CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761255Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation

- **Prefilled Syringe and Prefilled Pen:** Approval

(b) (4)

BLA Number: 761255
Review Number: 1
Review Date: October 24, 2022; December 7, 2022; December 12, 2022

Drug Name/Dosage Form	Idacio [adalimumab-aacf] Injection
Strength/Potency	• Single-dose prefilled glass syringe: 40 mg/0.8 mL • Single-dose prefilled pen: 40 mg/0.8 mL (b) (4)
Route of Administration	subcutaneous infusion
Rx/OTC dispensed	Rx
Indication	• Rheumatoid arthritis (RA) • Juvenile idiopathic arthritis (JIA) (2 years of age and older) • Psoriatic arthritis (PsA) • Ankylosing spondylitis (AS) • Crohn's disease (CD) in adults and pediatric patients 6 years of age and older • Ulcerative Colitis (UC) in adult patients • Plaque Psoriasis (PsO)
Applicant/Sponsor	Fresenius Kabi USA, LLC

Product Overview

Idacio (adalimumab-aacf, MSB11022) is a recombinant human IgG1 monoclonal antibody produced in CHO cells. MSB11022 binds to Tumour Necrosis Factor-alpha (TNFα) and neutralizes its biological function by blocking its interaction with TNF Receptors, TNFR1 (p55) and TNFR2 (p75), which in turn reduces inflammatory response. Idacio is a proposed biosimilar to US-licensed Humira in the 40 mg/0.8 mL strength and its proposed mechanism of action is the same as that of US-licensed Humira. (b) (4) Idacio drug product is a sterile solution (b) (4) and supplied as either a single-dose prefilled syringe (PFS), single-dose prefilled pen (PFP) (b) (4) at the 40 mg/0.8 mL strength.

Quality Review Team

	BLA	
Discipline	**Reviewer**	**Branch/Division**
Drug Substance and Drug Product	Jun Liu/Frances Namuswe	DBRRIII/OBP
Comparative Analytical Assessment	Jun Liu/Frances Namuswe	DBRRIII/OBP
Microbiology Drug Substance and Drug Product	Maria Candau-Chacon/ Virginia Carroll	DBM/OPMA
Facility	Richard Ledwidge/Virginia Carroll	DBM/OPMA
Labeling	Vicky Borders-Hemphill	IO/OBP
Immunogenicity	Ian Mcwilliams/Frances Namuswe	DBRRIII/OBP
CDRH reviewer	Jake Lindstrom	OPEQ/OHTIII/DHTIIIC
Application Team Lead	Frances Namuswe	DBRRIII/OBP
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Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
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Cross-disciplinary Team Lead	Anil Rajpal	OND/OII/DRTM
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Pharm/Tox	Eleni Salicru/ Tim Robison	OND/OII/DPTII
Clinical Pharmacology	Qianni Wu/ Ping Ji	OTS/OCP/DIIP
Clinical Statistics	Guoying Sun/ Wanjie Sun	OTS /OB/DBVII

1. Names:
   - a. Proprietary Name: Idacio
   - b. Trade Name: Idacio
   - c. Non-Proprietary/USAN: Adalimumab-aacf
   - d. CAS name and number: 331731-18-1
   - e. Common name: MSB11022
   - f. INN Name: Adalimumab-aacf
   - h. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [MSB11022]
   - i. Other names: G.20058801 (company code)

2. Pharmacological class: Tumor necrosis factor blocker

Submissions Reviewed

Submission:	Date Received:	Assessments Completed (yes or no)
SN 0001	12/13/2021	Yes
SN 0002	12/31/2021	Yes
SN 0003	1/18/2022	Yes
SN 0004	1/27/2022	Yes
SN 0007	2/18/2022	Yes
SN 0013	4/14/2022	Yes
SN 0014	4/22/2022	Yes
SN 0018	5/17/2022	Yes
SN 0020	5/18/2022	Yes
SN 0021	5/20/2022	Yes
SN 0025	6/30/2022	Yes
SN 0026	7/18/2022	Yes
SN 0027	7/29/2022	Yes
SN 0028	8/3/2022	Yes
SN 0029	8/4/2022	Yes
SN 0030	8/12/2022	Yes
SN 0032	8/17/2022	Yes
SN 0034	8/30/2022	Yes
SN 0035	9/16/2022	Yes
SN 0036	9/20/2022	Yes
SN 0037	9/27/2022	Yes

SN 0038	9/29/2022	Yes
SN 0040	10/11/2022	Yes
SN 0041	10/13/2022	Yes
SN 0042	10/14/2022	Yes
SN 0047	10/31/2022	Yes
SN 0050	11/09/2022	Yes
SN 0054	12/08/2022	Yes
SN 0055	12/09/2022	Yes
SN 0056	12/12/2022	Yes

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents

A. DMFs

DMF#	DMF Type	DMF Holder	Item Referenced	Code[1]	Date Assessment completed	LOA	Comment (status)
(b) (4)	III		(b) (4)	1	5/27/2021 6/26/2020	Yes	Adequate
	III			1	07/22/2021	Yes	Adequate
	III			3	N/A	Yes	Sufficient information included in BLA submission
	III			3	N/A	Yes	Sufficient information included in BLA submission
	II			3	12/8/2022	Yes	Sufficient information included in BLA submission
				3	12/8/2022	Yes	Sufficient information included in BLA submission
	III			3	N/A	Yes	Sufficient information included in BLA submission

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")

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application

Application Number	Description
IND	124098
[redacted] (b) (4)	

3. Consults

DISCIPLINE/TOPIC	DATE COMPLETED	REVIEWER	STATUS	RECOMMENDATION
CDRH for PFS, PFP [redacted] (b) (4)	12/12/2022	Jake Lindstrom	Complete	Approval

4. Environmental Assessment or Claim of Categorical Exclusion

Fresenius Kabi claims categorical exclusion from the requirement to prepare an environmental assessment per 21 CFR 25.31(b) and claims to their knowledge there are no extraordinary circumstances as described in 21 CFR 25.15(d). Categorical exclusion can be granted for Idacio.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Idacio PFS and PFP

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761255 for Idacio manufactured by Fresenius Kabi USA, LLC in the PFS and PFP. The data submitted in this application are adequate to support the conclusion that the manufacture of Idacio in the PFS and PFP is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Idacio is highly similar to US-licensed-Humira, 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.

[redacted] (b) (4)

(b) (4)

B. **Approval Action Letter Language for Idacio PFS and PFP**

- Manufacturing location:
  - **Drug Substance**:

    (b) (4)

  - **Drug Product**:

    (b) (4)

    Drug Product device assembly, labeling and secondary packaging:
    Fresenius Kabi Austria GmbH – (FK-Werndorf),
    Am Gewerbepark 6 8402 Werndorf, Austria
    FEI: 3003708554

- Fill size and dosage form:
  - Single-dose Prefilled Syringe: 40 mg/0.8 mL, Injection
  - Single-dose Prefilled Pen: 40 mg/0.8 mL, Injection

- Dating period:
  - Drug Product: 36 months at 2-8°C
  - Drug Substance: (b) (4) months at (b) (4) °C

- Exempt from lot release
  - Yes, Idacio is a specified product and exempted from lot release per FR 95-29960

C. (b) (4)

D.

Facility Inspections

(b) (4)

(b) (4)

E. Assessment Summary

Idacio is a proposed biosimilar to US-licensed Humira (referred to hereafter as US-Humira) and has the same dosage form, strength, and route of administration as US-Humira. Fresenius Kabi is seeking licensure for the following indications for which US-Humira is licensed: Rheumatoid arthritis (RA), Juvenile idiopathic arthritis (JIA) (2 years of age and older), Psoriatic arthritis (PsA), Ankylosing spondylitis (AS), Crohn's disease (CD) in adults and pediatric patients 6 years of age and older, Ulcerative Colitis (UC) in adult patients, Plaque Psoriasis (PsO).

The data submitted support that MSB11022 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).

Assessment of the manufacturing information provided in the application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for removal and control of adventitious agents. The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. CDRH's evaluation of the device component of the product and the PFS and PFP assembly site at Fresenius Kabi Austria GmbH-(FK-Werndorf) identified no approvability issues from a device component perspective.

From a facility standpoint, the recommendation is approval for Idacio in the PFS and PFP (b) (4)

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

F. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The following post marketing commitments were proposed and accepted by the Applicant for Idacio PFS and PFP:

Microbiology

4376-2 To repeat the bacterial retention study (b) (4)
Final Report Submission: 01/2023

4376-3 To repeat the sterilization validation (b) (4)
Final Report Submission: 01/2023

Product Quality

4376-4 To update the drug substance and drug product release and stability specifications for MSB11022 to include control for purity (monomer) by SE-HPLC and purity (main peak) by non-reduced CE-SDS with appropriately justified acceptance criteria. The updated drug substance and drug product release and stability specifications, method validation data, and other supporting data will be submitted to the BLA per 21 CFR 601.12.
Final Report Submission: June 2023

4376-5 To update the drug substance and drug product release specifications for MSB11022 to include justified analytical thresholds for new peaks detected by the peptide mapping and icIEF identity tests. The updated release acceptance criteria, method validation data, and other supporting information will be submitted to the BLA per 21 CFR 601.12.
Final Report Submission: June 2023

4376-6 To update the system suitability testing and criteria for the protein content by O.D. analytical method in the MSB11022 specifications. The updated method procedure, system suitability criteria, and supporting studies will be submitted to the BLA per 21 CFR 601.12.
Final Report Submission: March 2023

4376-7 To revise the in-process control (IPC) acceptance criteria (b) (4) to ensure meeting the label claim. The

updated IPC acceptance criteria and supporting studies and data will be submitted to the BLA per 21 CFR 601.12.
Final Report Submission: March 2023

4376-8 To implement identity test(s) for final MSB11022 drug product assembled in the prefilled syringe with the autoinjector (b) (4) devices after labeling and secondary packaging per 21CFR 610.14. The identity test(s) will distinguish MSB11022 drug product (Process C/Acetate) proposed for the US market from the Process A/Citrate drug product if manufactured at the same facility. The final identity test and supporting information will be submitted to the BLA per 21 CFR 601.12
Final Report Submission: June 2023

II. Evaluation of the Comparative Analytical Assessment

A. Overview and Conclusions

Fresenius Kabi is seeking approval of 40 mg/0.8 mL MSB11022 in a single-dose prefilled syringe (PFS), single-dose prefilled pen (PFP), (b) (4) U.S.-licensed-Humira is available at the 40 mg/0.8 mL strength in a PFS, PFP, and single-dose vial. To support a demonstration that MSB11022 is highly similar to US-licensed Humira (referred to hereafter as US-Humira), Fresenius Kabi performed a comparative analytical assessment using 41 lots of US-Humira (40 mg/0.8 mL PFS) with expiration dates ranging from May 2013 through October 2021, 30 lots of MSB11022 drug product (DP) (40 mg/0.8 mL PFS) and 3 lots of MSB11022 drug substance (DS). To support the analytical component of the scientific bridge, Fresenius Kabi used 30 lots of EU-approved Humira (EU-Humira, 40 mg/0.8 mL PFS) with expiration dates ranging from May 2012 through September 2021. The ages of US-Humira and EU-Humira at the time of testing were adequate to capture potential differences or variability over time for US-Humira and EU-Humira.

The MSB11022 manufacturing process underwent multiple changes during development. One of the major changes was change from a citrate formulation, the same formulation as US-Humira, to an acetate formulation to address patent issues. The other major change was from the initial DS manufacturing Process A to Process C to better align the glycan profile of MSB11022 with that of US- Humira. MSB11022 lots manufactured using the initial DS process and formulation (A/citrate), DS Process A and the acetate formulation (A/Acetate), and the final proposed commercial formulation and process (C/Acetate) were used in the clinical studies submitted to the BLA (See Table B below). Eight (8) independent lots of MSB11022 DP and 3 independent batches of DS from the proposed final commercial process and formulation (C/Acetate) are included in the CAA. In addition, 22 DP lots from the earlier DS manufacturing process and formulations (A/Citrate and A/Acetate) are included in the CAA because these lots were used in the clinical studies or in other process characterization studies that support the validated process and control strategy for the BLA.

(b) (4)

The change from DS Process A to C resulted in targeted changes in the glycan profile and other related quality attributes of proposed commercial MSB11022 such as ADCC activity (see Section D for details) to be more aligned with those of US-Humira. Other quality attributes of DS process A and C material are overall analytically comparable.

MSB11022 in PFP (b) (4) was not included in the CAA. This approach is acceptable because the Applicant provided adequate data to show that assembly of the PFS into the secondary packaging components of the PFP does not impact product quality attributes. In addition, the Applicant provided adequate data to support analytical comparability of drug product in the PFS (b) (4). The comparability and CAA results support the conclusion that MSB11022 40 mg/0.8 mL (whether in the (b) (4) PFS, or PFP) is highly similar to US-Humira 40 mg/0.8 mL.

The comparative analytical assessment included comparison of physicochemical and functional quality attributes of MSB11022, US-Humira and EU- Humira using an extensive set of orthogonal methods, as well as comparison of their degradation profiles under forced degradation conditions. The Applicant used a reasonable risk-based data analysis approach to evaluate the analytical results. The highest and moderate ranking risk attributes amenable to quantitative analysis were tested using quantitative assays and were evaluated using quality ranges (QR) calculated to account for reference product manufacturing variability, attribute criticality, and assay variability. For normally distributed data, QR were established as mean ± xSD, with x=2.58 for high criticality attributes and x=3 for selected moderate to high criticality attributes. The standard deviation multiplier used to establish each quality range was scientifically justified. In the cases where the normality of the distribution could not be assumed, the total range was used instead of Mean ± xSD. Low criticality attributes, attributes not amenable to quantitative analysis regardless of criticality, or those analyzed by quantitative comparison in orthogonal assays, were evaluated using visual graphical comparisons and descriptive statistics, where available. Results from method validation or qualification studies support the suitability of the methods used in the analytical assessment.

Our assessment of the MSB11022 and US-Humira data supports that MSB11022 40 mg/0.8 mL is highly similar to US-Humira 40 mg/0.8 mL, notwithstanding minor differences in clinically inactive components. MSB11022 40 mg/0.8 mL in a single-dose PFS, single-dose PFP, (b) (4) is manufactured to have the same strength, dosage form and route of administration as 40 mg/0.8 mL US-Humira in a single-dose PFS, single-dose PFP. (b) (4). The Applicant used a comprehensive set of analytical methods that were suitable to evaluate the critical quality attributes of MSB11022 and US-Humira to support that the products are highly similar. The number of lots tested and data analysis approaches used were appropriate to allow for a meaningful evaluation of the results of the analytical studies. The differences observed in a subset of the quality attributes do not preclude a determination that MSB11022 and US-Humira are highly similar and do not preclude a conclusion that clinical studies using MSB11022 manufactured from process A are relevant to the assessment of biosimilarity.

In addition, Fresenius used three-way pairwise comparisons of MSB11022 40 mg/0.8 mL, US-Humira 40 mg/0.8 mL, and EU-Humira 40 mg/0.8 mL to establish the analytical component of the scientific bridge between MSB11022, US-Humira, and EU-Humira to support the relevance of the data generated from clinical studies using EU-Humira as the comparator in the assessment of biosimilarity. Our

assessment of the data supports that the Applicant established the analytical component of the scientific bridge between MSB11022, US-Humira, and EU-Humira. This supports the relevance of the data generated from clinical studies using EU-Humira.

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	Amino acid sequence	Yes	Yes
	Molecular weight (Intact, heavy chain, light chain, glycated, C-terminal Lys truncated)	Yes	Yes
	N-terminal sequence	Yes	yes
	Disulfide mapping	Yes	Yes
Amino acid modifications	Methionine Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	Succinimide	Yes	Yes
	N-terminal pyroglutamate	Yes	Yes
	C-terminal Lys truncation	Yes	Yes
	C-terminal Proline amidation	Yes	Yes
Product related variants and impurities	Purity (monomer)	Yes	Yes
	Dimer and HMW Species	Yes	Yes
	Purity (HC + LC)	Yes	Yes
	LMW species	Yes	Yes
	Non-glycosylated HC	Yes	Yes
	isoelectric point by icIEF	Yes	Yes
	Isoform distribution (icIEF, with & w/out CPB)	Yes	Yes
Glycosylation	Total Afucosylation	Yes	Yes
	High Mannose	Yes	Yes
	Total Galactosylation and non-galactosylated	Yes	Yes
	Total Sialylation	Yes	Yes
	Types of sialylation (NANA, NGNA)	Yes	Yes
	Major glycans G0F, G1F, G1F iso	Yes	Yes
High Order Structure	Disulfide bonds	Yes	Yes
	Free thiol content	Yes	Yes
	Secondary structure	Yes	Yes
	Tertiary Structure	Yes	yes
	Melting Temperature	Yes	Yes
Bioactivity – Fab mediated	Tumor necrosis factor (TNF)-α neutralization (inhibition of sTNF-induced cytotoxicity)	Yes	Yes
	Reverse Signaling (Apoptosis induced in mTNFα-expressing cells)	Yes	Yes
	sTNF-α binding	Yes	Yes
	tmTNF-α binding	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar?	Supports the Analytical Component of the Scientific Bridge?
Bioactivity – Fc mediated	Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes	Yes
	Complement-dependent cytotoxicity (CDC)	Yes	Yes
	Induction of regulatory macrophages in an allogeneic MLR	Yes	Yes
	FcRn binding	Yes	Yes
	FcγRI binding	Yes	Yes
	FcγRIIa (R131 and H131) binding	Yes	Yes
	FcγRIIb binding	Yes	Yes
	FcγRIIIa (V158 and F158) binding	Yes	Yes
	FcγRIIIb binding	Yes	Yes
	C1q binding	Yes	Yes
Drug Product Attributes	Protein concentration	Yes	Yes
Forced degradation studies	Thermal Stress	Yes	Yes
	Oxidative stress	Yes	Yes
	High pH	Yes	Yes
	Low pH	Yes	Yes
	Light exposure	Yes	Yes
	Mechanical stress	Yes	Yes

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

The clinical development of MSB11022 included the six clinical studies summarized in the table below.

Table B Clinical Studies Submitted in the BLA

Study (Indication)	Study Type/Purpose	MSB11022-DP Lot No.	Application Device	Reference/Comparator
FKS022-002 (Healthy subjects)	Comparative PK study	BA050433P (C/Acetate)[1] BA058889P (C/Acetate)[1] BA058865 (A/Citrate) BA062864 (A/Citrate)	PFS	US-licensed Humira
EMR200588-001 (Healthy subjects)	Comparative PK study	AL1D003 (A/Citrate)	PFS	US-licensed Humira EU-approved Humira
EMR200588-002 (Plaque psoriasis)	Comparative efficacy and safety study	AL2F001 (A/Citrate) AL2F003 (A/Citrate)	PFS	EU-approved Humira
EMR200588-003 (Healthy subjects)	Comparative PK study	AL2F004 (A/Citrate) AL3F007 (A/Acetate)	PFS	EU-approved Humira
MS200588-0004 (Rheumatoid arthritis)	Safety study	AL3H002 (A/Acetate) AL3F007 (A/Acetate)	PFS	EU-approved Humira
FKS022-001 (Healthy subjects)	Comparative PK study	AI: BA050433PT (C/Acetate) PFS: BA050433P (C/Acetate)	PFS and AI	No comparator used

[1] To-be-marketed process and formulation.

Based on discussion with OND, four clinical studies FKS022-002, EMR200588-001, EMR200588-002 and FKS022-001 are used to support biosimilarity of MSB11022 in this BLA. EU-Humira was used as a comparator in the following two studies:

- Study EMR200588-001: A randomized, double-blind, parallel-group, single-dose study to compare the PK, safety/tolerability, and immunogenicity of MSB11022, US-Humira, and EU-Humira in healthy subjects
- EMR200588-002: A randomized, double-blind, confirmatory study to evaluate the efficacy, safety, and immunogenicity of MSB11022 compared with EU-Humira in subjects with moderate to severe chronic plaque psoriasis

To support the relevance of the clinical comparative data generated using EU-Humira as a comparator product, Fresenius Kabi performed a three-way analytical comparison of MSB11022 to US-Humira, MSB11022 to EU-Humira, and EU-Humira to US-Humira using the same analytical methods used for the assessment of highly similar between MSB11022 and US-Humira. The differences observed in the analytical studies (See section D below), do not preclude a determination that the three-way analytical component of the scientific bridge is acceptable. The results of the assessment support the analytical component of the three-way scientific bridge.

D. Assessment of Comparative Analytical Study Results

Comparative analytical assessment criteria were met for all attributes evaluated with quality ranges or visual comparison with the following exceptions:

Critical Quality Attributes with Differences	Related Critical Quality Attributes
Glycosylation • Afucosylation • Galactosylation • High mannose • Major glycans G0F, G1F	During development, per advice from the Agency, the Applicant made changes to the MSB11022 manufacturing process to better align the glycan profile of the proposed commercial material with that of US-Humira. As a result, most glycan species for the MSB11022 proposed commercial process (C/Acetate) are within the quality range (QR) of US-Humira and EU-Humira. These results, based on the analysis of 11 independent lots, support that the commercial (C/Acetate) material is highly similar to US-Humira and the establishment of the analytical component of the scientific bridge to justify the relevance of clinical data using EU-Humira as a comparator. However, the results for several glycan species including afucosylated species, galatosylated species, high mannose, and the major glycans G0F and G1F for the 22 process A lots (A/Citrate and A/Acetate) are generally either out of the QR of US-Humira or EU-Humira or trend towards the limits of these QRs. Because lots of MSB11022 manufactured using process A were used in some of the comparative clinical studies, these differences in glycosylation are evaluated to support the suitability of the corresponding clinical studies to the assessment of biosimilarity. • Afucosylated species may impact binding to Fcγ receptors, such as FcγRIIIa, which is the primary mechanism that can lead to ADCC activity. Therefore, differences in afucosylated species may result in differences in ADCC activity. Lower ADCC activity was observed for process A lots compared to the process C lots, US-Humira and EU-Humira. See below for further assessment of differences in ADCC activity.

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	• Increased galactosylation may increase C1q binding and CDC activity. Induction of CDC on tmTNF expressing target cells is a plausible mechanism of action for the Crohn's disease (CD) and ulcerative colitis (UC) indications. Of note, in addition to the differences in galactosylation levels for the Process A lots, the galactosylation levels for 4 out the 11 Process C lots ranging from 20.9 – 21.1% were also slightly higher than the QR upper limit 20.6% for US-Humira. However, the noted differences in galactosylation did not result in differences in CDC activity or C1q binding. Therefore, the observed differences in galactosylation of Process A and Process C lots do not preclude demonstration that MSB11022 is highly similar to US-Humira, determination that clinical studies using Process A lots are relevant to the assessment of biosimilarity, or establishment of the analytical component of the scientific bridge. • High mannose content may impact the PK of antibodies by increasing uptake of antibodies through the mannose receptor in the liver. In addition, because high mannose species are a subset of afucosylated, they could also impact ADCC activity. PK comparability between MSB11022 (A/Citrate) and MSB11022 (C/Acetate) was demonstrated (see section 5 in the BMER). Therefore, the differences observed in high mannose species between MSB11022 (A/Citrate) and MSB11022 (C/Acetate) do not preclude a determination that clinical studies using Process A lots are relevant to the assessment of biosimilarity. See below for further assessment of differences in ADCC activity.
Total Sialylation	MSB11022 (both Process A and C lots) has higher total sialylated species (1.1 - 1.8%) for Process A and (1.1 – 1.3 %) for Process C compared to US-Humira (0.29%) and EU-Humira (0.29%). While sialyation has a low potential to impact Fc effector functions, presence of significant levels of sialylated species in mAbs has the potential to impact other antibody functional domains and could result in differences in bioactivity related to the Fab arm functionality. In addition, sialylated glycan levels may increase serum half-life. However, the observed sialylated levels for MSB11022 are overall relatively low. These low levels are corroborated by results for sialylated glycan analysis by DMB-UPLC, which also show low levels of NANA species and no NGNC species for MSB11022, US-Humira and EU-Humira. Therefore, the noted differences are not expected to have a significant impact on product quality, biological activity or PK. This is supported by similar binding to sTNF-α and tmTNF-α and similar PK for MSB11022, US-Humira and EU-Humira (see section 5 in the BMER). Similar ADCC activity for MSB11022 (C/Acetate), US-Humira and EU-Humira further supports that the differences in sialylated species did not impact ADCC activity. Therefore, the observed differences in total sialylated species do not preclude a demonstration that MSB11022 is highly similar to US-Humira, a demonstration that clinical studies using Process A lots are relevant to the assessment of biosimilarity, or establishment of the analytical component of the scientific bridge.
FcγRIIIa binding	FcγRIIIa V158 and F158 binding for all MSB11022 (C/Acetate) lots and FcγRIIIa V158 binding for all Process A lots was within the QR of US-Humira and the EU-Humira. For FcγRIIIa F158 binding for Process A lots (5.3 – 10.8 KD), 6/22 and 5/22 lots are slightly outside the QR of US-Humira (4.4 – 9.5 KD) and EU-Humira (3.2 – 9.7 KD)), respectively. Differences could be due to method variability; however, because differences in FcγRIIIa binding could impact ADCC activity, see below for assessment of ADCC activity.
FcγRIIIb binding	FcγRIIIb binding for all MSB11022 lots is visually within the EU-Humira min-max range, and all C/Acetate lots are within the US-Humira min-max range. However, 6/22 process A lots

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	are out of the US-Humira min-max range, which could be due to method variability. FcγRIIIb binding has not been demonstrated to play a role in the efficacy or safety of adalimumab. Therefore, the noted differences in FcγRIIIb binding are not expected to adversely impact product quality and do not preclude a determination that clinical studies using Process A lots are relevant to the assessment of biosimilarity.
ADCC activity	ADCC activity for all MSB11022 (C/Acetate) lots using three different ADCC assays (whole blood cell ADCC-induced cytotoxicity, FcγRIIIa ADCC reporter assay, and NK-enriched PBMC ADCC-induced cell death assay) is within the QR of US-Humira and EU-Humira. However, ADCC activity for MSB11022 Process A lots trends lower or is below the QR of US-Humira and EU-Humira in all orthogonal assays. These differences are most evident with the NK-enriched PBMC ADCC-induced cell death assay for which all Process A lots (min-max range 23 – 52 KD) are outside the QR of US-Humira (58 – 136 KD), and EU-Humira (61 – 153 KD). These results are consistent with the targeted change in the glycan profile of MSB11022 to better match the proposed commercial Process C material with US-Humira and EU-Humira. TNF-α neutralization is the primary mechanism of action (MoA) of adalimumab products across all indications. ADCC activity is a potential MoA for the CD and UC indications, which were not directly studied in the MSB11022 clinical program. Thus, although there are differences in ADCC activity of MSB11022 Process A lots used in the comparative clinical study in patients with plaque psoriasis (EMR200588-002), these differences would not be expected to affect efficacy in this patient population. The proposed commercial Process C lots have similar ADCC activity as US-Humira and EU-Humira. Even though there are differences in ADCC activity between MSB11022 (A/Citrate) and MSB11022 (C/Acetate), these differences do not preclude a determination that clinical studies using Process A lots are relevant to the assessment of biosimilarity or establishment of the analytical component of the scientific bridge.
Melting Temperature	Three thermal transitions typical of an IgG1 were identified for MSB11022, US-Humira and EU-Humira. All MSB11022 lots (Process C and Process A) were within the QR of US-Humira for thermal transitions Tm-1 (CH2) and Tm-2 (Fab). However, for Tm-3 (CH3), 3 MSB11022 lots (C0101201, C0101301 and C0101401) all from the final commercial C/Acetate process are higher and out of the QR of both US-Humira and EU-Humira. In addition, 1 A/Acetate (AL3H002) and 1 C/Acetate (BA050433P) lot are slightly higher and out of the QR for EU-Humira, but within the QR of US-Humira. The Applicant provided sufficient data to support that these differences were likely due to analytical method variability between analytical sessions, as supported by results of bridging samples tested in different sessions. For example, Tm3 for reference standard RHS Adalimumab 2015/01 tested in earlier studies ranged from (b) (4) °C. Tm3 for the same reference standard was (b) (4) °C in the last session where the 3 lots from the final commercial C/Acetate process were tested. Therefore, the observed differences appear to be method related and do not reflect actual differences between the products. Therefore, they do not preclude a demonstration that MSB11022 is highly similar to US-Humira, a demonstration that clinical studies using Process A lots are relevant to the assessment of biosimilarity, or establishment of the analytical component of the scientific bridge.
Purity (HC + LC) and NGHC	Purity (HC+LC) by reduced CE-SDS for the Process C lots is within the QR of US-Humira (96.4 - 97.9%) and EU-Humira (94.8 – 99.1%), with a slightly higher (~≤0.5%) mean purity for Process C lots compared to US-Humira and EU-Humira. Purity for most of the Process A lots (97.5 – 98.4%) is out of the QR of US-Humira, with a mean purity ~1% higher than the mean purity for US-Humira and EU-Humira. Concomitantly, the level of non-

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	glycosylated heavy chain (NGHC) impurity by the same method is within US-Humira (mean = 1.31%; min-max 1.1 – 1.5%) and EU-Humira (mean = 1.27%; min-max 1.0 – 2.6%) ranges for most Process C lots (mix-max 0.9 – 1.6%) but lower for all process A lots (mean =0.60%; min-max 0.4 – 0.8%).The slightly higher purity for Process A lots does not adversely impact product quality of MSB11022. The observed differences do not preclude a demonstration that clinical studies using Process A lots are relevant to the assessment of biosimilarity or establishment of the analytical component of the scientific bridge.
Deamidation	The deamidated species for 33% of Process A and Process C MSB11022 lots (11 out of 33) are out of the QR for US-Humira and 41% (14 out of 33) are out of the QR for EU-Humira. For most of these lots, the deamidated species in the MSB11022 lots are lower than the QR of US-Humira and EU-Humira, and therefore do not adversely impact product quality of MSB11022. The deamidated species for two Process A MSB11022 lots are slightly above the QR of US-Humira and EU-Humira. These differences are not expected to impact product quality of MSB11022. Therefore, the differences do not preclude a demonstration of that MSB11022 is highly similar to US-Humira, a demonstration that clinical studies using Process A lots are relevant to the assessment of biosimilarity, or establishment of the analytical component of the scientific bridge.
Degradation under forced degradation conditions • Thermal stress • Low pH • Light exposure	• Under low pH, significant differences in the rate of change in main peak and acidic clusters by icIEF, oxidized species by SCX-HPLC, HMWS by SE-HPLC, purity by reduced CE-SDS, LMWS by non-reduced CE-SDS, and tertiary structure by intrinsic fluorescence were observed for US-Humira and EU-Humira lots compared to MSB11022 lots. US-Humira and EU-Humira were more adversely affected for all quality attributes above. The most significant differences were observed in rate of formation of LMW variants, with % change in LMWS by CE-SDS <2% for MSB11022, and as high as 10 – 45% for US-Humira and EU-Humira. The Applicant attributed the differences in LMWS formation to presence of protease host cell protein impurities such as cathepsin L in US-Humira and EU-Humira compared to MSB11022, and provided sufficient data to support that formation of LMWS in US-Humira and EU-Humira is significantly reduced in the presence of protease inhibitors. All the differences in the quality attributes noted above do not adversely impact product quality and safety of MSB11022. Therefore, they do not preclude a demonstration that MSB11022 is highly similar to US-Humira, or establishment of the analytical component of the scientific bridge. • Under light exposure, HMWS by SE-HPLC and LMWS by non-reduced CE-SDS increase significantly in MSB11022 A/Citrate and C/Acetate lots (up to 18.1% change in HMWS and 5.5% in LMWS) compared to US-Humira (up to 8.3% change in HMWS and 1.5% in LMWS) and EU-Humira (up to 8.5% change in HMWS and 2.5% in LMWS). Differences in HMWS and LMWS could impact biological activity or safety. However, potency stability trends by an in vitro potency assay that reflects the primary MOA for all 3 products are similar. Thus, although MSB11022 may be more susceptible to light stress, the differences do not significantly impact potency. In addition, because MSB11002 DP is protected from light by secondary packaging and the changes seen in MSB11022 under the proposed real time storage conditions are significantly low, the potential adverse impact of light exposure on MSB11022 product quality is low. Therefore, the observed differences do not preclude a demonstration that MSB11022 is highly similar to US-Humira, or establishment of the analytical component of the scientific bridge. • Under thermal stress, a slightly lower rate of HMWS formation by SE-HPLC was noted for MSB11022 C/Acetate (~ 1.2% change) compared to MSB11022 A/Citrate (~1.4 -

Critical Quality Attributes with Differences	Related Critical Quality Attributes
	1.7% change), US-Humira (1.5 – 1.9% change) and EU-Humira (1.5 – 1.6% change). These differences could be due to differences in formulation or age of samples at time of analysis. They do not negatively impact product quality and safety of commercial MSB11022; therefore, they do preclude the demonstration of that MSB11022 is highly similar to US-Humira or establishment of the analytical component of the scientific bridge.

E. Same Strength(s)

MSB11022 has the same dosage form and route of administration as U.S.-licensed Humira. Fresenius Kabi is seeking approval of 40 mg/0.8 mL MSB11022 in a single-dose prefilled syringe (PFS), single-dose prefilled pen (PFP) (b) (4) U.S.-licensed-Humira is available at the 40 mg/0.8 mL strength in a PFS, PFP, and single-dose vial[2]. Fresenius Kabi is seeking approval of MSB11022 40 mg/0.8 mL for the same strength as U.S.-licensed-Humira 40 mg/0.8 mL. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed (b) (6).

The proposed presentations of MSB11022 40 mg/0.8 mL 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 U.S.-licensed Humira (40 mg/0.8 mL). The strength of MSB11022 40 mg/0.8 mL in the PFS, PFP (b) (4) is the same as that of U.S.-licensed Humira 40 mg/0.8 mL.

III. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Tables 1 and 2 summarize the CQAs intrinsic to adalimumab-aacf API and the Idacio drug substance manufacturing process, respectively. These CQAs are based on both the Applicant's determined CQAs and quality attributes the Agency considers CQAs for this class of products, regardless of how they were classified by the Applicant.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy **(Additional comments)** (b) (6)
Identity (General)	Safety and Efficacy	Intrinsic to the molecule	
Primary Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule - Expression construct and cell line	

[2] U.S. Prescribing Information, U.S.-Licensed-Humira. Accessed December 6, 2022, from https://www.accessdata.fda.gov/scripts/cder/daf/

(b) (4)

Higher Order Structure	Efficacy and Immunogenicity	- Intrinsic to the molecule
TNF binding and neutralization (potency)	Efficacy	- Intrinsic to the molecule - Impacted by the DS manufacturing process
Potency (ADCC)	Efficacy	-Intrinsic to molecule -Impacted by the DS manufacturing process
Potency (CDC)	Efficacy	-Intrinsic to molecule -Impacted by the DS manufacturing process
Potency (reverse signaling)	Efficacy	-Intrinsic to molecule -Impacted by the DS manufacturing process
Glycosylation (product related variants)	Efficacy, PK	- Intrinsic to the molecule - Impacted by the DS manufacturing process
High Molecular Weight Species (product related impurities)	Efficacy and Safety, including Immunogenicity	- Manufacturing process - May increase on storage
Low Molecular Weight Species (product related impurities	Efficacy and Safety	- Manufacturing process - May increase on storage
Misfolded/disulfide mispairing species	Efficacy, immunogenicity, PK	-Manufacturing process
Charge Heterogeneity (product variants)	Potential impact on Efficacy, PK	- Intrinsic to the molecule (e.g., from PTMs) - DS and DP manufacturing process - May increase on storage (e.g., oxidation, deamidation)
Post-translation Modification (oxidation, deamidation, & succinimide)	Efficacy, safety, immunogenicity	-DS and DP manufacturing - May increase on storage
Sequence Variants	Efficacy, PK, immunogenicity	DS manufacturing process

B. Idacio [adalimumab-aacf] Drug Substance Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy (Additional comments)
Appearance (general)	Safety	- Manufacturing process	(b) (4)
pH (general)	Safety and DS stability	- Manufacturing process/formulation	
Protein Content (general)	Efficacy	- Manufacturing process/formulation	
Osmolality (general)	Patient discomfort	- Manufacturing process/formulation	
Host Cell Proteins (process impurity)	Safety and immunogenicity	Production cell line/Cell culture	
Host Cell DNA (Process impurity)	Safety and immunogenicity	Production cell line/Cell culture	
(b) (6)	Safety and immunogenicity	(b) (6)	
(Process impurity)		leachate	
Adventitious virus (Contaminant)	Safety	Raw materials and contamination during manufacturing	
Mycoplasma (Contaminant)	Safety	Raw materials and contamination during manufacturing	
Bioburden (Contaminant)	Safety, purity, and efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process	
Endotoxin (Contaminant)	Safety and purity	Raw materials and manufacturing process	
(b) (6)	Safety	Cell Culture	
(Process impurities)			
(b) (6)	Safety	Cell Culture	

(Process impurities)			
Leachables (Impurities)	Safety and product stability	Manufacturing equipment and container closure	(b) (6)

a. **Description**

Adalimumab-aacf is a recombinant human IgG1 monoclonal antibody consisting of two kappa light chains each with 214 amino acids and a molecular weight of approximately 24 kDa, and two IgG1 heavy chains each with 415 amino acids and a molecular weight of approximately 49 kDa. The total molecular weight of adalimumab is approximately 148 kDa with a total of 1330 amino acids. Each heavy chain contains a consensus glycosylation site on Asn 301 and the main glycan structures are G0F and G1F. The heavy and light chains are covalently linked by four inter-chain disulfide bonds.

b. **Mechanism of Action**

MSB1102 binds specifically to TNF-α and neutralizes its biological function by blocking its interaction with TNFR1 (p55) and TNFR2 (p75) cell surface receptors. TNF-α, expressed by immune cells and other cells in response to infection or inflammation, is expressed in soluble form (sTNFα) and membrane-bound form (tm-TNF-α). MSB11022I binds to sTNF-α and tm-TNFα and neutralizes its biological activity, which in turns reduces the inflammatory response. MSB11022 can also induce multiple Fc-dependent effector functions that depend on binding to tm-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.

c. **Potency Assay**

Three potency assays are included in the MSB11022 control strategy:

In vitro bioassay: This assay reflects the primary mechanism of action of adalimumab. It is based on the ability of MSB11022 to inhibit cytotoxicity induced by recombinant human TNF in a dose-dependent manner on the murine fibroblast cell line A9. Cells are incubated in the presence of cycloheximide, to sensitize the cells to TNF-alpha-induced apoptosis. The Applicant indicates the A9 cell line is derived from the L-929 parental cell line that is less sensitive to TNF-induced cytotoxicity. The reported potency value is the average of results from three independent assays. Biological activity of the sample is expressed as % of activity compared to the reference standard and is calculated from the dose-response curve of the sample and reference standard using a 4-PL regression analysis.

ADCC Reporter Bioassay: ADCC activity is a potential MoA for the CD and UC indications. This bioassay measures induction of the ADCC signaling pathway to determine ADCC activity of MSB11022. It measures cross-linking of target and effector cells by adalimumab and

subsequent activation of the effector cells. The effector cells are a recombinant Jurkat T cell line that expresses the FcγRIIIa complex and the luciferase reporter gene under the control of a nuclear factor of activated T-cells (NFAT) response element. The target cells are tmTNF expressing CHO-K1 cells. Binding of the antibody to both tmTNF (via the Fab arm) and the FcγRIIIa receptor (via the Fc region) crosslinks the cells, activating a biological signal, which is quantified through the luciferase activity readout from the NFAT pathway activation in the effector cells.

CDC Bioassay: The assay is based on the ability of MSB11022 to lyse tmTNF expressing cell line (tmTNF CHO-K1) via CDC by baby rabbit complement. The tmTNF CHO-K1 cells are incubated with a dose response curve of MSB11022 and a fixed concentration of complement. At the end of incubation, cell viability is measured by a luminescence assay reagent. Cell death is evaluated by the amount of ATP released by cells, which correlates with the decrease in luminescence.

d. **Reference Materials**

DS and DP potency and identity results are reported relative to the RS. The Applicant established a two-tier RS system for control of commercial DS and DP. (b) (4)

Protocols for qualification and requalification of primary and secondary RSs are adequate and will be approved with this BLA.

e. **Critical starting materials or intermediates**

(b) (4)

Raw materials used in commercial manufacture are of non-animal origin.

f. **Manufacturing process summary**

(b) (4)

(b) (4)

g. **Container closure**

(b) (4)

h. **Dating period and storage conditions:** (b) (6) months at (b) (6) °C.

C. Idacio Drug Product Quality Summary:

Table 3 provides a summary of the CQAs that derive from the drug product manufacturing process and general drug product attributes, their origin and associated risk, and control strategy. Because most of the drug product manufacturing process and general drug product attributes are the same between the PFS, PFP, (b) (4) the CQAs (b) (4) are captured below. CQAs unique to one presentation are indicated.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy **(Additional comments)**
Protein Quantity (General)	Efficacy	DP Manufacturing processes	(b) (4)
Appearance, color, clarity (General)	Safety, Efficacy, Product Stability	Manufacturing process, formulation, contamination, degradation	
Identity	Safety and Efficacy	Intrinsic to the molecule	

			(b) (4)
Sterility (Contaminant)	Safety, Purity, Efficacy	-Manufacturing process or failure of container closure integrity	
Endotoxin (Contaminant)	Safety, Purity	Raw materials and manufacturing process	
Container Closure Integrity (Sterility Assurance)	Safety (Sterility assurance)	Breach during manufacture or storage	
pH (General)	Stability and potentially PK	- Manufacturing process	
Osmolality (General)	Stability, Safety, Patient Discomfort	Manufacturing Process	
Particulate Matter: Visible and Sub-Visible Particulates (General)	Safety and Immunogenicity	-Manufacturing process, container closure system, storage, dose preparation	
Extractable volume - (General)	Dosing	-Manufacturing process	
Leachables (Impurities)	Safety and product stability	Manufacturing product contact equipment and container closure system	
PS80	Product Stability	- Manufacturing Process	
Device Essential Performance Requirements (PFS and PFP)	PFS and PFP device failure	In coming CCS components, device assembly process, shipping, storage	

a. **Potency and Strength:** Idacio is supplied as a 50 mg/mL sterile solution for injection in the (b) (4) presentations below: Potency is determined by an in vitro bioassay that reflects the primary mechanism of action of adalimumab. Same assay is used for DS.

- 40 mg/0.8 mL MSB11022 in single-dose prefilled syringe
- 40 mg/0.8 mL MSB11022 in a single-dose prefilled pen

(b) (4)

b. Summary of Product Design:

-Idacio PFS: DP is supplied in a 1 mL [redacted] glass prefilled syringe with a 29 gauge, 12 mm thin walled steel needle protected by a rigid needle shield, and closed with a [redacted] plunger stopper. Each PFS contains 40 mg/0.8 mL of MSB11022 solution for injection. The PFS is further assembled into a needle safety device based on the [redacted] passive anti-needle stick device.

- **Idacio PFP:** The autoinjector encloses a 40 mg/0.8 mL MSB11022 PFS. The PFS is the primary CCS. The pen assembly is a physioject disposable autoinjector (AI) device.

[redacted]

c. List of Excipients (nominal quantity per syringe [redacted]): Glacial acetic acid (0.5 mg), trehalose [redacted] mg), polysorbate 80 (0.8 mg), sodium chloride (2.3 mg) and Water for Injection, final pH 5.2. All excipients meet compendial standards (USP/NF, Ph. Eur.) and are commonly used for formulation of biological products. No excipients are of human or animal origin.

d. Reference Materials: The same reference standards are used for DS and DP testing.

e. Manufacturing process summary: [redacted]

[redacted]

f. Container closure:

- **PFS**: 1 mL [redacted] glass syringe with a 29 gauge, 12.7 mm, thin-walled stainless steel needle, protected with a rigid needle shield. The syringe is closed with a [redacted] plunger stopper [redacted]. The PFS is assembled with a [redacted] device (a passive safety device designed to prevent needle stick injuries)

- **PFP**: the primary CCS for the PFP is the PFS described above. The pen assembly is a physioject disposable autoinjector (AI) device

- [redacted]

g. Dating period and storage conditions: 36 months at 2-8°C. Idacio may be stored at a maximum of 25°C for up to 28 days.

h. List of co-package components, if applicable: [redacted]

D. **Novel Approaches/Precedents:** N/A

E. **Any Special Product Quality Labeling Recommendations:**

- Store Idacio refrigerated at 36°F to 46°F (2°C to 8°C) in original carton to protect from light. Do not freeze. Do not store in extreme heat or cold.
- Idacio may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 28 days, with protection from light.

F. Establishment Information

OVERALL RECOMMENDATION: Approve for PFS and PFP; [redacted]			
Drug Substance			
Function	**Site Information**	**DUNS/FEI Number**	**Current Recommendation**
• Drug substance manufacturing and QC testing • MCB and WCB preparation and storage	[redacted]	[redacted]	Approve-based on inspection
• DS Viral Testing • Cell Bank Storage			Approve - Based on Previous History
• Mycoplasma Testing			Approve - Based on Previous History
• DS QC testing			

	(b) (4)		Approve - Based on Previous History
Drug Product PFS and PFP			
• Drug product manufacturing • DP QC and Stability testing	(b) (4)		Approve - Based on Waiver granted by OPMA/OBP
• DP QC and Stability testing	Fresenius Kabi Austria GmbH – (FZ-Graz) Hafnerstraße 36 8055 Graz, Austria	FEI: 3003708554	Approve - Based on Previous History
• Device Assembly, Labeling and Secondary Packaging	Fresenius Kabi Austria GmbH – (FK-Werndorf) Am Gewerbepark 6 8402 Werndorf, Austria	FEI #: 3003708554	Approve - Based on Previous History
(b) (4)			

G. **Facilities:** An overall recommendation for the GMP facilities associated with the manufacture of Idacio drug substance (DS) and drug product (DP) is approve for the PFS and PFP (b) (4)

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided (b) (4) proposed for adalimumab DS manufacture, (b) (4) proposed for DP manufacture in pre-filled syringes, (b) (4)

(b) (4)

A PLI of (b) (4) proposed for drug substance manufacture was conducted from (b) (4) The inspection concluded with a three-item FDA Form 483 with a manufacturing facility recommendation of approve.

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

H. Lifecycle Knowledge Management

a. Drug Substance

i. **Protocols approved (PFS and PFP only):** The following protocols are approved for the **PFS and PFP**
   1. Annual post-approval stability protocol
   2. Protocols for qualification and requalification of primary and working reference standards
   3. Protocols for concurrent validation (b) (4)
   4. Master cell bank and working cell bank stability protocols

ii. **Outstanding review issues/residual risk:**
   1. **PFS and PFP:** See PMCs in Section 1F (b) (4)

iii. **Future inspection points to consider:** None

b. Drug Product

i. **Protocols approved (PFS and PFP only):** The following protocols are approved for the **PFS and PFP**
   1. Annual post-approval stability protocol

ii. **Outstanding review issues/residual risk:**
   1. **PFS and PFP:** See PMCs in Section 1F (b) (4)

iii. **Future inspection points to consider:** (b) (4)

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/s/

FRANCES NAMUSWE
12/13/2022 10:46:48 AM

MARIA T GUTIERREZ LUGO
12/13/2022 11:10:16 AM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 7, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Jun Liu, Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761255
Applicant:	Fresenius Kabi USA, LLC
Submission Date:	December 13, 2021
Product:	Idacio (adalimumab-aacf)
Dosage form(s):	Injection
Strength and Container-Closure:	Single-dose prefilled pen: 40 mg/0.8 mL Single-dose prefilled glass syringe: 40 mg/0.8 mL
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, medication guide, instructions for use (submitted on December 6, 2022), container labels (submitted on November 4, 2022), and carton labeling (submitted on November 29, 2022 and December 6, 2022) were assessed and found to be acceptable (see Appendix C) 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, instructions for use (submitted on December 6, 2022), container labels (submitted on November 4, 2022), and carton labeling (submitted on November 29, 2022 and December 6, 2022) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information and Medication Guide (submitted on December 13, 2021 \\CDSESUB1\evsprod\bla761255\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-uspi-and-medication-guide.docx)

Instructions for Use (submitted on December 13, 2021

(b) (4)

[redacted]

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

Appendix B: Evaluation Tables
Evaluation Tables: Label[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

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

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

[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."

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

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: Add 'Rx Only' to container labels

Applicant's response: The "Rx Only" statement is present on all the cartons, however, it has not been added to the container labelling as the labels are small. *Applicant's response is acceptable*

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

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

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

(b) (4)

(b) (4)

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, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

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

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 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add a linear barcode to the container labels and ensure the linear bar code appears on the container label and surrounded by enough white space to facilitate proper scanning *Applicant's response: The Applicant will add a scannable barcode on all the container labels per 21 CFR 201.25 (c) (2). The Applicant will ensure that it is surrounded by sufficient white space to allow for scanning. The barcode will also contain the NDC number. Currently, the container labels have a placeholder to add the barcodes.*

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
(b) (4)	

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

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: Consider adding the dosage form below the proper name or so that the proper name appears within parenthesis if the proper name and dosage form appear on the same line *Applicant revised as requested*

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

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ 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.

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

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

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

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 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

(b) (4)

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

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

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

(b) (4)

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

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 ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, glacial acetic acid, trehalose, and polysorbate 80.

The established names have been revised to the USP monograph titles. Also, per the USP monograph definition, trehalose amount is calculated on the anhydrous basis. Confirm the calculated amount of trehalose revised (b) (4) to the anhydrous calculation as 54.7 mg per the monograph definition.
Revise the ingredient names and amounts as follows:

Each 0.8 mL of IDACIO contains adalimumab-xxxx (40 mg) and glacial acetic acid (b) (4) (0.5 mg), trehalose (b) (4) 54.7 mg), polysorbate 80 (0.8 mg), sodium chloride (2.3 mg), and ~~water~~ Water for ~~injection~~Injection. Sodium hydroxide is added to adjust pH.

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the trehalose anhydrous calculation. Ensure that all inactive ingredients with a USP monograph are provided as such.

Applicant's response: The nominal quantity of trehalose anhydrous per 0.8 mL dose of MSB11022 DP corresponds to 54.8 mg. (b) (4)

Add the four-letter suffix to the proper name in the ingredient list
The Applicant revised as requested

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

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

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for adalimumab products (i.e., there is no specific test method described in regulation for adalimumab 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 Idacio because lot variability

is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling. Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable. Although this statement appears on the carton labeling of the reference product, Humira, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for this product's carton labeling. *The Applicant revised as requested*

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

Comment/Recommendation: Ensure that the package type term 'single-dose' appears consistently on the carton labeling instead of 'single-use' *The Applicant revised as requested*

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
(b) (4)	

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

Comment/Recommendation: Revise from "Dosage and administration: See package insert." to read as a statement of dosage follows: "Dosage: See Prescribing Information" *The Applicant revised as requested* Revise from 'package insert' to 'Prescribing Information' in the contents statement on carton labeling *The Applicant revised as requested*

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

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

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

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

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: Revised to the color based on release specification acceptance criterion the acceptance criterion for degree of coloration is "(b) (4) ", and it is described as "colorless to pale yellow".
The Applicant revised as requested

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

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, glacial acetic acid, trehalose, and polysorbate 80.

The established names have been revised to the USP monograph titles. Also, per the USP monograph definition, trehalose amount is calculated on the anhydrous basis. Confirm the calculated amount of trehalose revised (b) (4) to the anhydrous calculation as 54.7 mg per the monograph definition.

Revise the ingredient names and amounts as follows:

Each 0.8 mL of IDACIO contains adalimumab-xxxx (40 mg) and glacial acetic acid (b) (4) (0.5 mg), trehalose (b) (4) 54.7 mg), polysorbate 80 (0.8 mg), sodium chloride (2.3 mg), and ~~water~~ Water for ~~injection~~Injection. Sodium hydroxide is added to adjust pH.

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes the trehalose anhydrous calculation. Ensure that all inactive ingredients with a USP monograph are provided as such.

Applicant's response: The nominal quantity of trehalose anhydrous per 0.8 mL dose of MSB11022 DP corresponds to 54.8 mg. (b) (4)

Applicant revised as requested

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16:	☐ Yes ☐ No ☒ N/A

xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

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

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: Added the qualifying phrase "Manufactured by:" *Applicant revised as requested*

Medication Guide Evaluation

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

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

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

Comment/Recommendation: The established names have been revised to the USP monograph titles and to match your prescribing information (deleted 'dihydrate'). *Applicant revised as requested*

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

Comment/Recommendation: Added your US license number to your manufacturer's information *Applicant revised as requested*

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

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on December 6, 2022 \\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-pi-clean.docx)

Medication Guide (submitted on December 6, 2022 \\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-medication-guide-clean.docx)

Instructions for Use (submitted on December 6, 2022 \\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-pfs.docx, \\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu-ai-pfp.docx, \\CDSESUB1\EVSPROD\bla761255\0053\m1\us\114-labeling\114a-draft-label\draft-labeling-text-starter-pack-ifu.docx)

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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/07/2022 12:05:34PM
GUID: 50814c7000007a3d59329f660d8ddf02

Jun Liu

Digitally signed by Jun Liu
Date: 12/07/2022 12:16:10PM
GUID: 55088b540009d43d4fb3b19bd75582e9