FDA U.S. FOOD & DRUG ADMINISTRATION

Addendum to Initial Review March 22nd, 2022:
Assessor Comment: *To clarify the assessment of the strength of 10 mg/0.2 mL Hyrimoz this addendum was prepared. In the Justification section below we originally stated:*

Based on the above assessment, the information provided in the original supplement and its amendments support that the product quality of GP2017 10 mg/0.2 mL PFS presentation meets the US market requirements and that GP2017 10 mg/0.2 mL strength is highly similar to the US-licensed Humira 10 mg/0.2 mL strength. Therefore, I recommend approval of this supplement from a product quality perspective.

This section was updated to state:

Based on the above assessment, the information provided in the original supplement and its amendments support that the product quality of GP2017 10 mg/0.2 mL PFS presentation meets the US market requirements and that GP2017 10 mg/0.2 mL strength is highly similar to the US-licensed Humira 10 mg/0.2 mL strength notwithstanding minor differences in clinically inactive components and the strength of GP2017 10 mg/0.2 mL is the same as that of US-licensed Humira. Therefore, I recommend approval of this supplement from a product quality perspective.

The initial conclusions of the assessment do not change with this addendum.

Memorandum of Review:

Submission Tracking Number (STN):	BLA 761071, supplement 11 (eCTD 0112/SDN113) Information request (IR) responses (eCTD0126/SDN127, eCTD0128/SDN129)
Subject:	CMC Prior Approval Supplement (PAS): 1) New pediatric presentation (10 mg/0.2 mL strength). 2) Introduction of the manufacturing site of the 10 mg/0.2 mL Hyrimoz (adalimumab-adaz) bulk drug product (DP) presentation: Sandoz, GmbH, Schaftenau FEI: 3004828473 DUNS: 301698247 3) Addition of a new finished dosage form (FDF) manufacturing site as an assembly, labeling and packaging site, as well as testing and release site for the GP2017 10 mg/0.2 mL FDF: (b) (4)
Stamp Date:	September 28, 2021
Review/Revision Date:	March 8, 2022
Primary Reviewer:	Yetao Jin, Ph.D., CDER/OPQ/OBP/DBRR II
Secondary Reviewer:	Brian Roelofs, Ph.D., CDER/OPQ/OBP/DBRR II
Tertiary Reviewer:	Xianghong (Emily) Jing, Ph.D., CDER/OPQ/OBP/DBRR II
Applicant:	Sandoz Inc.
Product:	Hyrimoz (adalimumab-adaz) injection

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Target and Mechanism of Action:	Hyrimoz binds and neutralizes the activity of soluble and membrane-bound anti-human tumor necrosis factor alpha (TNF-α). Binding of soluble TNF-α blocks TNF-α interaction with p55 and p75 cell surface receptors. TNF-α is a cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF-α play an important role in both pathologic inflammation and joint destruction. In addition, antibody dependent cell mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), antibody mediated reverse signaling, and induction of regulatory macrophages have been identified as potential mechanisms of action for anti-TNF-α monoclonal antibody products in inflammatory bowel diseases.
Indication:	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis
Consults	ICCR# 00795844 to CDRH for prefilled syringe (PFS) with a safety device
Filing Action Date:	November 27, 2021
Action Due Date:	March 28, 2022

I. Summary Basis of Recommendation:

a. Recommendation:

I recommend approval of this supplement from a product quality perspective.

b. Justification:

In this Prior Approval supplement (PAS), the applicant proposed to develop a new pediatric presentation (10 mg/0.2 mL strength prefilled syringe (PFS)) for patients who weigh between 10 kg and 15 kg as part of the fulfillment of PMR 3506-4. Additionally, addition of the Sandoz, GmbH, Schaftenau (FEI: 3004828473) site for manufacture of bulk DP and (b) (4) is added as the facility for assembly, labeling, packaging, testing, and release of the FDF of this strength.

With regards to Chemistry, Manufacture and Controls (CMC), the 10 mg/0.2 mL strength differs from the approved 40 mg/0.8 mL strength (b) (4)

- Syringe filling volume
- Overfill
- Related in-process controls (IPCs)
- Drug product (DP) batch release and stability studies,
- Site for assembly, labeling, packaging, testing and release of the FDF.

The sources of drug substance (DS) and excipients, the DP manufacturing process from the beginning to the end of bulk solution preparation and related process parameters (PPs) and IPCs, the acceptance criteria for quality attributes in the DP specifications for release and stability (except the extractable volume), and the container closure system (CCS) are the same among all strengths. The capability of manufacturing process and control of the new strength is demonstrated by the successful manufacture of the process validation batches as well as acceptable results from IPC, batch release, and stability studies. Transport validation of the bulk DP of the new strength from the DP manufacturing site to the assembly and packaging site is covered by the transport validation performed on the FDF level.

The original comparative analytical assessment (CAA) between this product and the reference product, US-licensed Humira, was performed using the 40 mg/0.8 mL strength, it is acceptable to establish analytical similarity between GP2017 10 mg/0.2 mL and US-licensed Humira (10 mg/0.2 mL) by leveraging the comparability study results between 10 mg/0.2 mL and 40 mg/0.8 mL strengths. The

comparability between 10 mg/0.2 mL and 40 mg/0.8 mL strengths is supported by acceptable analytical results from the following studies:

- Comparison of DP batch release data
- Comparison of extended characterization results
- Comparison of stability study data.

The applicant had originally submitted the Sandoz, GmbH, Schaftenau (FEI: 3004828473) site as a manufacturing site for the 40 mg/0.8 mL (b) (4) The same facility was included as the manufacturer for the 10 mg/0.2 mL PFS presentation proposed in supplement 11. (b) (4) The information about DP manufacturers, control of excipients, analytical procedures and validation, characterization of impurities, reference standards, post-approval stability protocol and stability commitment, and a protocol for introducing new products to the Sandoz GmbH, Schaftenau manufacturing site were provided and considered to be a major amendment with a two-month clock extension. The information was assessed in the memo and found acceptable.

Based on the above assessment, the information provided in the original supplement and its amendments support that the product quality of GP2017 10 mg/0.2 mL PFS presentation meets the US market requirements and that GP2017 10 mg/0.2 mL strength is highly similar to the US-licensed Humira 10 mg/0.2 mL strength notwithstanding minor differences in clinically inactive components and the strength of GP2017 10 mg/0.2 mL is the same as that of US-licensed Humira. Therefore, I recommend approval of this supplement from a product quality perspective.

The decision on whether an on-site inspection for the DP manufacturing facility at Schaftenau and the assessment of the microbiology controls and facility are deferred to the Office of Pharmaceutical Manufacturing Assessment (OPMA) review team. Regarding FDF device assembly site, the need of an inspection at (b) (4) and the review of the proposed PFS is deferred to the Center for Devices and Radiological Health (CDRH).

II. Suggested Language for Action Letter

Assessor comment:

The BLA 761071 supplement 11 submission is a CMC supplement intended to fulfill PMR 3506-4, and the supplemental BLA includes relevant labeling changes for pediatric patients in addition to the proposed DP manufacturing site transfer. Therefore, this supplement is managed by Office of New Drug (OND), Office of Immunology and Inflammation (OII), Division of Rheumatology and Transplant Medicine (DRTM). The approval letter for BLA 761071 supplement (b) (4) ill be drafted and issued by OND/OII/DRTM. The following "Suggested Language" is prepared from a CMC perspective as requested by the OND clinical RPM.

Please refer to your supplemental biologics license application (sBLA) dated and received September 28, 2021, and your amendments, submitted under section 351(k) of the Public Health Service Act for Hyrimoz (adalimumab-adaz) injection.

We acknowledge receipt of your major amendment dated January 19, 2022, which extended the goal date by two months.

This Prior Approval sBLA provides for the following:

1. A new presentation (10 mg/0.2 mL strength) for pediatric patients who weigh 10 kg to less than 15 kg.
2. Introduction of the manufacturing site of the 10 mg/0.2 mL Hyrimoz (adalimumab-adaz) bulk drug product presentation:
   Sandoz, GmbH, Schaftenau
   FEI: 3004828473
   DUNS: 301698247
3. Addition of a new finished dosage form (FDF) manufacturing site as an assembly, labeling and packaging site, as well as testing and release site for the GP2017 10 mg/0.2 mL FDF:
   [redacted] (b) (4)

APPROVAL & LABELING

We have completed our review of this sBLA as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

III. Assessment:

Unless otherwise noted, figures and tables in the assessment were adapted or copied directly from the submission.

(1) Product Introduction

Hyrimoz (also referred to as GP2017) is an IgG1 human monoclonal antibody and was approved as a biosimilar to US-licensed Humira on 10/30/2018. In the approval letter issued by the Agency, the applicant agreed to the following PMR:

PMR 3506-4:
Develop a presentation that can be used to accurately administer Hyrimoz (adalimumab-adaz) to pediatric patients who weigh less than 30 kg

Final report submission date: September 2021

Assessor comments:

The OBP review team is responsible for the quality assessment of 10 mg/0.2 mL strength and the related facility changes to fulfill PMR 3506-4. The determination of PMR 3506-4 fulfillment status is deferred to DRTM clinical review team.

(2) Scope of Changes

The submission of this CMC PAS (supplement 11) is intended to fulfill PMR 3506-4 listed in the BLA approval letter issued on 10/30/2018. [redacted] (b) (4)

In addition to the 10 mg/0.2 mL strength presentation, the applicant is proposing to add Sandoz GmbH (Schaftenau, Austria; FEI: 3004828473, DUNS: 301698247) as a new DP manufacturing site and [redacted] (b) (4) as a new FDF manufacturing site for assembly, labeling, packaging, and release of the GP2017 [redacted] (b) (4).

(3) Addition of a New 10 mg/0.2 mL FDF presentation and Associated Manufacturing Facilities

3.2.P.1 Description and Composition of the Drug Product

GP2017 40 mg, (b) (4) and 10 mg solution for injection is a colorless to slightly yellowish solution intended for subcutaneous administration. The 10 mg/0.2 mL bulk DP PFS is identical to the 40 mg/0.8 mL (b) (4) strengths with regards to its composition and primary packaging material established at Sandoz GmbH, Schaftenau. Only the fill volume and associated filling parameters are different. The proposed fill and overfill volumes for all strengths are shown in the following table:

Table 1-1 Overview of strength presented

Concentration	Strength	Nominal fill volume	Overfill
40 mg/0.8 mL	40 mg	0.8 mL	(b) (4)
(b) (4			
10 mg/0.2 mL	10 mg	0.2 mL	

The solution is filled in pre-filled syringes (clear glass barrel with fixed needle) and closed with a plunger stopper. In the final presentation (FDF), the bulk DP PFS is assembled with a backstop (*i.e.*, an add-on finger flange) and a plunger rod, labeled, and packed into a folding box along with the package insert(s).

As indicated in the following table the GP2017 DP formulation is identical across all three strengths:

Table 2-1 Composition of one unit of 40 mg/0.8 mL, (b) (4) and 10 mg/0.2 mL

Component	Amount per syringe (0.8 mL (b) (4) 0.2 mL)	Function	Reference to quality standards[1]
Active Ingredient			
Adalimumab[2]	40 mg (b) (4) 10 mg	Active substance	[3.2.S.4.1]
	Other Ingredients		
Adipic acid	2.69 mg (b) (4) /0.67 mg	(b) (4)	Ph. Eur./USP
Citric acid monohydrate	0.206 mg/ /0.051 mg		Ph. Eur./USP
Sodium chloride	4.93 mg /1.23 mg		Ph. Eur./USP
Mannitol	9.6 mg 2.4 mg		Ph. Eur./USP
Polysorbate 80	0.8 mg 0.2 mg		Ph. Eur./USP
Sodium hydroxide	q.s.		Ph. Eur./USP
Hydrochloric acid			
Water for injections	ad 0.8 mL (b) (4) ad 0.2 mL		Ph. Eur./USP

[1] current edition of the pharmacopoeia is used

[2] adalimumab is supplied as GP2017 drug substance bulk solution containing adalimumab (b) (4) with adipic acid (b) (4)

Assessor comments:

The applicant indicated that GP2017 10 mg/0.2 mL shares the same DP composition and primary packaging material with the 40 mg/0.8 mL (b) (4) strengths. Per USP <1151>, the recommended excess volume for the labeled size of 0.5 mL is 0.1 mL, which is equal to 20% of the label claim. A target fill volume over 20% in 0.5 mL or smaller labelled size would pose a risk of overdose. Because the proposed overfill of (b) (4) for 10 mg/0.2 mL is below 20%, the risk associated with overdose is low. In addition, the syringe dead volume study in 3.2.P.2, the target fill weight testing in IPC, and extractable volume control in release specifications ensure that the overfill volume is sufficient to allow withdrawing the claimed dose for patients. The proposed GP2017 overfill is acceptable to avoid the potential for overdose.

3.2.P.2 Pharmaceutical Development

Assessor notes:

The applicant provided a single 3.2.P.2 Pharmaceutical Development document for all currently proposed presentations. The following sections were updated to support the introduction of a new 10 mg/0.2 mL strength:

Update	*Assessor comments*
Section 3.2.7. Overfill/ fill volume: the relevant information regarding the overfill volume defined for the 10 mg /0.2 mL strength.	*Assessed in this section.*
Section 4.3.5. Updated that (b) (4) is also not required for 10 mg/0.2 mL.	*Assessed in this section.*
Section 4.3.6. Filling accuracy study for 10 mg/0.2 mL.	*Assessed in this section.*
Section 5.2. Break-loose and gliding force: addition of 10 mg/0.2 mL strength relevant information and addition of Table 5-1 and Table 5-2.	*Deferred to CDRH reviewers for assessment.*
Section 6.3.2.2. Leachable study for 29G syringe: the study is final (30 months data) therefore the sentence "(b) (4) " was removed.	*The editorial update is acceptable. No further assessment is needed since no data was provided in this section.*

(b) (4)

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(b) (4)

[redacted]

3.2.P.8.2 Post-approval Stability protocol and Stability Commitment
In the response to the Agency's IR received in eCTD0128 dated 1/19/2022, the applicant added a document title "postapproval-stability.pdf" to eCTD to the common folder node within supplement 11 for completeness. [redacted] (b) (4) No other content update.

3.2.P.8.3 Stability Data
Section 3.2.P.8.3 has been updated with the stability data of the 10 mg /0.2 mL DP batches summarized below. Refer to Section "3.2.P.5.4 Batch Analyses" of this assessment for additional information of the batches.

Summary of submitted stability data on 10 mg/0.2 mL DP batches (by the assessor)

Batch#	Manufacturing date	Storage conditions	Data available [months, in bold]
HP6143*	06/2017	Intended condition (long-term) 5 ± 3°C	**0 (7), 2 (9), 5 (12), 11 (18), 17 (24), 23 (30)**
		OOF end (25 ± 2°C, 14 days)	**0 (7), 23 (30)**
HP6145*	07/2017	Intended condition (long-term) 5 ± 3°C	**0 (7), 2 (9), 5 (12), 11 (18), 17 (24), 23 (30)**
		OOF end (25 ± 2°C, 14 days)	**0 (7), 23 (30)**
HP6147*	08/2017	Intended condition (long-term) 5 ± 3°C	**0 (7), 2 (9), 5 (12), 11 (18), 17 (24), 23 (30)**
		OOF end (25 ± 2°C, 14 days)	**0 (7), 23 (30)**
HP6148*	08/2017	Intended condition (long-term) 5 ± 3°C	**0 (7), 2 (9), 5 (12), 11 (18), 17 (24), 23 (30)**
		OOF end (25 ± 2°C, 14 days)	**0 (7), 23 (30)**
KC4535	10/2019	Intended condition (long-term) 5 ± 3°C	**0, 3, 6, 9, 12,** 18, 24, 30
		Accelerated condition 25 ± 2°C/ 60 ± 5% r.h.	**0, 1, 2, 3, 6**
		Stress condition 40 ± 2°C/ 75 ± 5% r h.	**0, 1, 3**
KN9329	05/2020	Intended condition (long-term) 5 ± 3°C	**0, 3, 6,** 9, 12, 18, 24, 30
		Accelerated condition 25 ± 2°C/ 60 ± 5% r.h.	**0, 1, 2, 3, 6**
		Stress condition 40 ± 2°C/ 75 ± 5% r h.	**0, 1, 3**
KP3977	05/2020	Intended condition (long-term) 5 ± 3°C	**0, 3, 6,** 9, 12, 18, 24, 30
		Accelerated condition 25 ± 2°C/ 60 ± 5% r.h.	**0, 1, 2, 3, 6**
		Stress condition 40 ± 2°C/ 75 ± 5% r h.	**0, 1, 3**

* For Batches #HP6143, #HP6145, #HP6147, #HP6148, study started 7 months after batch filling.

Editorial correction: the footnote "corr., corresponds to reference" was added where missing from Table footnotes.

Assessor comments:
The applicant updated this section to include the stability data obtained from on the above summarized 10 mg/0.2 mL DP batches stored under intended (5 ± 3°C), accelerated (25 ± 2°C/60 ± 5%RH), stress (40

± 2°C/75 ± 5%RH), and 14-day OOF end conditions. The stability studies have been conducted following the test methods and the analytical test program provided in Section 4 of 3.2.P.8.1. The stability studies on Batches #HP6143, #HP6145, #HP6147, and #HP6148 were started 7 months after batch filling. Based on the data collected at the intended condition (long-term) and OOF end (25 ± 2°C, 14 days) condition, these batches are representative of the quality of 10 mg/0.2 mL DP batches. The updated stability data are assessed below:

1. *At the intended storage condition of 5 ± 3°C, all results from the evaluated batches are within the shelf-life specification of GP2017 DP. The parameters appearance of the container, osmolality, color of solution, clarity, pH, extractable volume, content, identity by CEX, aglycosylated heavy chain (HC) determined by CE-SDS, bioactivity, identity by peptide mapping, and particulate matters did not show significant changes. The following changes and trends over time were observed:*
    - *SEC: HMW (increasing), p50 fragment (increasing), main peak + p100 fragment by SEC (decreasing)*
    - *CEX: main variant (decreasing), acidic variants (increasing)*
    - *CE-SDS (non-reduced): purity (decreasing).*

    These methods are considered stability indicating. No unexpected trends were observed.

2. *At the accelerated condition of 25 ± 2°C/60 ± 5% r.h., the same trends as were observed under the intended storage condition were shown. The values of main variant and acidic variants by CEX and p50 fragment by SEC exceeded the shelf-life limit after six months at accelerated conditions. All other results were within the shelf-life specification set for the intended storage condition.*

3. *At the stress condition of 40 ± 2°C/75 ± 5% r.h., the same trends as were observed under the intended storage condition and the accelerated condition were shown more pronounced over three months. The p50 fragment by SEC, the sum of HMW variants detected by SEC, the main variant and the acidic variants by CEX, and purity by non-reducing CE-SDS were found exceeding the corresponding acceptance criteria in the shelf-life specification. All other results are within the shelf-life specifications for the intended storage condition.*

4. *The OOF end study was conducted to evaluate the impact of storage temperature intervention on product quality of aged DP. The applicant provided the stability data obtained from process validation lots HP6143, HP6145, HP6147, and HP6148 to support the proposed OOF end period up to 14 days for the 10 mg/0.2 mL presentation. The results for all tested attributes under the studied conditions are within the shelf-life specifications. This supports the proposed final DP labeling claim: "HYRIMOZ may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to (b) (4) days, with protection from light."*

The stability studies on DP batches of 40 mg/0.8 mL (b) (4) in this submission were submitted and evaluated previously. Based on the provided stability data for all three strengths obtained at intended, accelerated, stress, or OOF conditions, the 40 mg/0.8 mL, (b) (4) strengths of the DP are comparable with regards to the degradation rate and pathways.

OBP defers to OPMA and CDRH assessors for the assessment of the stability data for microbiological and device functionality attributes, respectively.

(4) 3.2.R Regional Information
4.1 Comparability DP 40 mg – 10 mg

4.1.1 Comparability program

This study is intended to demonstrate analytical comparability between the 40 mg/ 0.8 mL formulation and the pediatric 10 mg/0.2 mL formulation (40 mg/ 0.8 mL produced at (b) (4) and Sandoz; 10 mg/0.2 mL formulation only produced at Sandoz). The same DP process is used for manufacturing the two strengths expect that their fill volumes are different. Comparability was assessed on the physicochemical, and in vitro functional level to ensure that identity, purity, and potency of the 10 mg/0.2 mL dosage strength are comparable to the 40 mg / 0.8 mL formulation. State-of-the-art analytical methods were used to thoroughly characterize the GP2017 DP. Critical quality attributes potentially impacted by the DP process were investigated to compare the GP2017 DP.

The 40 mg/0.8 mL batches were produced at (b) (4) and at (b) (4) Sandoz Biopharmaceuticals, Schaftenau, Austria from April 2012 to July 2020 and are compared to 10 mg/0.2 mL batches produced at the same site ((b) (4) Sandoz Biopharmaceuticals, Schaftenau, Austria) from June 2017 to July 2020. The batch information for this comparability study is detailed in the document "comparability-dp-40mg-10mg.pdf" in section 3.2.R at the link: \\CDSESUB1\evsprod\bla761071\0112\m3\32-body-data\32r-reg-info\comparability-dp-40mg-10mg.pdf
Including 24 lots of 40 mg/ 0.8 mL from (b) (4) and 7 lots of 10 mg/0.2 mL from Schaftenau.

Assessor comments:

GP2017 (adalimumab) (40 mg/0.8 mL in PFS and autoinjector) was developed as a biosimilar to the reference product US-licensed Humira. The applicant did not perform the comparative analytical assessment (CAA) of the 10 mg/0.2 mL strength between the GP2017 bulk DP lots and US-licensed Humira lots for this biosimilar product in this supplement. The DP manufacturing process for GP2017 was established (b) (4) and transferred to Sandoz GmbH, (b) (4) Schaftenau, Austria (Sandoz) for the 40 mg / 0.8 mL dosage strength. The manufacturing process for the pediatric 10 mg/0.2 mL strength is the same as the 40 mg/0.8 mL strength with the only exception for the different fill volumes. Also, the 10 mg/0.2 mL and 40 mg/0.8 mL strengths are the same in formulation, protein concentration, primary CCS, and storage conditions. Though the original CAA between this product and the reference product, US-licensed Humira, was performed using the 40 mg/0.8 mL strength, it is reasonable that the comparability study results between 10 mg/0.2 mL and 40 mg/0.8 mL strengths can be used to support the demonstration that GP2017 10 mg/0.2 mL is highly similar to US-licensed Humira (10 mg/0.2 mL). (b) (4)

The DP lots of both strengths used for this study are quality representative therefor are acceptable.

4.1.2 Comparability protocol

The applicant used following strategy to demonstrate the analytical comparability of the GP2017 DP PFS manufacturing process between the 40 mg/0.8 mL and the 10 mg/0.2 mL dosage strengths:

Summary of the protocol for comparability between the 40 mg/0.8 mL and the 10 mg/0.2 mL dosage strengths (by the assessor)

Comparability study	Comparability criteria
Release testing	The release specifications shown in [Module 3.2.P.5.1]. Limits of expected comparability ranges (mean ± 3×SD) were calculated based on the historical release data of the 40 mg/0.8 mL batches. With the exception of extractable volume data of all 10 mg/0.2 mL batches must be within the calculated comparability ranges when the statistical evaluation of the results is feasible.
Extended characterization#	Comparable results, chromatograms, electropherograms, or levels where applicable.

Stability upon storage at intended (5 ± 3°C), accelerated (25±2°C/60% ± 5% r.h.) and stress conditions (40 ± 2°C/75% ± 5% r.h.)	A descriptive evaluation of the stability results of the two GP2017 DP dosage strengths.

[#]Only physicochemical attributes are assessed in this memo. Defer to OPMA and CDRH for the assessment of CCIT and gliding force, respectively.

Assessor comments:

The protocol for comparability between the 40 mg/0.8 mL and the 10 mg/0.2 mL dosage strengths includes the comparison of batch release data, results from extended characterization, and stability data generated under intended, accelerated, and stress conditions. Based on the summary of the comparability studies below, where no significant differences in analytical results between the 40 mg/0.8 mL and the 10 mg/0.2 mL strengths were observed, this protocol is acceptable.

Regarding the comparison of biological activities, the applicant only provided comparative results for the reporter gene assay (RGA) and cell-based TNF-α apoptosis inhibition assay to demonstrate TNF-α neutralization in the comparability studies. From the proposed mechanism of action (MOA), GP2017 binds to soluble and membrane-bound TNF-α and neutralizes TNF-α bioactivity. In addition, Fc-mediated antibody effector functions such as ADCC and CDC have been identified as part of MOA for GP2017. Usually, additional characterization for these attributes is expected. However, such information was not submitted in this supplement. (b) (4) *the applicant provided justifications to the requested information. The justifications were assessed and deemed acceptable.* (b) (4) *According to the scope of changes to the manufacture and storage of the 10mg/0.2mL strength submitted in this supplement and the associated risks, the applicant's justifications provided* (b) (4) *are still valid. Therefore, no additional information was requested.*

4.1.3 Results from the comparability studies

4.1.3.1 Release data

The comparison of the results of release data for DP comparability between 40 mg/0.8mL and 10 mg/0.2mL strengths is summarized below:

Summary of comparison of release results for 40 mg/0.8 mL and 10 mg/0.2 mL DP lots*(by the assessor)

Test	Acceptance criteria	40 mg/0.8 mL			10 mg/0.2 mL	
		Mean	Mean - 3SD	Mean + 3SD	Min	Max
Description						
Color of solution	(b) (4)	complies			complies	
Clarity		15.8	1.0	30.0	21	22
pH		5.2	5.1	5.4	5.2	5.3
Extractable volume		0.8	0.8	0.8	0.2	0.2
Appearance of container		corresponds			corresponds	
Osmolality		325	304	346	327	331
Identity						
Primary Structure	Corresponds to reference	corresponds			corresponds	

Charge	Corresponds to reference	corresponds			corresponds	
Purity						
Purity by SEC	(b) (4)	99.6	99.3	99.8	99.4	99.5
		0.4	0.1	0.6	0.3	0.5
		n.a.	n.a.	n.a.	n.a.	n.a.
Charge variants by CEX		80.5	77.5	83.6	78.7	82.2
		8.9	7.0	10.7	8.5	9.8
		10.6	6.9	14.4	8.9	11.6
Purity by CE-SDS (non-reduced)		96.4	94.8	98.0	96.2	97.1
Purity by CE-SDS (reduced)		0.5	0.3	0.7	0.5	0.5
Particulate contamination subvisible: sub-visible particles		244	<0	764	85	368
		2	<0	9	1	4
Particulate contamination: visible particles		complies, practically free from extraneous particles, or corresponds			corresponds	
Content						
Assay		50.3	48.3	52.3	50.0	50.8
Potency						
Bioactivity#		96	85	108	94	98
		99	78	119	93	99

*CCIT, bacterial endotoxins (LAL), sterility, break loose force, and gliding force are not summarized in this table since the assessment is differed to OPMA or CDRH assessors
#At the time of validation, the reporter gene assay (RGA) was used for TNF-α neutralization. Based on a health authority request the RGA was replaced by an apoptosis inhibition assay and is reflected within [Module 3.2.P.5.1].

Assessor comments:
All the release results for 40 mg/0.8 mL PFS produced at (b) (4) *and the 10 mg/0.2 mL PFS produced from Sandoz GmbH, Schaftenau, Austria lots in comparison comply with the comparability criteria, i.e., the applicable release specifications. The release results for 10 mg/0.2 mL DP lots are tighter and well within the limits of expected comparability ranges calculated from the historical release data of the 40 mg/0.8 mL batches with the exception that extractable volume data of 10 mg/0.2 mL batches are expected to be different from that of the 40 mg/0.8 mL batches. The comparison of the DP batch release data supports that the 10 mg/0.2 mL and 40 mg/0.8 mL DP lots are comparable with regards to physicochemical attributes and bioactivity.*

We defer to OPMA and CDRH assessors for the assessment of microbiological attributes and device functionality, respectively.

4.1.3.2 Results for extended characterization
The comparison of the results of extended characterization for DP comparability between 40 mg/0.8mL and 10 mg/0.2mL strengths is summarized below:

Summary of comparison of extended characterization results for 40 mg/0.8 mL and 10 mg/0.2 mL DP lots* (by the assessor)

Test parameter	Method	Data for used evaluation	Comparability criteria	Results	
				40mg/0.8ml	10mg/0.2ml
Particulate contamination					
Sub-visible particles	MFI	T0 from stability	Comparable results	≥ 2 µm - < 5 µm: 9630 ± 215 to 63429 ± 273	≥ 2 µm - < 5 µm: 22115 ± 670 to 39462 ± 377
				≥ 5 µm: 490 ± 28 to 5643 ± 172	≥ 5 µm: 1281 ± 124 to 2568 ± 36
				≥ 10 µm: 31 ± 9 to 495 ± 29	≥ 10 µm: 34 ± 6 to 290 ± 9
				≥ 25 µm: 1 ± 1 to 22 ± 1	≥ 25 µm: 0 ± 0 to 2 ± 1
Identity					
Amino acid sequence	Peptide mapping (UV)	Overlays of release analyses	Comparable chromatograms	The chromatograms of all investigated batches were comparable to that of the reference standard at the time of release.	
Variants					
Fragments	low molecular weight variants: non-reducing CE-SDS	Overlays of release analyses	Comparable electropherograms	The overlays of the electropherograms demonstrate that the 40 mg/0.8 mL and 10 mg/0.2 mL batches are comparable with respect to low molecular weight variants.	
	N-glycan site occupancy by reducing CE-SDS	Overlays of release analyses	Comparable electropherograms	The overlays of the electropherograms confirm that 40 mg/0.8 mL and 10 mg/0.2 mL batches are comparable in levels of non-glycosylated heavy chain.	
Oxidation (M256)	Peptide mapping (UV)	T0 from stability	Comparable levels of oxidation	Mean 0.6 Mean - 3×SD 0.0 Mean + 3×SD 1.4	Min 0.4 Max 0.7
Charge variants	CEX	Overlays of release analyses	Comparable chromatograms	The obtained chromatograms for 10 mg/0.2 mL batches and 40 mg/0.8 mL batches are comparable.	

*CCIT and Gliding force are not summarized in this table since the assessment is differed to OPMA or CDRH reviewers.

Assessor comments:
All the results for 40 mg/0.8 mL and 10 mg/0.2 mL DP lots from the extended characterization comply with the comparability criteria as summarized in the table above. Sub-visible particle count by MFI for all sizes and Oxidation (M256) in 10 mg/0.2 mL batches are lower than those in 40 mg/0.8 mL batches. The comparison of extended characterization for the DP batch supports that the 10 mg/0.2 mL and 40 mg/0.8 mL DP lots are comparable with regards to physicochemical attributes.

The assessment of microbiological attributes and device functionality in extended characterization is deferred to the OPMA and CDRH assessment teams respectively.

4.1.3.3 Results of stability data

Observations from the results of stability data for DP comparability between 40 mg/0.8mL and 10 mg/0.2mL strengths are summarized below:

Summary of comparison of stability data for 40 mg/0.8 mL and 10 mg/0.2 mL DP lots * (by the assessor)

Storage conditions	Observation

Intended storage condition (5°C ±3°C)	• All values from the evaluated batches remained within the shelf-life specifications of GP2017 DP for up to 30 months in case of the 40 mg/0.8 mL strength as well as for the 10 mg/0.2 mL strength. • Relevant changes and trends over time were observed in the results according to the shelf-life specification for the following parameters: HMW variants by SEC (increasing), p50 fragment by SEC (increasing), main variant by CEX (decreasing), acidic variants by CEX (increasing) and purity by CE-SDS (non-reduced; decreasing). These methods are therefore considered stability indicating. • For each stability indicating parameter, data of the 10 mg/0.2 mL batches is within the range of the 40 mg/0.8 mL data at every pull point.
Accelerated condition (25 ±2°C, 60 ±5% RH)	• For the stability indicating parameters, degradation is more pronounced at the accelerated condition. Other parameters remained unchanged during storage for up to 6 months. • For each stability indicating parameter, data of the 10 mg/0.4 mL batches is within the range of the 40 mg/0.8 mL data at every pull point.
Stress storage condition (40 ±2°C, 75 ±5% RH)	• For the stability indicating parameters, degradation is more pronounced at the stress storage condition than at the accelerated condition. Oxidation of Methionine 256 increases during storage. Bioactivity slightly decreased, however, it remained within specifications. Other conditions remained unchanged during storage for up to 6 months. • For each stability indicating parameter and the oxidation of Methionine 256, data of the 10 mg/0.2 mL batches are within the range of the 40 mg/0.8 mL data at every pull point.

*Microbiological attributes and device functionality parameters are not summarized in this table since the assessment is differed to OPMA or CDRH reviewers.

Assessor comments:

The applicant conducted a descriptive evaluation of the stability results of the two GP2017 DP dosage strengths for this comparability exercise. All available stability data from samples stored upon storage at intended conditions complied with the applicable specifications. No OOS or unexpected trends were observed. The stability data from accelerated and stress conditions demonstrated that the degradation pathways for the two strengths are the same. Under all conditions, the two strengths showed comparable degradation rates. The provided data support that batches for both strengths have comparable stability behavior with regards to physicochemical attributes and bioactivity.

According to the above comparisons of results from DP batch release, extended characterization, and stability studies, the provided information in the document titled "comparability-dp-40mg-10mg.pdf" support that the 40 mg/0.8 mL and 10 mg/0.2 mL batches are analytically comparable. We defer to OPMA and CDRH assessors for the assessment of microbiological attributes and device functionality, respectively.

4.2 Protocol for new Product - DP

GP2017 DP is currently manufactured at the multiple-product facility Sandoz GmbH, Schaftenau, Austria. At the DP manufacturing line, several additional products are manufactured. In the response facility IR in eCTD0128 received 1/19/2022, the applicant submitted a Protocol for new Product – DP. Whenever a new DP shall be added to the Schaftenau DP manufacturing line, the steps/procedures, including change control, risk evaluation, cleaning validation, and identity testing, are applied. Specifically, the identity testing includes:

- Identity of GP2017 DS and DP is confirmed via different physico-chemical testing methods.
- (b) (4)

Assessor comments:
The identity test in place for GP2017 DP is peptide mapping by Lys-C proteolytic cleavage followed by RP-HPLC and UV detection. The proposed identity testing for differentiating the newly introduced product from other products produced at the line it acceptable. OBP defers to OPMA assessors for the evaluation of other parts of this protocol.

IV. Review Conclusions:
In this CMC PAS, the applicant developed a new pediatric presentation (10 mg/0.2 mL strength) for patients weighing between 10 kg and 15 kg and added a new site for assembly, labeling and packaging, and FDF testing and release for this strength to fulfill PMR 3506-4. The 10 mg/0.2 mL strength only defers from the approved 40 mg/0.8 mL strength (b) (4) in syringe filling volume, overfill, related controls, and the manufacturing and testing site for FDF. The capability of the DP manufacturing process and the control of the new strength are demonstrated by the successful manufacture of 4 process validation batches and the acceptable results from IPC, batch release, and stability studies. Transport validation of the bulk DP of the 10 mg/0.2 mL strength from the DP manufacturing site to the assembly and packaging site is covered by the transport validation performed on FDF level.

This product has been developed as a biosimilar to US-licensed Humira. The original CAA was preformed using the 40 mg/0.8 mL strength. In this supplement, the applicant determined that GP2017 10 mg/0.2 mL is highly similar to US-licensed Humira (10 mg/0.2 mL) using the comparability study results between the 10 mg/0.2 mL and the 40 mg/0.8 mL strengths. The comparability between 10 mg/0.2 mL and 40 mg/0.8 mL strengths is supported by analytical results from DP batch release, extended characterization, and stability studies.

In conclusion, I recommend approval of this PAS application.

V. Future Inspection Items:
None.

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