

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761071Orig1s000**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review/ Division Director Summary Review

<b>Date</b>	<i>Electronic Stamp Date</i>
<b>From</b>	Nikolay P. Nikolov, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review Division Director Summary Review
<b>BLA #</b>	351(k) BLA 761071
<b>Applicant</b>	Sandoz
<b>Date of Submission</b>	October 30, 2017
<b>BsUFA Goal Date</b>	October 30, 2018
<b>Proprietary Name (Proposed) / Nonproprietary names</b>	Hyrimoz GP2017, <sup>1</sup> adalimumab-adaz
<b>Dosage Forms / Strength</b>	<ul style="list-style-type: none"> <li>• 40 mg/0.8 mL solution in a single-dose prefilled syringe (PFS) and</li> <li>• 40 mg/0.8 mL solution in a single-dose Sensoready autoinjector (AI)</li> </ul>
<b>Route of Administration</b>	Subcutaneous
<b>Proposed Indication(s)</b>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis (RA)</li> <li>• Juvenile idiopathic arthritis (JIA) in patients 4 years of age and older</li> <li>• Psoriatic arthritis (PsA)</li> <li>• Ankylosing spondylitis (AS)</li> <li>• Adult Crohn’s disease (CD)</li> <li>• Ulcerative colitis (UC)</li> <li>• Plaque psoriasis (PsO)</li> </ul>
<b>Recommended:</b>	<i>Approval</i>

### 1) Introduction

Sandoz (also referred to as “the Applicant” in this document) has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for GP2017, a proposed biosimilar to US-licensed Humira (adalimumab). Sandoz is seeking licensure of GP2017 for the following indications for which US-licensed Humira is licensed:<sup>2</sup>

<sup>1</sup> In this document, we generally refer to Sandoz’s proposed product by the Applicant descriptor “GP2017” which was the name used to refer to this product during development. Both “Hyrimoz”, the proposed proprietary name, and “adalimumab-adaz”, the proposed nonproprietary name are conditionally accepted until the application is approved.

<sup>2</sup> FDA-approved Humira labeling

- 1) Rheumatoid Arthritis (RA):
  - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- 2) Juvenile Idiopathic Arthritis (JIA):
  - Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- 3) Psoriatic Arthritis (PsA):
  - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- 4) Ankylosing Spondylitis(AS):
  - Reducing signs and symptoms in adult patients with active AS.
- 5) Adult Crohn's Disease (adult CD):
  - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- 6) Ulcerative Colitis (UC):
  - Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of Hyrimoz has not been established in patients who have lost response to or were intolerant to TNF blockers.
- 7) Plaque Psoriasis (PsO):
  - The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

Although the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the lead division for this application and provided the written clinical review, clinical input pertaining to their respective indications was obtained from the Division of Gastroenterology and Inborn Errors Products (DGIEP), and the Division of Dermatology and Dental Products (DDDP) during the course of the review.

The application consists of:

- Extensive analytical data intended to support (i) a demonstration that GP2017 and US-licensed Humira are highly similar, (ii) a demonstration that GP2017 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards and (iii) a justification of the relevance of comparative data generated using the European Union (EU)-approved Humira to support a demonstration of biosimilarity of GP2017 to US-licensed Humira.

- Two single-dose pharmacokinetic (PK) studies (GP17-101 and GP17-104) in a total of 537 healthy subjects providing a 3-way comparison of GP2017, US-licensed Humira, and EU-approved Humira intended to (i) support PK similarity of GP2017 and US-licensed Humira and (ii) provide a PK bridge to support the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of GP2017 to US-licensed Humira. An additional two supportive PK studies, GP17-102 and GP17-103 were conducted in 286 healthy subjects to support the development of an autoinjector (AI) and technical transfer of drug substance manufacturing, respectively.
- A comparative clinical study (GP17-301) between GP2017 and US-licensed Humira or EU-approved Humira (depending on study site location) in patients with moderate to severe psoriasis to support a demonstration of no clinically meaningful differences in terms of safety, purity, and potency. This was a 51-week, multicenter, randomized, double-blind, active-controlled, comparative study in 465 patients with moderate to severe chronic plaque-type psoriasis. The primary objective of this study was to demonstrate equivalent efficacy of GP2017 and US-licensed Humira or EU-approved Humira in patients with moderate to severe chronic plaque-type psoriasis with respect to Psoriasis Area Severity Index 75% response (PASI75) rate at Week 16. A secondary objective was the comparison of the functional ability, as measured by the Health Assessment Questionnaire - Disability Index (HAQ-DI), in patients with a medical history of PsA. Subjects were randomized 1:1 to GP2017 or US-licensed Humira at US sites and EU-approved Humira at EU sites). Patients received a loading dose of 80 mg subcutaneously (SC), followed by 40 mg doses every other week SC. The study included Treatment Period 1 (TP1, Day 1 to Week 17), Treatment Period 2 (TP2, Week 17 to 35) and an Extension Period (EP, Week 35 to 51). At Week 17, subjects who achieved 50% response on the PASI score (PASI50 response) were re-randomized 2:1 to either continue their originally randomized treatment or to receive three alternating treatments with GP2017 or either US-licensed Humira or EU-approved Humira for six consecutive weeks for Weeks 17 to 35. After Week 35, subjects received their originally randomized treatment. Of note, the study design of study GP17-301 includes multiple switching periods during TP 2 (Weeks 17 and 35). The FDA did review the safety and immunogenicity data collected from the entire study period, which included the multiple switches.
- A scientific justification for extrapolation of data to support licensure of GP2017 as a biosimilar to US-licensed Humira in each of the additional indications for which Sandoz is seeking licensure, specifically rheumatoid arthritis, juvenile idiopathic arthritis in patients 4 years of age or older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and ulcerative colitis.

Sandoz submitted comparative analytical data on the GP2017 lots used in clinical studies and on lots of the proposed commercial product. Based on our review of the data provided, Sandoz's comparative analytical data for GP2017 demonstrates that GP2017 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components.

Sandoz used a non-US-licensed comparator (EU-approved Humira) in some clinical studies intended to support a demonstration of biosimilarity to US-licensed Humira. Accordingly, Sandoz provided scientific justification for the relevance of data from those studies to support a demonstration of biosimilarity of GP2017 to US-licensed Humira by establishing an adequate scientific bridge (analytical and PK) between EU-approved Humira, US-licensed Humira, and GP2017.

The results of the comparative clinical efficacy, safety, immunogenicity, and PK studies indicate that Sandoz's data support a demonstration that there are no clinically meaningful differences between GP2017 and US-licensed Humira in terms of safety, purity, and potency in the studied populations. Further, the single transition from US-licensed Humira or EU-approved Humira to GP2017 compared to patients who remained on US-licensed Humira or EU-approved Humira during the TP2 in patients with PsO did not result in different safety or immunogenicity profiles. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to GP2017.

In considering the totality of the evidence, the data submitted by Sandoz support a demonstration that GP2017 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between GP2017 and US-licensed Humira in terms of the safety, purity, and potency of the product, in the studied indication of PsO.

The Applicant has also provided an extensive data package to address the scientific considerations for the extrapolation of data to support biosimilarity in other conditions of use and licensure of GP2017 for each of the indications for which US-licensed Humira is currently licensed and for which Sandoz is seeking licensure.

## **2) Background**

### ***The BPCI Act***

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product (the “reference product”). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Section 351(i) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety,

purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining can be assessed with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The ‘totality of the evidence’ submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

### ***Reference Product***

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with a reference product. When an applicant’s proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product,

the applicant should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

***Relevant Regulatory History***

The first interaction between Sandoz and the FDA on the GP2017 development program occurred at a Type B pre-IND meeting held on January 14, 2013. At the meeting, FDA provided product quality, nonclinical, and clinical comments, including recommendations to the Applicant regarding clinical development. IND 115732 for GP2017 was opened on November 11, 2013 with the proposed clinical study, GP17-301. Additional interactions occurred to discuss the initial Pediatric Study Plan (iPSP) with an agreement on the iPSP on April 13, 2016. BLA 761071 was originally submitted on August 25, 2016. However, because a proposed manufacturing site was not available for a pre-license inspection during the BLA review timeframe the BLA was withdrawn at the request of the Applicant. The withdrawal acknowledgement letter was issued on November 4, 2016. Of note, Sandoz did not request a BPD Type 4 pre-BLA meeting to discuss that submission. The withdrawal acknowledgement letter provided a list of deficiencies identified by the review team for the Applicant to address in a future re-submission. Sandoz re-submitted the BLA on October 30, 2017.

**3) CMC/Product Quality**

<b>Discipline</b>	<b>Reviewer</b>
Drug Substance	Yanming An
Drug Product, Immunogenicity	Chih-Jung Hsu
Analytical Similarity	Yanming An
CMC Stats	Tianhua Wang, Meiyu Shen (Team Leader)
Labeling	Vicky Borders-Hemphill
Facility	Michael Shanks
Facility Team Lead	Peter Qiu
Microbiology Drug Substance	Scott Norris
Microbiology Drug Product	Lindsey Brown
Microbiology Team Lead	Reyes Candau Chacon
Regulatory Business Process Manager	Keith Olin/ Anh-Thy Ly
Application Team Lead	Cristina Ausin
OBP Tertiary Reviewer	Susan Kirshner
CDRH Reviewer	Kathleen Fitzgerald
CDRH Team Leader	John McMichael
CDRH Branch Chief	Alan M. Stevens
CDRH Office of Compliance	Phillip Lafleur
CDRH Office of Compliance	Laurence D. Coyne

- **General product quality and device considerations**

GP2017 is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). GP2017 is an antibody with human derived heavy and light chain variable regions and human IgG1κ constant regions. GP2017 is produced by recombinant DNA technology in a Chinese hamster ovary cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. The GP2017 drug substance (DS) is manufactured at Sandoz GmbH Schaftenu: Biochemiestrasse 10, 6336 Langkampfen, Austria (FEI 3004828473) and (b) (4)

(b) (4) The stability data support a GP2017 DS expiration dating period of (b) (4) months when stored at (b) (4) °C.

GP2017 is supplied as a sterile, preservative-free solution for subcutaneous administration. The drug product (DP) is supplied as either a single-dose, pre-filled auto-injector pen (Sensoready Pen) or as a single-dose, pre-filled 1 mL glass syringe with needle guard and add-on finger flange. Both are platform devices used in previously-approved drug-device combination products with minor autoinjector device differences including the rear end cover, plunger rod, and plunger spring differences (b) (4)

(b) (4) These differences were assessed to not have an impact on product quality or the performance of the device from device constituent and human factor perspective. Enclosed within the Pen is a single-dose, 1 mL pre-filled glass syringe. The solution of GP2017 is clear, colorless to slightly yellowish, with a pH of about 5.2. Each 40 mg/0.8 mL GP2017 single-dose pre-filled Sensoready Pen or GP2017 single-dose pre-filled syringe delivers 0.8 mL of drug product. Each 0.8 mL solution contains GP2017 40 mg, adipic acid (2.69 mg), citric acid monohydrate (0.206 mg), mannitol (9.6 mg), polysorbate 80 (0.8 mg), sodium chloride (4.93 mg), and Water for Injection, USP. Hydrochloric acid and sodium hydroxide are added as necessary to adjust pH. The GP2017 DP is manufactured at (b) (4)

(b) (4) The stability data support GP2017 DP expiration dating period of 24 months when stored at 2 to 8°C.

The GP2017 final DS and DP processes are fully validated, and the manufactured product is of a consistent quality. The controls that have been established for the routine manufacture of GP2017 DS and GP2017 DP meet regulatory requirements. However, the product quality review team recommends post-marketing commitments (PMCs), as detailed in the section on Recommendation for other Postmarketing Requirements and Commitments at the end of this document. I agree with these recommendations.

The proposed devices, PFS and Sensoready Pen, were reviewed by the Center for Devices and Radiological Health (CDRH), General Devices Branch review team with no outstanding concerns.

- **Analytical Similarity Assessment**

To determine whether GP2017 is highly similar to US-licensed Humira, and to establish the adequacy of the analytical portion of the scientific bridge between GP2017, US-licensed

Humira, and EU-approved Humira, Sandoz evaluated and compared analytical data from 22 GP2017 DP lots, up to 35 US-licensed Humira lots and up to 42 EU-approved Humira lots. The FDA performed confirmatory statistical analysis of the submitted data. All methods were validated or qualified prior to the time of testing and demonstrated to be suitable for their intended use.

Statistical equivalence testing of the results from the neutralization of soluble TNF- $\alpha$  induced apoptosis assay and from the TNF- $\alpha$  binding assay met the predefined acceptance criteria for the three pair-wise comparisons between GP2017, US-licensed Humira and EU-approved Humira (GP2017 v. US-licensed Humira, GP2017 v. EU-approved Humira, and US-licensed Humira v. EU-approved Humira) and the product quality review team concluded, and I agree, that the data support a demonstration that GP2017 is highly similar to US-licensed Humira. The statistical analyses also support the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Humira and GP2017 product to support a demonstration of biosimilarity to US-licensed Humira.

Regarding the attributes analyzed using a quality range approach, 90% of GP2017 lots were within the quality ranges calculated for US-licensed and EU-approved Humira with the following exceptions:

- All GP2017 lots have higher galactosylation than US-licensed Humira and EU-approved Humira (23.7-37.4% vs. 14.7-23.1%). However, while higher galactosylation levels could impact CDC activity or C1q binding, there were no observed differences between the three products for these attributes.
- All GP2017 lots have higher afucosylation (2.4-3.2% vs. 0.5-0.9%) and lower high mannose content (0.9-1.3% vs. 3.9-6.6%) than US-licensed Humira and EU-approved Humira. However, while higher afucosylation and lower high mannose could affect ADCC activity or Fc $\gamma$ RIIIa binding, there were no observed differences between the three products for these attributes.
- Several GP2017 lots have slightly lower acidic variants content than US-licensed Humira and EU-approved Humira (6.8-10.7% vs. 9.2-13.9%). The main acidic variants are the result of deamidation and iso-Asp formation. Sandoz evaluated the bioactivity of these variants using the TNF $\alpha$  binding assay and the TNF $\alpha$  neutralization reporter gene assay and showed the variants had comparable potency to the unmodified moiety. Therefore, these acidic variants were considered to have low risk of affecting GP2017 potency.
- All GP2017 lots have lower basic variants content than US-licensed Humira and EU-approved Humira (12.9-17.7% vs. >20.3%). This difference is caused by differences in the presence of C-terminal lysine and proline amide variant, which is a C-terminal modification following the clipping of lysine and glycine. It is well-established that C-terminal lysine is enzymatically removed from therapeutic antibodies in serum. Therefore, this difference in basic variants has a low risk of affecting the clinical performance of GP2017.
- Some GP2017 lots have slightly higher levels of high molecular weight (HMW) variants than US-licensed Humira and EU-approved Humira. However, in all cases

the amount is  $\leq 0.5\%$ , which is proportionally very low and has a low risk of affecting the clinical performance of GP2017.

Based on the above considerations, the product quality review team concluded, and I agree, that the residual uncertainty raised by these results is mitigated by the totality of the analytical similarity data and do not preclude the demonstration that GP2017 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and supports the analytical portion of the scientific bridge to justify the relevance of comparative data generated using EU-approved Humira to support a demonstration of biosimilarity of GP2017 to US-licensed Humira. The product quality review team, including Division of Microbiology Assessment and CDRH, further recommended, and I agree, that this BLA be approved from a sterility assurance and microbiology product quality perspective and from a device perspective.

- **Facilities review/inspection**

FDA's Office of Process and Facilities (OPF) conducted an assessment of the manufacturing facilities for this BLA. The OPF team recommended that BLA 761071 be approved from the standpoint of facilities assessment. The CDRH Office of Compliance also recommended approval of this application. We concur with these recommendations.

## 4) Nonclinical Pharmacology/Toxicology

*Pharmacology/Toxicology Reviewer: Brett Jones, Ph.D.*

*Pharmacology/Toxicology Supervisor: Andrew Goodwin, Ph.D.*

The GP2017 nonclinical development program was considered adequate to support clinical development. The Pharmacology and Toxicology team concluded, and I agree, that the results of the comparative animal studies using GP2017, which include a single dose pharmacokinetic study in rabbits and a 4-week repeat dose toxicity study in cynomolgus monkeys, can be taken together with the data from the analytical bridging studies (refer to the CMC section of this document for details) to support the totality of the evidence that demonstrate GP2017 is biosimilar to US-licensed Humira. The Pharmacology and Toxicology team also provided recommendations to the labeling related to Pregnancy and Lactation Labeling Rule (PLLR).

## 5) Clinical Pharmacology/Biopharmaceutics

*Clinical Pharmacology Reviewer: Mohammad (Abir) Absar, Ph.D.*

*Clinical Pharmacology Team Leader: Anshu Marathe, Ph.D.*

- **General clinical pharmacology/biopharmaceutics considerations**

The objectives of the GP2017 clinical pharmacology program were to evaluate the pharmacokinetic similarity between GP2017 and US-licensed Humira, and to support the pharmacokinetic portion of the scientific bridge between GP2017, US-licensed Humira, and EU-approved Humira in order to justify the relevance of comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of GP2017 to US-licensed Humira.

The clinical development for GP2017 included five clinical studies (GP17-101, GP17-104, GP17-102, GP17-103 and GP17-301), and the key design features of the studies are summarized in Table 1. Pharmacokinetic (PK) similarity between GP2017 and US-licensed Humira was evaluated in two double-blind, three-arm, parallel studies to determine the pharmacokinetics and safety of GP2017, EU-approved Humira, and US-licensed Humira following a single 40 mg SC injection in healthy subjects (studies GP17-101 and GP17-104). PK and immunogenicity were also assessed for GP2017, US-licensed Humira, and EU-approved Humira in patients with PsO in the comparative clinical study GP17-301. In addition, the Applicant conducted two supportive clinical pharmacology studies. An open-label, parallel study was conducted to determine the PK and safety of GP2017 following a single 40 mg SC injection by an autoinjector (AI) or by a pre-filled syringe (PFS) in healthy male subjects (study GP17-102). A double-blind, two-arm parallel study was conducted in healthy male subjects following a single SC injection to determine the PK, safety and immunogenicity of GP2017 from two drug substance production facilities – Schaftenau, Austria and (b) (4) (study GP17-103).

Immunogenicity of GP2017, US-licensed Humira and EU-approved Humira was assessed in healthy subjects in Studies GP17-101, GP17-102, GP17-103 and GP17-104, and in patients with psoriasis in Study GP17-301. Similar incidences of anti-drug antibody (ADA) were observed between GP2017 and US-licensed Humira.

A bioanalytical assay was used to quantify plasma concentrations of GP2017, US-licensed Humira and EU-approved Humira in the GP2017 clinical program. Based on the bioanalytical inspection report, Office of Study Integrity and Surveillance (OSIS) recommended that data from Study GP17-104 and other studies using similar methods be accepted for further Agency review.

**Table 1. Key Design Features of GP2017 Clinical Studies**

Study ID	Design	Objective	Subjects	Dose	Treatments
<b>Clinical Pharmacology PK Similarity Studies</b>					
GP17-101	R, DB, SD, 3-arm, PG	PK, immunogenicity, safety	Healthy male and female (n=219)	40 mg SC	GP2017 PFS (n=73) US-Humira PFS (n=73) EU-Humira PFS (n=73)
GP17-104	R, DB, SD, 3-arm, PG	PK, immunogenicity, safety	Healthy male (n=318)	40 mg SC	GP2017 PFS (n=107) US-Humira (n=105) EU-Humira (n=106)
<b>Comparative Clinical Study</b>					
GP17-301	R, DB, MC, PG TP1: 0-17W TP2: 17-35 W Ext: 35-51 W	Efficacy, safety, immunogenicity, PK	Patients with plaque psoriasis (n=465)	80 mg SC loading dose followed by 40 mg every other week SC	GP2017 PFS (n=231) US-Humira/EU-Humira (n=234)
<b>Supportive Clinical Pharmacology Studies</b>					
GP17-102	R, OL, SD, PG	PK, immunogenicity, safety	Healthy male (n=108)	40 mg SC	GP2017 PFS (n=54) GP2017 AI (n=54)
GP17-103	R, DB, SD, PG	PK, immunogenicity, safety	Healthy male (n=176)	40 mg SC	GP2017 PFS- (b) (4) (n=86) GP2017 PFS-Schaftenau (n=90)
Abbreviations: R – randomized; DB – double blind; OL – open label; PG – parallel group; TP – treatment period; SD – single dose; MC – multicenter; SC – subcutaneous; PFS – pre-filled syringe; AI – autoinjector Source: Adapted from Clinical Pharmacology Review, Table 2					

In Study GP17-101, the 90% confidence intervals (CIs) for the geometric mean ratios (GMR) of GP2017 to US-licensed Humira for the PK parameters (i.e.,  $C_{max}$ ,  $AUC_{0-last}$  and  $AUC_{0-inf}$ ) were all within the pre-specified acceptance interval of 0.80–1.25 (data not shown). However, the 90% CI for the GMR of GP2017 to EU-approved Humira and US-licensed Humira to EU-approved Humira were outside the pre-specified upper limit of 1.25 for the PK parameters  $AUC_{0-last}$  and  $AUC_{0-inf}$ , while GMR for  $C_{max}$  were within the pre-specified acceptance interval for both comparisons (data not shown). The Applicant conducted a root cause analysis with the aim to identify reasons for the failure to demonstrate PK similarity, but no single root cause related to the product or study conduct was identified. However, the observed variability for  $AUC_{0-last}$  of >40% was higher than the anticipated variability of 31% used for powering the study. Therefore, the Applicant conducted Study GP17-104 with increased sample size.

PK similarity was demonstrated between GP2017 and US-licensed Humira in Study GP17-104. In this study, the 90% CI for the GMR of GP2017 to US-licensed Humira, GP2017 to EU-approved Humira, and US-licensed Humira to EU-approved Humira for  $C_{max}$ ,  $AUC_{0-last}$

and  $AUC_{0-inf}$  were all within the PK similarity acceptance interval of 0.8 to 1.25. The study also established the PK portion of the scientific bridge between GP2017, US-licensed Humira, and EU-approved Humira, which supports the use of EU-approved Humira in the comparative clinical study (study GP17-301). The clinical pharmacology results support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira. In addition, PK was demonstrated to be comparable between GP2017 administered from an autoinjector and that from the pre-filled syringe in study GP17-102 (data not shown). Analytical comparability was demonstrated for GP2017 from two drug substance production facilities. In addition, PK was, in general, comparable between drug products formulated from drug substance manufactured at these two different manufacturing sites in study GP17-103 (data not shown).

**Table 2. Statistical Analysis for PK Parameters (Study GP17-104)**

Comparison	PK Parameter	GMR (90% CI)
GP2017 vs US-licensed Humira	$C_{max}$	1.00 (0.94, 1.06)
	$AUC_{0-last}$	1.05 (0.96, 1.14)
	$AUC_{0-inf}$	1.08 (1.00, 1.18)
GP2017 vs EU-approved Humira	$C_{max}$	1.05 (0.99, 1.11)
	$AUC_{0-last}$	1.06 (0.97, 1.15)
	$AUC_{0-inf}$	1.04 (0.96, 1.13)
EU-approved Humira vs US-licensed Humira	$C_{max}$	0.95 (0.90, 1.01)
	$AUC_{0-last}$	0.99 (0.91, 1.08)
	$AUC_{0-inf}$	1.04 (0.96, 1.13)

Source: Adapted from Clinical Pharmacology Review, Table 1

The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, PK similarity has been demonstrated between GP2017 and US-licensed Humira and that the PK data supported the scientific bridge justifying the relevance of the comparative data generated using EU-approved Humira to support a demonstration of the biosimilarity of GP2017 to US-licensed Humira. The OCP has concluded that the clinical pharmacology results from the GP2017 program add to the totality of evidence to support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira. We concur with this assessment. The PK studies have not raised any new uncertainties and the clinical pharmacology data contribute to the totality of evidence that support a demonstration of biosimilarity between GP2017 and US-licensed Humira.

## 6) Clinical Microbiology

Not applicable.

## 7) Clinical/Statistical-Efficacy

*Primary Statistical Reviewer: Kathleen Fritsch, Ph.D. (DDDP)*

*Statistical Team Leader: Mohamed Alosh, Ph.D. (DDDP)*

*Primary Statistical Reviewers: Rebecca Rothwell, Ph.D. (DPARP)*

*Statistical Team Leader: Gregory Levin, Ph.D. (DPARP)*

*Primary Clinical Reviewers: Gary Chiang, M.D., M.P.H. (DDDP), Mark Borigini, M.D. (DPARP)*

*Clinical Team Leaders: David Kettl, M.D. (DDDP), Nikolay Nikolov, M.D. (DPARP)*

### **Overview of the Clinical Program**

To support the demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira, in addition to the PK similarity studies in healthy subjects, discussed in the section on Clinical Pharmacology above, Sandoz submitted clinical safety, immunogenicity, and efficacy data from one comparative clinical study (study GP17-301) in patients with PsO, described in detail in this section below. The key design features of these studies are summarized in Table 1 above.

Study GP17-301 was a 51-week, multicenter, randomized, double-blind, active-controlled, comparative study in 465 patients with moderate to severe chronic plaque-type PsO. The primary endpoint of this study was Psoriasis Area Severity Index 75% response (PASI75) rate at Week 16. A secondary endpoint was functional ability, as measured by the HAQ-DI, in patients with a medical history of PsA. Subjects were randomized 1:1 to GP2017 or US-licensed Humira at US sites and EU-approved Humira at EU sites. Patients received a loading dose of 80 mg subcutaneously (SC), followed by 40 mg doses every other week SC. The study included Treatment Period 1 (TP1, Day 1 to Week 17), Treatment Period 2 (TP2, Week 17 to 35) and an Extension Period (EP, Week 35 to 51). At Week 17, subjects who achieved 50% response on the PASI score (PASI50 response) were re-randomized 2:1 to either continue their originally randomized treatment or to receive three alternating treatments with GP2017 or US-licensed Humira or EU-approved Humira for six consecutive weeks for Weeks 17 to 35. After Week 35, subjects received their originally randomized treatment. Of note, the study design of study GP17-301 includes multiple switching periods during TP 2 (Weeks 17 and 35).

The study was conducted as planned. Treatment groups were balanced with respect to demographics and disease characteristics. Questions were raised regarding the comparability of results between the US and EU sites because response rates differed more between subjects receiving US-licensed Humira or EU-approved Humira (53% vs. 68%), while subjects receiving GP2017 in the US or EU were similar (58% vs. 58%). Only 17% of the data was collected on European subjects. The differences between regions were smaller when comparing the percent change in PASI at Week 16 (reductions of 79% for GP2017 in the US vs. 83% in the EU, and reductions of 77% for Humira in the US vs. 87% in the EU). Given the variability observed between the US and EU results, and because of the questions surrounding the reliability of the data collected at Center 1268 in the US (see discussion in

Section Other Relevant Regulatory Issues, OSI Audits), the DDDP statistical review team considered sensitivity analyses based only on US subjects, and analyses based on US subjects excluding those treated at Center 1268. The results of these two subgroup analyses were consistent with the overall analyses, and the results of the subgroup analyses also meet the protocol-specified criteria of having the 90% confidence intervals fall within the prespecified margin of  $\pm 18\%$ . Table 3 presents the results for the overall population (all subjects US + EU), the subset of US subjects, and the subset of US subjects excluding Center 1268. In each case, the results were generally consistent, and the 90% confidence intervals were contained within the pre-specified similarity criterion. The secondary endpoints of percent change in PASI and Investigator’s Global Assessment (IGA) success were consistent with the results of the primary endpoint analysis.

**Table 3. PASI 75 Response Rates at Week 16 in Study GP17-301**

	GP2017	US-licensed Humira or EU-approved Humira	Difference GP2017 – (US-licensed Humira or EU-approved Humira), % (90% CI)	
<i>Per Protocol Set</i>				
Overall	N=197	N=196		
	67%	65%	1.8%	(-6.0, 9.7)
US	N=157	N=157		
	68%	63%	5.3%	(-3.5, 14.1)
US Excluding Site 1268	N=143	N=143		
	75%	69%	5.6%	(-4.5, 15.7)
<i>Full Analysis Set</i>				
Overall	N=231	N=234		
	58%	56%	2.2%	(-5.4, 9.7)
US	N=188	N=190		
	58%	53%	4.7%	(-3.6, 13.1)
US Excluding Site 1268	N=174	N=171		
	63%	59%	3.5%	(-4.9, 12.0)

Source: Adapted from DDDP Statistical review, Table 1

The study population in the comparative clinical study included 98 subjects with a diagnosis of PsA. Within this subgroup, the change from baseline in the HAQ-DI was used, as supportive analyses, to assess the patient’s level of physical functional ability and activity restriction. Though sample sizes were small within this subset and assessments were limited to descriptive statistics, the DPARP statistical review team concluded that effects of GP2017 compared to US-licensed Humira or EU-approved Humira on physical function as measured by HAQ-DI were similar.

The DDDP and DPARP statistical review teams concluded, and we concur, that the results from the comparative clinical study GP17-301 support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

None.

## 8) Safety

*Primary Clinical Reviewers: Gary Chiang, M.D., M.P.H. (DDDP), Mark Borigini, M.D. (DPARP)*

*Clinical Team Leaders: David Kettl, M.D. (DDDP), Nikolay Nikolov, M.D. (DPARP)*

- **Studies contributing to safety analyses**

The primary safety data were derived from one comparative clinical study in 465 patients with PsO (study GP17-301). Subjects were randomized 1:1 to GP2017 or US-licensed Humira at US sites and EU-approved Humira at EU sites. Patients received a loading dose of 80 mg subcutaneously (SC), followed by 40 mg doses every other week SC. The study included Treatment Period 1 (TP1, Day 1 to Week 17), Treatment Period 2 (TP2, Week 17 to 35) and an Extension Period (EP, Week 35 to 51). At Week 17, subjects who achieved 50% response on the PASI score (PASI50 response) were re-randomized 2:1 to either continue their originally randomized treatment or to receive three alternating treatments with GP2017 or US-licensed Humira or EU-approved Humira for six consecutive weeks for Weeks 17 to 35. After Week 35, subjects received their originally randomized treatment. Supportive safety and immunogenicity information was also provided from the four single dose PK studies in healthy subjects (studies GP17-101, 102, 103, and 104). The safety and immunogenicity data were reviewed for each individual study. Overall, the safety database is adequate to provide a reasonable comparative safety assessment to support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

Overall, there were no notable differences in adverse events (AEs), serious adverse events (SAEs), or AEs leading to discontinuations between the treatment groups. Infections were the most common AE in the treatment groups. Adverse events leading to discontinuation were infrequent and balanced between treatment arms. Reports of hypersensitivity and injection site reactions were balanced between treatment arms with no cases of anaphylaxis reported. No new safety signals were identified in the GP2017 group compared to the known adverse event profile of US-licensed Humira, as described in the FDA-approved labeling for Humira.<sup>3</sup>

### ***Death***

No deaths were reported in the single dose PK studies.

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<sup>3</sup> FDA-approved Humira labeling

There were no deaths in the initial 17 weeks of the treatment with GP2017 in study GP17-301. One subject with psoriasis in the continued GP2017 group of study GP17-301 died due to completed suicide on Day 178 (Treatment Period 2); the subject's death was not considered to be related to study treatment.

#### ***Nonfatal Serious Adverse Events (SAE)***

The proportion of patients who experienced at least one SAE was similar between the treatment groups during the controlled period of clinical studies. The most frequently reported SAEs were infections, which were similar overall between the treatment groups. SAEs across the system organ classes (SOCs) showed a similar distribution with minor numerical differences between each group. There was no notable difference in the incidence of SAEs following a single transition in treatment period 2 from the US-licensed Humira or EU-approved Humira comparator to GP2017 in study GP17-301. The different SOC of SAEs or the pattern of SAEs in the GP2017 clinical program were consistent with the known safety profile of US-licensed Humira as presented in the FDA-approved Humira labeling.

#### ***Discontinuations due to Adverse Events (AE)***

The proportions of subjects who discontinued for any reason were similar between the two treatment groups, and the main reason for discontinuation were subject/guardian decision, protocol deviation, lost to follow-up, adverse event, and lack of efficacy. The proportion of patients discontinuing due to an adverse event was similar between the two groups; 1.3% (3/231) in GP2017 and 2.1% (5/234) in the US-licensed Humira or EU-approved Humira group, during treatment period 1. There was no notable difference in the incidence of treatment discontinuation due to adverse events following the single transition from the US-licensed Humira or EU-approved Humira comparator to GP2017 in treatment period 2 of study GP17-301.

#### ***Adverse Events of Special Interest (AESI)***

The selection of AESI was informed by the known safety profile of US-licensed Humira as presented in the FDA-approved Humira labeling and other published data. Overall, the incidence of AESI, including serious infections, hypersensitivity reactions, malignancy, and liver abnormalities, between the GP2017 and US-licensed Humira or EU-approved Humira treatment arms was similar across the controlled portions of the clinical studies. No increase in AESI was observed following a single transition from US-licensed Humira to GP2017 in treatment period 2 of study GP17-301.

#### ***Common AE***

Nasopharyngitis, upper respiratory tract infections, and headaches were the most common adverse events in study GP17-301 with event rates similar between GP2017 and the US-licensed Humira or EU-approved Humira groups. Following the single transition in treatment

period 2 of study GP17-301, the common adverse event profile remained consistent and similar between subjects who underwent the single transition from US-licensed Humira to GP2017 and those who continued on the US-licensed Humira or EU-approved Humira comparator. The incidence and types of common adverse events were generally similar between the treatment arms and were consistent with the known safety profile of US-licensed Humira as presented in the FDA-approved Humira labeling, further supporting a demonstration that there are no clinically meaningful differences between GP2017 and US-licensed Humira in the indication studied.

### ***Laboratory Abnormalities, Vital Signs and Electrocardiograms (ECGs)***

No unexpected laboratory findings were reported in the GP2017 clinical program.

- **Immunogenicity**

Immunogenicity of GP2017, US-licensed Humira and EU-approved Humira was assessed in healthy subjects in studies GP17-101, GP17-102, GP17-103 and GP17-104, and in patients with psoriasis in study GP17-301. Similar incidences of anti-drug antibody (ADA) were observed between GP2017 and US-licensed Humira. The determination of ADA consisted of a multi-tiered approach comprising a validated ECL bridging immunogenicity assay for the (i) screening, (ii) confirmation and (iii) titration of binding ADA, and a validated competitive ligand binding assay (neutralizing antibody (Nab) assay) for the (iv) assessment of the neutralizing capacity of the antibodies. A single assay was used for the detection of ADAs against GP2017 and the US-licensed Humira or EU-approved Humira comparators, and the capability of the assay to detect antibodies against all products equally was demonstrated during assay validation, as assessed by the product quality team.

#### ***Immunogenicity in Study GP17-301***

In Study GP17-301, ADAs were assessed at sequential time points starting at baseline. As shown in Table 4, a similar proportion of patients tested positive for both ADAs with majority of the being neutralizing antibodies (nAbs), between patients treated with GP2017 and US-licensed Humira or EU-approved Humira comparators at multiple time points. Further, the incidence of these antibodies remained similar between the three groups and did not increase following a single transition from the US-licensed Humira or EU-approved Humira comparator to GP2017.

**Table 4. Proportion of ADA Status Following Repeat Dosing in Study GP17-301**

TP 1	GP2017 N=231			US-licensed Humira or EU-approved Humira N=234								
	Positive	Negative	Missing	Positive	Negative	Missing						
Baseline	3	221	7	3	222	9						
Week 3	41	173	17	32	179	23						
Week 7	26	181	24	20	186	28						
Week 11	45	159	17	38	158	38						
Week 17	48	139	44	43	139	52						
<b>TP2 + EP</b>	<b>Continued Original Treatment</b>			<b>Switched Treatments</b>								
	Cont'd GP2017 N=126			Cont'd US or EU Humira N=127			US or EU Humira to GP2017 N=63			GP2017 to US or EU Humira N=63		
	Pos	Neg	Miss	Pos	Neg	Miss	Pos	Neg	Miss	Pos	Neg	Miss
Week 17	23	95	8	26	92	9	12	45	6	17	42	4
Week 51	16	80	30	19	80	29	15	30	18	13	33	17
Continued GP2017: GP2017 continued from Period 1 Continued US or EU Humira: US or EU Humira continued from Period 2 Switched GP2017: Switched to treatment sequence US or EU Humira>GP2017> US or EU Humira in Period 2 Switched US or EU Humira: Switched to treatment sequence GP2017> US or EU Humira>GP2017 in Period 2 Pos=Positive, Neg = Negative, Miss=Missing Source: Adapted from Clinical Review												

*Immunogenicity in Single Dose PK Studies*

In Studies GP17-101 and GP17-104, the incidence of ADAs following a single dose of 40 mg SC of study drug to healthy subjects was, in general, comparable among all three treatment arms, GP2017, US-licensed Humira, and EU-approved Humira, as summarized in Table 5.

**Table 5. Summary of Binding and Neutralizing ADAs in Healthy Subjects**

	Healthy subjects (Study GP17-101)			Healthy subjects (Study GP17-104)		
	GP2017 (n=73)	EU-Humira (n=73)	US-Humira (n=73)	GP2017 (n=107)	EU-Humira (n=106)	US-Humira (n=105)
<b>ADA+, n (%)</b>	49 (67%)	55 (75%)	50 (68%)	62 (58%)	74 (69%)	73 (69%)
<b>NAb+ n (%)</b>	44 (60%)	46 (63%)	37 (51%)	58 (54%)	68 (64%)	66 (63%)
Source: Adapted from Clinical Pharmacology team review, Table 9						

*Impact of immunogenicity on clinical endpoints*

The development of ADAs appears to increase clearance of the products in healthy subjects and in PsO patients; however, the impact of ADAs on PK was similar for GP2017, US-licensed Humira, and EU-approved Humira (data not shown).

To investigate the potential impact of the ADA on clinical outcomes, the relationship between ADA, primary efficacy endpoint (PASI75), and select relevant safety outcomes associated with ADA was examined in study GP17-301 in PsO. We acknowledge that such analyses are exploratory in nature and limited by the small sample sizes within subgroups and the non-randomized nature of comparisons, as ADA status is a post-randomization variable and observed differences in efficacy or safety outcomes (or lack thereof) could be attributable to ADA formation or to other confounding variables. In the ADA positive subpopulation, the clinical responses were numerically lower than in the ADA negative group but were similar by ADA status between GP2017 and the US-licensed Humira or EU-approved Humira group (Table 6). The overall incidence of adverse events in Study GP17-301 were similar between ADA-positive and ADA-negative subjects.

**Table 6. Logistic Regression Analysis on PASI75 Response at Week 16 by ADA Status, Study GP17-301**

	<b>Treatment</b>	<b>n/N</b>	<b>Adjusted response rate (SE) [%]</b>
<b>Total</b>	GP2017	132/197	66.8 (3.33)
	US-licensed Humira or EU-approved Humira	127/196	65.0 (3.38)
<b>ADA negative</b>	GP2017	111/149	74.3 (3.58)
	US-licensed Humira or EU-approved Humira	105/146	72.1 (3.70)
<b>ADA positive</b>	GP2017	17/40	42.8 (7.72)
	US-licensed Humira or EU-approved Humira	15/38	39.2 (7.80)

Source: Adapted from Clinical Pharmacology team review, Table 11

*Conclusions about immunogenicity*

Immunogenicity data from the single dose healthy subject studies, and study GP17-301 in patients with PsO, does not show an increased risk of development of ADAs with treatment of GP2017 as compared with US-licensed Humira. ADA formation also did not increase following a single transition from the US-licensed Humira or EU-approved Humira comparator to GP2017. Therefore, the data support similar immunogenicity between GP2017 and US-licensed Humira and further support a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira.

- **Discussion of primary reviewer’s comments and conclusions**

The safety database submitted for GP2017 is adequate to provide a reasonable descriptive comparison between the GP2017 and the US-licensed Humira or EU-approved Humira comparator. The safety and immunogenicity analysis of the GP2017 clinical program in the studied condition of use, PsO, and in healthy subjects in the PK single dose studies, has not identified notable differences in the safety profile between GP2017, US-licensed Humira, and EU-approved Humira. No new safety signals have been identified compared to the known adverse event profile of US-licensed Humira. Further, the single transition from US-licensed Humira to GP2017 after Week 17 in study GP17-301 did not result in an increase in adverse events, supporting the safety of the clinical scenario where non-treatment naïve patients transition to GP2017. The FDA safety analysis is consistent with the Applicant's analysis.

The primary review teams, including DPARP, are in agreement that the submitted safety and immunogenicity data and analyses are adequate to support the conclusion of no clinically meaningful differences between GP2017 and US-licensed Humira in the indication studied.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion**

None.

## **9) Extrapolation of Data to Support Biosimilarity in Other Conditions of Use**

Sandoz is seeking licensure of GP2017 for the following indications for which US-licensed Humira is licensed (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, UC, and PsO). The GP2017 clinical program, however, provides clinical efficacy and safety data from a comparative clinical study in patients with PsO.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data supporting a demonstration of biosimilarity, including data from clinical study(ies) performed in another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry: "*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*," if a biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed.<sup>4</sup> The Applicant needs

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<sup>4</sup> Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (April 2015)  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>

to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought,
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations,
- The immunogenicity of the product in different patient populations,
- Differences in expected toxicities in each condition of use and patient population,
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the above FDA guidance, Sandoz has provided adequate scientific justification for the proposed extrapolation of data and information in the application to support licensure as a biosimilar for the additional conditions of use, which are approved for US-licensed Humira and for which Sandoz is seeking licensure, as summarized in this section.

First, Sandoz's extensive analytical characterization data support a demonstration that GP2017 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components. In addition, the data support a demonstration there are no clinically meaningful differences between GP2017 and US-licensed Humira in terms of safety, purity and potency based on similar clinical pharmacokinetics, and similar efficacy, safety, and immunogenicity in PsO.

Further, the additional points considered in the scientific justification for extrapolation of data to support biosimilarity in the indications for which US-licensed Humira is approved and for which Sandoz is seeking licensure (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, and UC) include:

- Similar PK was demonstrated between GP2017 and US-licensed Humira, as discussed in the section on Clinical Pharmacology above. Importantly, GP2017 was demonstrated to be highly similar to US-licensed Humira, as discussed in the section on CMC/Product Quality, and there are no product-related attributes that would increase the uncertainty that the PK/biodistribution may differ between GP2017 and US-licensed Humira in the indications sought for licensure. Thus, a similar PK profile would be expected between GP2017 and US-licensed Humira in patients across all the indications being sought for licensure.
- In general, immunogenicity of US-licensed Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced

by the type of immunoassay used.<sup>5</sup> As stated previously in this document, the Agency has concluded that there are sufficient data to support similar immunogenicity between GP2017 and US-licensed Humira with repeat dosing in patients with PsO, and between GP2017, EU-approved Humira, and US-licensed Humira after a single dose in healthy subjects. Accordingly, similar immunogenicity would be expected between GP2017 and US-licensed Humira in patients with RA, JIA, PsA, AS, adult CD, and UC.

- A similar clinical safety profile with chronic dosing was demonstrated between GP2017 and US-licensed Humira in patients with PsO, and between GP2017, EU-approved Humira, and US-licensed Humira following single doses in healthy subjects. As analytical and PK similarity was demonstrated between GP2017 and US-licensed Humira, a similar safety profile would be expected between GP2017 and US-licensed Humira in patients with RA, JIA, PsA, AS, adult CD, and UC.
- The mechanism(s) of action (MOA) relevant to the extrapolation of data to support biosimilarity in specific indications are summarized in Table 7 and discussed below.

**Table 7. Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Humira in the Conditions of Use Sought for Licensure of GP2017**

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; JIA: juvenile idiopathic arthritis; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

Source: FDA summary of current literature on the topic of mechanisms of action of TNF inhibitors<sup>6,7,8</sup>

<sup>5</sup> FDA-approved Humira labeling

<sup>6</sup> Oikonomopoulos A et al., *Current Drug Targets*, 2013, 14, 1421-1432.

<sup>7</sup> Tracey D et al., *Pharmacology & Therapeutics* 117 (2008) 244-279.

<sup>8</sup> Olesen, C.M, et.al., *Pharmacology & Therapeutics* 159 (2016), 110-119.

### *Extrapolation of Data to Support Biosimilarity in RA, JIA, PsA, and AS*

The primary MOA of adalimumab products is direct binding and blocking of TNF receptor-mediated biological activities (see Table 7 above). Adalimumab products bind to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream pro-inflammatory cascade of events. The published scientific literature indicates that this MOA is the primary MOA in RA, JIA, PsA, AS, and PsO. The data provided by Sandoz showed similar TNF binding and potency to neutralize TNF- $\alpha$ , supporting the demonstration of analytical similarity pertinent to this MOA. Therefore, based on the above considerations, it is reasonable to conclude that the data support extrapolation to support licensure of for GP2017 as a biosimilar to US-licensed Humira for the indications sought, specifically RA, JIA in patients 4 years of age and older, PsA, and AS.

### *Extrapolation of Data to Support Biosimilarity in Inflammatory Bowel Disease (IBD) Indications*

TNF plays a central role in the pathogenesis of the IBD indications (Crohn's Disease and ulcerative colitis), and TNF inhibition is important in treating the diseases, as evidenced by the efficacy of the approved TNF monoclonal antibodies, but the detailed cellular and molecular mechanisms involved have not been fully elucidated.<sup>9</sup> However, the available scientific evidence suggests that for TNF inhibitors in IBD, in addition to binding and neutralization of sTNF, other MOA, listed in Table 7 may play a role.<sup>10</sup> Binding to sTNF and tmTNF involves the Fab region of the antibody, while the other plausible mechanisms of action involve the Fc region of the molecule.

As outlined in the section on CMC/Product Quality above, Sandoz provided experimental data supporting a demonstration that GP2017 and US-licensed Humira are highly similar based on extensive structural and functional analytical characterization. Further, Sandoz addressed each of the known and potential mechanisms of action of US-licensed Humira listed in Table 7 and submitted data to support the conclusion that GP2017 and US-licensed Humira have the same mechanisms of action for each of the requested indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Thus, the DGIEP review team concluded, and I agree, that based on the totality of the data, it is reasonable to extrapolate data and information submitted in the application to support licensure of GP2017 as a biosimilar in the IBD conditions of use sought for licensure.

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<sup>9</sup> Oikonomopoulos A et al., "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?", *Current Drug Targets*, 2013, 14, 1421-1432

<sup>10</sup> Tracey D et al., "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review", *Pharmacology & Therapeutics* 117 (2008) 244-279

In aggregate, based on the above considerations, extrapolation of data and information submitted in the application to support licensure of GP2017 as a biosimilar to US-licensed Humira for the indications sought (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, and UC) is scientifically justified.

## 10) Advisory Committee Meeting

An Advisory Committee (AC) meeting was determined not to be necessary as there were no issues where the Agency needed input from the committee.

## 11) Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, pediatric assessment**

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(1) of the FD&C Act added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

Following revisions to the initial pediatric study plan (iPSP), based on the Agency's feedback, Sandoz submitted an agreed iPSP and a pediatric assessment under the BLA, to address the PREA requirements for the following indications as detailed below:

- Rheumatoid Arthritis (RA), Polyarticular juvenile idiopathic arthritis (JIA): Polyarticular JIA has been considered the condition of use to address PREA for products approved for RA. With this BLA, Sandoz proposed that the pediatric assessment is complete, for JIA patients between 4 and 17 years old, in part by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to GP2017. Sandoz requested a deferral of the requirements to submit a pediatric assessment for JIA patients 2 to < 4 years of age until the expiration of orphan exclusivity in September 2021. Further, the Applicant proposed to develop a pediatric (b) (4) presentation to treat the pediatric population that require lower doses, patients with body weight <30 kg, as indicated in the FDA-approved Humira labeling. The Applicant has also submitted requests for waiver of the requirement to submit a pediatric assessment for patients < 2 years old because the

condition is rare in this age group and such studies would be impossible or highly impracticable.

- Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA): The Applicant has submitted requests for full waiver of the requirement to submit a pediatric assessment for juvenile AS and juvenile PsA because the studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.
- Plaque Psoriasis (PsO): Consistent with the agreed iPSP, with this submission, the Applicant submitted a request for a waiver of the requirements to submit a pediatric assessment for patients with pediatric chronic severe plaque psoriasis ages 0 to 17 years old due to safety concerns with increased risk of lymphoma and other cancers associated with the use of TNF blockers in children and adolescents. However, the current view by the DDDP and the Division of Pediatric and Maternal Health (DPMH) is that a full waiver should be granted for pediatric studies in patients with plaque psoriasis based on the rationale that the product fails to represent a meaningful therapeutic benefit<sup>11</sup> over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients, as described below:
  - GP2017, a TNF-alpha inhibitor, does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients. Another TNF-alpha inhibitor is an approved product for the treatment of pediatric patients 4 years and older with moderate to severe plaque psoriasis. In addition, as a class, TNF-alpha inhibitors are generally not currently the most recommended approved therapies for the treatment of patients with moderate to severe psoriasis; more narrowly-targeted agents are recommended as first-line therapeutic options for children with psoriasis who are in need of treatment with a systemic agent.

Based on the above considerations, DDDP has concluded, and DPMH agrees, that GP2017 would not provide for the meaningful therapeutic benefit over these existing therapies for pediatric patients.

- GP2017 is not likely to be used in a substantial number of pediatric patients because, based on DDDP's evaluation of use data, TNF-alpha inhibitors were used to treat psoriasis in only a very limited number of pediatric patients ((b)(4))% share of total use of all TNFs). For adalimumab, the reported number of uses was even lower (approximately ((b)(4))).<sup>12</sup>

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<sup>11</sup> See section 505B(c) of the FD&C Act.

<sup>12</sup> Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Jan 2009 - Jun 2015. Extracted September 2015

- **Crohn's Disease:** The Applicant requested a deferral of the requirement to submit a pediatric assessment for patients with Crohn's disease 6 to 17 years of age until the expiration of US-licensed Humira orphan exclusivity on 23 September 2021. As a scientific matter, based on emerging epidemiologic data, the Agency has determined that under PREA, pediatric studies would be required for patients with CD down to 2 years of age. However, the Agency has also determined that dedicated studies for patients with CD limited to ages 2 to <6 years old would be impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age. Thus, the Applicant requested a waiver of the requirement to submit a pediatric assessment for patients <6 years old.
- **Ulcerative Colitis:** The Applicant requested a deferral of the requirement to submit a pediatric assessment for patients with ulcerative colitis 5 to 17 years of age (b) (4). As a scientific matter, based on emerging epidemiologic data, the Agency has determined that under PREA, pediatric studies would be required for patients with UC down to 2 years of age. However, the Agency has also determined that dedicated studies for patients with UC limited to ages 2 to <5 years old would be impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age. Thus, the Applicant requested a waiver of the requirement to submit a pediatric assessment for patients < 5 years old.

The GP2017 pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting on September 12, 2018. The PeRC agreed with the requested waivers and deferrals for RA, JIA, AS, PsA, PsO, CD, and UC. PeRC also recommended that PREA post-marketing requirements (PMR) be issued for Sandoz to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age, patients with UC 5 to 17 years of age, and for Sandoz to develop an age appropriate presentation so that this product may be accurately administered to pediatric JIA patients who weigh less than 30 kg and children with CD who weigh less than 40 kg. I agree with PeRC's recommendations.

## 12) Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues.
- **Exclusivity**— There is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Humira (adalimumab) (BLA 125057; AbbVie Inc.) that would prohibit the approval of GP2017.
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **OSI audits**—Two clinical sites that enrolled patients in the comparative clinical study GP17-301 in PsO were selected for inspection. Site 1268 could not be inspected because of a fire that had occurred at the site in August 2016 in which all study source documents, except for study documents in the regulatory binder, were destroyed by

fire or water damage. As a result, OSI reviewed select monitoring reports and all correspondence between the Applicant, the monitoring contract research organization (CRO), and the site related to the study and reported fire. Another clinical investigator site was selected as a replacement inspection for site 1268. Based on the results of these inspections, the OSI review team concluded that the study appears to have been conducted adequately, and the data generated by these sites appear acceptable to support the current BLA. Supportive statistical sensitivity analyses were conducted excluding Center 1268.

- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—Not applicable.

### 13) Labeling

- **Proprietary name**

The Applicant submitted the proposed proprietary name “Hyrimoz” for review. The name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP, formerly the Division of Drug Marketing and Advertising) and was found to be conditionally acceptable. I agree with this assessment.

- **Non-proprietary/Proper name**

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Sandoz’s Hyrimoz product is necessary to distinguish this proposed product from US-licensed Humira (adalimumab) and from other biosimilar adalimumab products. As explained in FDA’s Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance of biological products.<sup>13</sup>

The Applicant submitted a list of suffixes to be used in the nonproprietary name of GP2017 along with supporting analyses intended to demonstrate that the proposed suffixes satisfied the factors described in section VI of the Guidance for Industry, Nonproprietary Naming of Biological Products. The DMEPA review concluded, and I agree, that Sandoz’s proposed distinguishing suffix “adaz” is acceptable and the nonproprietary name “adalimumab-adaz” should be reflected in the product label and labeling accordingly.

- **Important issues raised by brief discussion of OPDP and OSE Division comments**

#### Device Considerations:

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<sup>13</sup> See the FDA Guidance for Industry on Nonproprietary Naming of Biological Products (January 2017). The guidances referenced in this document are available on the FDA Drugs guidance Web page at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

The drug product is supplied as either a single-dose, pre-filled pen (Sensoready Pen) or as a single-dose, pre-filled glass syringe (PFS) with needle guard and add-on finger flange. Both devices are platform devices used in previously-approved drug-device combination products with minor device differences including the rear end cover, plunger rod, and plunger spring differences. These differences were assessed to not have an impact on product quality or the performance of the device. The PFS was used in the comparative clinical study GP17-301 and the PK similarity studies GP17-101 and GP17-104, and the Sensoready Pen was used in the PK study GP17-102. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factor (HF) data submitted by the Applicant in support of the two presentations. DMEPA consult team concluded that no additional HF studies are needed to support the usability of the Hyrimoz PFS. With regards to the Sensoready Pen presentation, DMEPA finds no additional HF data was necessary for the adult populations. In addition, the consult team found the proposed carton labeling, container labels, instructions for use, and prescribing information acceptable for the adult populations from a medication error perspective. With respect to the pediatric/adolescent JIA patients, the DMEPA team disagreed with the Applicant's justification for not needing HF validation studies in that patient population for the Sensoready pen presentation and deferred to DPARP on appropriate labeling for this user group for the Sensoready Pen presentation. The Division acknowledged the DMEPA assessment and recommendations. However, in reviewing the DMEPA recommendations, the Division also considered the following:

- Irrespective of whether the patient is an adult with RA or a JIA patient, it is expected that the patient will only self-administer Hyrimoz when willing to do so, having received appropriate training, and having demonstrated the ability to self-inject. This is explicitly stated in the product labeling, Section 2. Dosage and Administration:

*HYRIMOZ is intended for use under the guidance and supervision of a physician. A patient may self-inject HYRIMOZ or a caregiver may inject HYRIMOZ using either the HYRIMOZ single-dose pre-filled Sensoready® Pen or the HYRIMOZ single-dose pre-filled syringe with needle guard and add-on finger flange if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.*

Additional instructions are included in Section 17. Patient Counseling Information, and Instruction for Use of both Hyrimoz PFS and Sensoready Pen.

Considering the above contextual information, the Division concluded that no additional HF studies are needed in JIA for this application and the current labeling is appropriate and sufficient to ensure the safe and effective use of both the Hyrimoz PFS and Sensoready Pen when used as labeled.

- **Physician labeling**

The Applicant-proposed labeling is closely tracking the labeling of US-licensed Humira.

During the BLA labeling review, revisions were made for consistency with the Guidance for Industry, Labeling for Biosimilar Products (January 2017). Additionally, references to (b) (4) and related information were omitted from the GP2017 labeling and it was determined that such information was not essential for the safe and effective use of GP2017 (b) (4).

The proprietary name “Hyrimoz” and the non-proprietary name “adalimumab-adaz” should be reflected in the product labeling as appropriate.

- **Carton and immediate container labels**

As discussed above in the DMEPA review and recommendations, the proprietary name “Hyrimoz” and the non-proprietary name “adalimumab-adaz” should be reflected in the product Patient labeling/Medication guide as appropriate.

- **Patient labeling/Medication guide**

The Applicant proposed a Patient labeling/Medication guide closely tracking that of US-licensed Humira. The proprietary name “Hyrimoz” and the non-proprietary name “adalimumab-adaz” should be reflected in the product Patient labeling/Medication guide as appropriate.

## **14) Recommendations/Risk Benefit Assessment**

- **Recommended Regulatory Action**

We recommend approval of the 351(k) BLA 761071 for GP2017 to receive licensure as a biosimilar to US-licensed Humira for each of the following indications for which US-licensed Humira is currently licensed and Sandoz is seeking licensure of GP2017: RA, JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC.

- **Totality of the Evidence**

The conclusion of the comparison of the structural and functional properties of GP2017 (clinical and proposed commercial product lots) and US-licensed Humira was that they were highly similar, notwithstanding minor differences in clinically inactive components.

Sandoz provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved Humira to support a demonstration of biosimilarity of GP2017 to US-licensed Humira.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between GP2017 and US-licensed Humira, and (2) establish the PK component

of the scientific bridge to justify the relevance of the data generated using EU-approved Humira.

The results of the clinical development program indicate that Applicant's data meet the requirement for a demonstration of no clinically meaningful differences between GP2017 and US-licensed Humira in terms of safety, purity, and potency in the indication studied. Specifically, the results from the comparative clinical efficacy, safety, and PK studies, which included the use of a chronic dosing regimen of GP2017 and US-licensed Humira in patients with PsO, adequately support a demonstration that there are no clinically meaningful differences between GP2017 and US-licensed Humira in PsO. The single transition from the US-licensed Humira or EU-approved Humira comparator to GP2017 during treatment period 2 in study GP17-301, did not result in a different safety or immunogenicity profile. This would support the safety of a clinical scenario where non-treatment naïve patients may undergo a single transition to GP2017.

The Applicant has also provided an extensive data package to address the scientific considerations that adequately justify extrapolation of data to support licensure of GP2017 for conditions of use not directly studied, for which US-licensed Humira is currently licensed, and for which Sandoz is seeking licensure.

In considering the totality of the evidence submitted, the data submitted by the Applicant show that GP2017 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between GP2017 and US-licensed Humira in terms of the safety, purity, and potency of the product. The information submitted by the Applicant demonstrates that GP2017 is biosimilar to US-licensed Humira for each of the following indications for which US-licensed Humira is currently licensed and Sandoz is seeking licensure of GP2017: RA, JIA in patients 4 years and older, PsA, AS, PsO, Adult CD, and UC and should be licensed.<sup>14</sup>

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

None.

- **Recommendation for other Postmarketing Requirements and Commitments**

**Postmarketing Requirement (PMR):**

The current GP2017 presentations are not designed to allow for accurate administration of doses less than 40 mg, which impacts children with JIA who weigh less than 30 kg and children with CD who weigh less than 40 kg. For accurate weight-based dosing, an age-

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<sup>14</sup> The proposed GP2017 labeling states: "Biosimilarity of HYRIMOZ has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information."

appropriate presentation is required under PREA. Therefore, we recommend a PREA PMR for the development of a presentation that can be used to accurately administer GP2017 to pediatric patients with JIA who weigh less than 30 kg. Also, under PREA, Sandoz is required to submit a pediatric assessment for patients with JIA 2 to <4 years of age, patients with CD 6 to 17 years of age ( [REDACTED] (b) (4) [REDACTED] patients with UC 5 to 17 years of age. Thus, to address the PREA requirements, I recommend the following PREA PMRs:

1. Assessment of Hyrimoz (adalimumab-adaz) for the treatment of juvenile idiopathic arthritis (JIA) in patients ages 2 to <4 years of age.

Final Report Submission Date: September 2021

2. Assessment of Hyrimoz (adalimumab-adaz) for the treatment of pediatric Crohn's disease in patients 6 years to 17 years of age.

Final Report Submission Date: September 2021

3. Assessment of Hyrimoz (adalimumab-adaz) for the treatment of pediatric ulcerative colitis in patients 5 to 17 years of age.

Final Report Submission Date: December 2020

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

### **Postmarketing Commitments (PMC):**

I concur with the post-marketing commitments recommended by the OBP, product quality review team, as listed below:

1. Conduct a drug product (DP) transport validation study during summer time, shipping DP from [REDACTED] (b) (4) [REDACTED]

Final Report Submission: December 2018

2. Implement an apoptosis inhibition assay for release and shelf life testing of GP2017 drug substance and drug product. Submit the proposed specification as a Prior Approval Supplement in accordance with 21 CFR 601.12 (b).

Final Report Submission: March 2019

3. Develop and implement a comprehensive and robust control strategy to control for effector function of GP2017. Submit the proposed specification as a Prior Approval Supplement in accordance with 21 CFR 601.12 (b).

Final Report Submission: March 2019

4. Qualify the bioburden test method for the [REDACTED] (b) (4) [REDACTED] at Sandoz Schafftenau using 10 mL test volumes.

Final Report Submission: March 2019

5. Qualify the bioburden test for the [REDACTED] (b) (4) using the [REDACTED] (b) (4) [REDACTED] and implement the new bioburden test method.

Final Report Submission: March 2019

- **Recommended Comments to Applicant**

None.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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NIKOLAY P NIKOLOV

10/30/2018

Signed under the authority delegated by Dr. Sally Seymour, Acting Division Director,  
DPARP.