drug substance is (b) (4) months when stored at (b) (4) °C. (b) (4) months of real time stability results were provided for clinical and pre-commercial stability lots manufactured by a process representative of the intended marketing process, as well as (b) (4) months of data for PPQ lots. Accelerated and stressed stability data also support that (b) (4) month expiration dating can be given to DS stored at (b) (4) °C based on the data available. The post-approval DS stability protocol proposes to place one lot of DS annually on stability.

C. Drug Product YUSIMRY Quality Summary:

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information, see the OBP quality technical assessment and the Drug Product Microbiology and Facilities technical assessment in Panorama.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process or failure of container closure integrity	(b) (4)	-
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		-
Container Closure Integrity (Contaminant)	Safety (Sterility assurance)	Breach during manufacture or storage		-
Deliverable Volume	Efficacy	DP manufacturing		-
Protein concentration	Efficacy	DS/DP manufacturing		-
Particulate matter/ Visible Particles	Impact on immunogenicity and safety	DS/DP manufacturing		-

Sub-visible particulates	Impact on immunogenicity and safety	DS/DP manufacturing	(b) (4)	-
pH	Impacts product stability and potentially PK/PD	Formulation, DS/DP manufacturing		-
Osmolality	Stability, safety, patient discomfort	Formulation, DS/DP manufacturing		-
Leachables (Process-related impurity)	Safety	Manufacturing equipment and container closure system (CCS)		-

- Potency and Strength:
  Potency for CHS-1420 is defined as the percent inhibition of the ability of TNFα to induce apoptosis in U937 cells, a human monocyte cell line that expresses TNFα receptors.

  CHS-1420 DP is supplied as a 40 mg/0.8 mL single-dose prefilled syringe.

- Summary of Product Design:
  YUSIMRY PFS: DP is supplied in a 1 mL long Type (b) (4) glass prefilled syringe with a 27 gauge thin walled ½ inch needle. Each PFS contains 40 mg/0.8 mL of CHS-1420 solution for injection.

- List of Excipients:
  There are no changes (b) (4) Each YUSIMRY PFS contains 0.8 mL of 50 mg/mL CHS-1420, (b) (4) histidine, (b) (4) glycine, (b) (4) NaCl, (b) (4) Polysorbate 80 (PS80), at pH 5.3. Additional excipient information is located in the Product Quality primary technical assessment in Panorama.

- Reference Materials:
  Reference materials for the DP are the same materials as used for the DS.

- Manufacturing process summary:
  (b) (4)

- Container closure:

The 40 mg/0.8 mL YUSIMRY drug product is supplied in a single-use 1 mL glass (b) (4) type (b) (4) PFS with a fixed 27 gauge, ½ inch stainless steel needle and a (b) (4) and latex-free elastomeric needle shield.

- **Dating period and storage conditions:**
  The YUSIMRY DP expiry will be 36 months or the age of the DS subtracted from 48 months, whichever is shorter, stored at 2 - 8° C. YUSIMRY may also be stored at a maximum of 25°C for a single period up to 14 days but not exceeding the original expiration date. The drug product (b) (4) .

D. Biopharmaceutics Considerations: N/A

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None.

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
(b) (4)			NAI	None	Approve
			Facility adequate	N/A	Approve
			Facility adequate	N/A	Approve
			Facility adequate	N/A	Approve
			Facility adequate	N/A	Approve
			Facility adequate	N/A	Approve
			Facility adequate	N/A	Approve
			Facility adequate	N/A	Approve

(b) (4)					
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)			Approve - Based on Previous History	PLI Waived	Approve
			Approve - Based on Previous History	N/A	Approve
			Approve - Based on Previous History	N/A	Approve
			Pre-license inspection requested	NAI	Approve

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) and (b) (4) proposed for adalimumab-aqvh DS and CH-1420 DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. (b) (4) Monitoring Protocols
2. Protocol for stability monitoring of the MCB
3. Protocol for the preparation, qualification, and storage of new WCB
4. Protocol for stability monitoring of new WCB
5. Protocol for the preparation, qualification, storage, and stability monitoring of new PRS and SRS
6. Drug substance post-approval stability protocol and stability commitment

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
    1. Drug product post-approval stability protocol and stability commitment
ii. Outstanding assessment issues/residual risk: None
iii. Future inspection points to consider: None

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

/s/

JENNIFER F SWISHER
11/19/2021 05:55:59 PM

RACHEL L NOVAK
11/22/2021 08:40:05 AM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	11/19/2021
Assessor:	Jim Barlow, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Jennifer Swisher PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research LRT 2
Application:	BLA 761216
Applicant:	Coherus BioSciences, Inc.
Submission Date:	December 18, 2020; May 6, 2021; September 20, 2021 and November 18, 2021
Product:	Yusimry (adalimumab-aqvh)
Dosage form(s):	Injection
Strength and Container-Closure:	40 mg/0.8 mL in a prefilled single-dose syringe
Purpose of assessment:	The Applicant submitted a biologics license application for CHS-1420 (conditionally approved nonproprietary name: adalimumab-aqvh), has been developed as a proposed biosimilar to the reference product, Humira® (adalimumab), licensed in the United States under Section 351(a) of the Public Health Service Act (AbbVie, Inc., North Chicago, IL 60064 U.S.A). This Biologics License Application is submitted for the purpose of licensure under Section 351(k) of the Public Health Service Act.
Recommendations:	The prescribing information, medication guide, patient labeling, instructions for use, container labels, and carton labeling are **acceptable** from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information, medication guide and instructions for use submitted on November 18. 2021 and the container labels and carton labeling submitted on 9/20/2021 were assessed and found to be acceptable from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on May 6, 2021)
- \\CDSESUB1\evsprod\bla761216\0008\m1\us\drft-pi.docx

- Medication Guide (submitted on May 6, 2021)
  \\CDSESUB1\evsprod\bla761216\0008\m1\us\drft-medguide.docx

- Instructions for Use (submitted on May 6, 2021)
  \\CDSESUB1\evsprod\bla761216\0008\m1\us\drft-chs-1420-pfs-ff-ifu.docx

- Container Labels for Blister Tray (submitted on May 6, 2021)

- Container Labels Prefilled Syringe (submitted on May 6, 2021)

- Carton Labeling (submitted on May 6, 2021)

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards
Container[4] Label Evaluation

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

Comment/Recommendation:
To applicant: Revise to include parenthesis around the proper name per recommended labeling practices.

RESPONSE: Revised as requested.

[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.

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

Comment/Recommendation:

To applicant: Revise to utilize the qualifying phrase "Manufactured by" to be in alignment with recommended labeling practices. (BLISTER only)

RESPONSE: Revised as requested.

To applicant: We recommend revising it to (b) (4) to read, "DO NOT FREEZE. Do not use if frozen, even if it has been thawed. Do not shake."

RESPONSE: Revised as requested.

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(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
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Acceptable

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

Comment/Recommendation: Considered a partial label therefore not required.

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**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

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

RESPONSE: The container label is transparent and does not cover the entire circumference and length of the syringe barrel, allowing for visual inspection

ACCEPTABLE

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

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

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

April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☒ N/A

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

Comment/Recommendation:

To applicant: Revise to include the package-type term "Single-Dose" beneath the route of administration

RESPONSE: Revised as requested

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
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-*	✓ Yes ☐ No ☐ N/A

512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic	

Comment/Recommendation: Acceptable

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Considered partial label. Not required.

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

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

Package[6] Labeling Evaluation

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

Comment/Recommendation:
To applicant: Revise your labeling so the proprietary name and non-proprietary name read as follows utilizing parenthesis to be in alignment with recommended labeling practice
Yusimry
(adalimumab-aqvh)
Injection

RESPONSE: Revised as requested. Acceptable

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

Comment/Recommendation:
To applicant: Revise to use the qualifying phrase "Manufactured by" as required. See 21 CFR 610.64.

RESPONSE: Revised as requested. Acceptable

Lot number or other lot identification (package labeling)	Acceptable

[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.

Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

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

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

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

Comment/Recommendation: States "Contains no preservatives." Acceptable

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation:
To applicant: We recommend revising it to [redacted] (b) (4) to read, "DO NOT FREEZE. Do not use if frozen, even if it has been thawed. Do not shake."

RESPONSE: Revised as requested.

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

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

Comment/Recommendation: States" For subcutaneous use only" Acceptable

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:
To Product Quality Reviewer: Is natural rubber utilized?

Natural Rubber is not utilized? Yes, the RNS is constructed of [redacted] (b) (4) made with no natural rubber latex.

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No

	☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: We recommend you list the inactive ingredients as listed in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients and include the pH adjusters to satisfy 21 CFR 201.100 (b)(5). to read as follows:
Each 40 mg/0.8 mL single-dose pre-filled syringe contains:
Adalimumab-aqvh.....40 mg
Glycine.....9.61 mg
L-histidine.....0.51 mg
L-histidine HCl monohydrate.....4.34 mg
Polysorbate 80.....0.80 mg
Sodium Chloride.....2.06 mg
Water for Injection, USP
Sodium hydroxide is added as necessary to adjust the pH.

RESPONSE: Revised as requested. Acceptable

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: States "No US Statement of Potency". Acceptable

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No

	☒ N/A

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

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

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

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
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

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

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**

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

Comment/Recommendation:
To applicant: Revised to be in alignment with most recently approved Humira labeling to read:
Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe (3)
RESPONSE: Applicant revised as requested. Acceptable

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

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

Comment/Recommendation:

To Product Quality Reviewer: Is the description of the drug substance accurate? Note that it is different than HUMIRA.
RESPONSE:
"clear to slightly opalescent, colorless to slightly yellow" is accurate and acceptable

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Product Quality Reviewer:
Is this MW accurate? Yes
Are these quantitative amounts accurate? Yes
Are you ok switching NaCl to sodium chloride? Yes
Were any pH adjuster utilized? Yes, Sodium Hydroxide was used to adjust the pH as necessary.
Is this pH accurate? Yes

To applicant: Revised to include the specific cell line to be in alignment with HUMIRA labeling. "(Chinese Hamster Ovary (CHO))"

RESPONSE: Revised as requested. Acceptable

To applicant: To Applicant: Revise to be in alphabetical order. pH adjustors information added per 21 CFR 201.100(b)(5).

RESPONSE: Applicant revised as requested. Acceptable

Full Prescribing Information	
(b) (4)	

[redacted] (b) (4)	

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

Comment/Recommendation:
To Product Quality Reviewer: Is this proposed drug product

Sterile? Yes

Preservative-free? Yes

Clear to slightly opalescent, colorless to slightly yellow? Yes

To Product Quality Reviewer:

Natural Rubber is not utilized? Yes, the RNS is constructed of [redacted] (b) (4) made with no natural rubber latex.

To Product Quality Reviewer:
Is the temperature/storage supported by data?
Do not Freeze?
Protect from light?

RESPONSE: Yes, all the proposed storage conditions are supported by the data.
To Product Quality Reviewer: is this 14 day stability at room temperature listed supported by data?

RESPONSE: Yes, all the proposed storage conditions are supported by the data.

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

Comment/Recommendation:

To applicant: Revised to utilize qualifying statement "Manufacture by".

RESPONSE: Revised as requested. Acceptable

Medication Guide Evaluation

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

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

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

Comment/Recommendation:
To applicant: Revised the order of the ingredients to match the order in section 11 of the Full PI.

RESPONSE: Revised as requested. Acceptable

To applicant: pH adjustors information added per 21 CFR 201.100(b)(5).

RESPONSE: Revised as requested. Acceptable

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
To applicant: Revised to include Manufacturing information to be in alignment with 21 CFR 208.20(b)(8)(iii).

RESPONSE: Revised as requested.

Patient Information Labeling Evaluation N/A

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
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 Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). 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

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
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *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:
To applicant: Revised to include Manufacturing information to be in alignment with 21 CFR 201.1.

RESPONSE: Revised as requested.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on 11/18/2021)
  \\CDSESUB1\evsprod\bla761216\0024\m1\us\drft-pi.docx
- Medication Guide (submitted on 11/18/2021)
  \\CDSESUB1\evsprod\bla761216\0024\m1\us\drft-medguide.docx
- Instructions for Use (submitted on 11/18/2021)
  \\CDSESUB1\evsprod\bla761216\0024\m1\us\drft-chs-1420-pfs-ff-ifu.docx
- Container Labels (submitted on 9/20/2021)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

James Barlow

Digitally signed by James Barlow
Date: 11/22/2021 08:54:30AM
GUID: 508da70800028bcca2d0465dabab258f
Comments: GM Jen, Attached is the labeling assessment (approval) for 761216. Thx for your help. All the best. Jim

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 11/23/2021 10:39:27AM
GUID: 508da6d7000262dc015dcdc5f6541612