Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Summary Review
NDA/BLA # **Supplement #**	BLA 125057 Supplement 394
Applicant Name	AbbVie, Inc.
Date of Submission	December 18, 2014
PDUFA Goal Date	October 16, 2015 Clock Extension to January 16, 2016
Proprietary Name / Established (USAN) Name	Humira (adalimumab)
Dosage Forms / Strength	Proposed: new 40 mg/0.4 mL prefilled syringe (PFS) Currently approved: 40 mg/0.8 ml prefilled pen, 40 mg/0.8 ml PFS, 20 mg/0.4 ml PFS, 10 mg/0.2 ml PFS, 40 mg/0.8 ml single-use glass vial
Proposed Indication(s)	No change to currently approved indications
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Janet Maynard, MD, MHS
Medical Officer Review	Raj Nair, MD
Pharmacology Toxicology Review	Primary: Eleni Salicru, PhD; Secondary: Timothy Robison, PhD, DABT
CMC Review/OBP Review	Primary: Jun Park, PhD; Secondary: Joel Welch, PhD
Microbiology Review	Primary: Steven Fong, MS PhD
Clinical Pharmacology / Pharmacometrics Review	Primary: Ping Ji, PhD; Secondary: Yaning Wang, PhD, Suresh Doddapaneni, PhD
OPDP	Adewale Adeleye, PharmD, MBA
OSE/DMEPA	Primary: Teresa McMillan, PharmD; Secondary: Kendra Worthy, PharmD
OMP/DMPP (Patient Labeling)	Primary: Aman Sarai BSN, RN; Secondary: Marcia Williams, PhD

OND=Office of New Drugs
CDTL=Cross Discipline Team Leader
CMC/OBP = Chemistry, Manufacturing, Controls/Office of Biotechnology Products
OPDP = Office of Prescription Drug Promotion
OSE/DMEPA = Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis
OMP/DMPP = Office of Medical Policy/Division of Medical Policy Programs

1. Introduction

This is a supplemental biologics license application (sBLA) for a new higher concentration [100 mg/mL (40 mg/0.4 mL)] formulation of Humira® (adalimumab) in a prefilled syringe (PFS). The 100 mg/mL adalimumab formulation contains only two of the excipients (mannitol and polysorbate-80) included in the currently approved 50 mg/mL adalimumab formulation and has no new excipients. The drug substance (active ingredient), adalimumab, is the same and there is no change in the cell line used in manufacturing. In addition, there is no change in the manufacturing process other than at the (b) (4) step. The Applicant proposes to use the (b) (4) 29 G PFS for the new formulation. The proposed PFS has a smaller needle gauge (29 G) than the currently approved PFS (27 G).

To support this sBLA for the 40 mg/0.4 ml PFS, the Applicant is primarily relying on:

- Pharmacokinetic (PK) data from studies M12-159 and M10-867, which evaluated the bioavailability of the proposed 100 mg/mL formulation compared to the currently approved 50 mg/mL formulation in healthy volunteers
- The established safety and efficacy profile for the currently approved 50 mg/mL formulation.

In addition, the Applicant has provided efficacy and safety data from a 24-week clinical study (M13-390) in patients with rheumatoid arthritis (RA) and its 24-week open label extension (M13-692). Also, the Applicant provided an assessment of injection site pain in two single-dose, crossover studies (M11-964 and M12-783).

2. Background

Adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab binds to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab was first approved in the United States (US) for the treatment of RA in 2002. Subsequent approvals include polyarticular Juvenile Idiopathic Arthritis (pJIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), adult Crohn's disease (CD), pediatric CD, ulcerative colitis (UC), plaque psoriasis (Ps), and hidradenitis suppurativa. The approved doses and dose regimens for Humira are summarized in Table 1 below.

The currently available dosage forms and strengths include: 40 mg/0.8 mL in a single-use prefilled pen, 40 mg/0.8 mL in a single-use PFS, 20 mg/0.4 mL in a single-use PFS, 10 mg/0.2 mL in a single-use PFS, and 40 mg/0.8 mL in a single-use glass vial. In this sBLA, the Applicant is seeking approval of a 40 mg/0.4 mL single-use PFS, which will be added to the currently available dosage forms.

The Applicant's rationale for the new high concentration (100 mg/ml) formulation is that it requires half the injection volume compared to the currently marketed 50 mg/ml formulation

to deliver the same SC dose. In addition, the Applicant believes that the new formulation may contribute to increased patient comfort through less injection-related pain based on reduced injection volume and removal of some of the excipients in the currently marketed formulation that may contribute to pain sensation. Lastly, the new formulation may increase production efficiency through smaller drug substance lot sizes and larger drug product lot sizes with a higher number of PFS's per batch. The Applicant plans (b) (4) .

Table 1: Approved Indications, Doses, and Dose Regimens for Humira (All Subcutaneous)

Indication	Initial Doses	Maintenance Dose
Rheumatoid arthritis* Psoriatic arthritis Ankylosing spondylitis	___	40 mg EOW (*40 mg EW for ongoing disease activity)
Juvenile idiopathic arthritis	___	10 mg EOW (10 to <15 kg) 20 mg EOW (15 to <30 kg) 40 mg EOW (≥30 kg)
Adult Crohn's disease Ulcerative colitis	160 mg on Day 1, then 80 mg 2 weeks later	40 mg EOW
Pediatric Crohn's disease	80 mg on Day 1, then 40 mg 2 weeks later (17 to <40 kg) 160mg on Day 1, then 80 mg 2 weeks later (≥40 kg)	20 mg EOW (17 to <40 kg) 40 mg EOW (≥40 kg)
Plaque psoriasis	80 mg on Day 1	40 mg EOW
Hidradenitis suppurativa	160mg on Day 1, then 80 mg 2 weeks later	40 mg EOW

Abbreviations: EOW=every other week; EW=Every Week
Source: Cross-Discipline Team Leader Memorandum by Dr. Janet Maynard

Regulatory History

The Agency had multiple pre-submission interactions with the Applicant between to discuss the requirements to support the proposed formulation changes (Type C meeting: June 16, 2011; Type C Written Responses: May 28, 2013; Type C meeting: February 12, 2014; Teleconference: May 20, 2014; a pre-sBLA meeting: October 17, 2014).

At the Type C meeting on June 16, 2011 (meeting minutes dated July 15, 2011), the Division questioned the rationale for the proposed changes and noted that changes in the excipients to the Humira drug product could result in changes in the exposure of adalimumab, which could raise questions about the efficacy and/or safety of the new formulation. The Applicant was told to submit additional chemistry, manufacturing, and controls (CMC) data to the IND application to support comparability and help assess if additional non-clinical or clinical studies were needed. Further, to address concerns about differences between the old formulation and the new formulation, the Applicant could submit efficacy data using a continuous responder outcome (e.g., DAS28, ACR hybrid, ACR-n) in RA patients to support their contention that the formulations were similar. The Applicant was asked to evaluate C_{max}, AUC_{0-t}, and AUC_{0-inf} in the pivotal PK studies.

In Type C written responses dated May 28, 2013, in addition to C_{max} and AUC_t, the Applicant was asked to provide data from AUC_{inf} in order to assess PK comparability. It was noted that if the Applicant believed there were adequate data to support the CMC, PK, and clinical comparability of the new 100 mg/mL to the approved 50 mg/mL, they could submit this application as a supplemental BLA. If there were major differences between the products, then a stand-alone BLA might be required.

At a Type C meeting dated February 12, 2014 (meeting minutes dated March 13, 2014), concerns were raised regarding whether PK comparability had been established between the 50 mg/ml and 100 mg/ml formulations. Furthermore, it was noted that in the clinical study in patients with RA, M13-390, there were statistically significant differences between the formulations when stratified by methotrexate use at 12 weeks. (b) (4) Other potential paths forward were explored, including modification of the proposed formulation so that the PK/PD data were more comparable. It was noted that the development program for the 100 mg/ml formulation would likely rely on some of the information used to support the currently approved Humira formulation, but it might need a separate label and potentially clinical studies in each of the indication where the high concentration formulation is thought to be particularly important or relevant.

Given the broad regulatory implications of the formulation change, on April 25, 2014, a Regulatory Briefing was held to discuss the proposed 100 mg/ml Humira formulation. The Division sought input regarding whether it was reasonable to approve the proposed 100 mg/ml formulation for all of adalimumab's indications despite the observed PK and PD differences with currently approved 50 mg/ml adalimumab. In addition, the Division sought input regarding the appropriate nomenclature for the new 100 mg/mL adalimumab formulation. Briefing participants thought that the Applicant could provide data to justify that the minor PK differences between the formulations and that the observed differences would not preclude relying on the safety and efficacy data for the 50 mg/mL formulation to support approval of the proposed 100 mg/mL formulation. Further, the minor PD differences observed were felt to be unlikely to be clinically significant or to adversely affect the safety or efficacy of Humira for its approved indications. Regarding the Applicant's proposal to use the same tradename of "Humira" for the 100 mg/mL formulation, the briefing participants believed that this was at the Applicant's discretion, as this was unlikely to result in a safety concern.

Subsequently, a teleconference was held with the Applicant on May 20, 2014. Two potential paths forward for development of the 100 mg/ml formulation were proposed:

1. If the Applicant wished to pursue the proposed 100 mg/ml formulation with slightly higher PK exposure compared to the currently approved adalimumab formulation, the Applicant could provide justification that the higher PK exposure would not substantially impact efficacy or safety. It was noted that this justification could be obtained from existing data and no additional clinical studies were needed.
2. The Applicant could reformulate the 100 mg/mL formulation to closer approximate the PK and PD characteristics of the currently marketed adalimumab formulation.

The Applicant decided to proceed with a sBLA for the 100 mg/mL formulation that had been developed. A pre-sBLA meeting was held on October 17, 2014. In general, the Applicant and the FDA were in agreement on the content of the proposed submission for the 40 mg/0.4 mL PFS. It was noted that whether the 100 mg/mL formulation could be approved and applied to all existing conditions would be a review issue. In addition, it was noted that the introduction of the (b) (4) 29 G PFS as the primary packaging could introduce additional

hazards for users. Specifically, the wall thickness of the 29 G needle is reduced compared to the approved 27 G needle and might be more susceptible to mechanical failure, such as bending or breaking during actual use. The Applicant was asked to provide justification that the proposed alternative syringe system does not introduce additional hazards for users.

3. CMC/Device

The CMC review team found the information in this sBLA submission to be adequate to support the introduction of the 100 mg/mL adalimumab formulation and the new drug product container closure, the (b) (4) syringe system. The Applicant's proposal to allow a (b) (4) -month shelf-life for the drug substance (when stored at (b) (4) C) and 24 months for the drug product (when stored at 2-8°C) was considered appropriate based on 48 months of real time drug substance stability data and comparability relative to the existing process. Three primary stability lots of drug product provided 24 months of real time data and are adequate to support a 24 month shelf-life.

The 100 mg/mL adalimumab formulation contains only two of the excipients (i.e., mannitol and polysorbate 80 while removing sodium chloride, sodium citrate (b) (4), disodium phosphate dihydrate, and sodium dihydrogen phosphate dihydrate) included in the 50 mg/mL adalimumab formulation. The active ingredient, adalimumab, is unchanged and there is no change in the cell line used in manufacturing. There is no change in the drug substance manufacturing process other than at the (b) (4) step to achieve the desired concentration/formulation.

The (b) (4) syringe container closure system is used as the primary packaging for Adalimumab Solution for Injection, 100 mg/mL, Pre-filled Syringes. These utilize a (b) (4) needle shield and a (b) (4) plunger stopper. The 29 G thin wall needle has a similar inner diameter (minimum (b) (4) inches) relative to the 27 G regular wall needle (minimum (b) (4) inches) used for the 50 mg/mL formulation ((b) (4) 27 G syringe system). Given the thinner wall, concerns were raised prior to submission regarding the possibility of needle bending and breaking. The Applicant submitted device functional testing specifically related to needle bending, general characteristics, and plunger forces to support the proposed 29 G needle. These data were reviewed by Center for Devices and Radiological Health (CDRH), General Hospital Devices Branch who determined the appropriate device functional testing for the prefilled syringe combination product had been completed. No specific concerns were identified from a device or product quality perspective.

Product Quality Microbiology

During the secondary review of the product quality microbiology, deficiencies were identified regarding (b) (4) Drug Master File (DMF) (b) (4) references provided in the efficacy supplement for the primary container closure system (syringe barrel and plunger) (b) (4) Originally, a letter of authorization (LOA) for (b) (4) DMF (b) (4) was not provided and a complete listing of sites for (b) (4) of the syringe barrel system

and for the sites of plunger stopper (b) (4) were not identified. An information request (IR) was sent to the sponsor on 2/9/15 requesting this information. The sponsor provided a response on 2/12/15 but did not identify sites for component depyrogenation. A follow up IR requesting the component (b) (4) sites was sent on 5/27/15. The sponsor responded on 6/4/15, and included not only component (b) (4) sites but also added new component (b) (4) sites, including two that were not listed on the DMF (b) (4) LOA. These new sites were identified by the secondary reviewer, Dr. Colleen Thomas, late in the review cycle. Dr. Thomas noted that a DMF review would be needed for at least one of the new sites. A clock extension was requested on the grounds that addition of component (b) (4) sites would typically constitute a major amendment. An extension letter was sent to the sponsor on 10/16/15, and a teleconference with the sponsor was held on 10/22/15 to explain the rationale for the clock extension. During the teleconference, the sponsor suggested they could withdraw the new sites and the Agency agreed this would facilitate expeditious close-out of this sBLA. However, before close-out of this sBLA, the Agency requested that the sponsor provide an updated DMF (b) (4) LOA that clearly identifies the components and the (b) (4) and (b) (4) sites relevant to the high concentration Humira drug product, and provide an updated sBLA section 3.2.P.7 with the manufacturing (b) (4), and (b) (4) sites for the primary container closure system components. This was provided in a response submitted 10/26/15 and was determined upon review to be adequate.

Therefore, ultimately, the product quality review team has concluded that the data in this application are now adequate to support approval, but also recommended a postmarketing commitment related to the following issue: the proposed drug product solution hold time from (b) (4) was supported by validation data from a single commercial scale run, which is fewer than currently expected by the Agency. The Applicant has agreed to a postmarketing commitment to provide the data from at least 3 commercial scale runs from the (b) (4) site to support the proposed drug product solution hold time of (b) (4) hours at (b) (4) C from (b) (4). The three runs will include either drug product solution or a growth-promoting medium. These data will be provided by October 31, 2016.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The foundation of the clinical development program was a pharmacokinetic (PK) assessment of the proposed 100 mg/mL formulation compared to the currently approved 50 mg/mL formulation. The relative bioavailability of the 100 mg/mL adalimumab formulation was compared to the currently approved 50 mg/mL adalimumab formulation in two single-dose

studies in healthy subjects (M12-159 and M10-867) and two multiple dose studies in RA patients (M13-390 and M13-390).

Study M12-159 tested 3 different 100 mg/mL concentration formulations compared to the current Humira formulation in a single-dose randomized, parallel-arm relative bioavailability study in healthy males and females (50 subjects/arm). Two of the formulations resulted in similar exposure to the current Humira formulation:

- One formulation contained all the excipients of the current Humira formulation except for sodium chloride. This formulation's PK parameters would have met traditional bioequivalence criteria, with a 90% confidence interval (CI) within 80 to 125% (0.8 to 1.25) of the current Humira formulation.
- The second formulation included fewer excipients, i.e., mannitol, polysorbate 80 and water for injection. The C_{max} and AUC_{0-360} of this formulation fell within the 90% CI of 80 to 125% of the current Humira formulation but was outside this range (0.899-1.266) for AUC_{0-1334}. This was the formulation selected for further development and is the formulation proposed for approval in this application.

Study M10-867 was the pivotal relative bioavailability study of the chosen 100 mg/mL concentration formulation compared to the currently marketed 50 mg/mL Humira formulation. Results from this study are summarized in Table 2 below, and are consistent with the results of Study M12-159 in that this 100 mg/mL formulation provides a slightly higher exposure compared to the current 50 mg/mL Humira formulation across all PK parameters. However the 90% CI of all parameters except for $AUC_{0-\infty}$ fall within 80 to 125% of the reference. While the 90% CI of the $AUC_{0-\infty}$ would mean that the 100 mg/mL formulation does not meet traditional bioequivalence criteria, meeting these criteria has not been strictly required for product reformulations, as long as there is adequate justification that the PK differences observed would not preclude reliance on the established efficacy and safety data of the product.

Table 2: Pharmacokinetic Results of Pivotal Relative Bioavailability Study M10-867

	Central Value[a]		Relative Bioavailability	
PK parameter	**100 mg/mL formulation [Test](n=149)**	**Current 50 mg/mL formulation [Reference](n=147)**	**Point Estimate[b]**	**90% Confidence Interval (CI)**
C_{max}	3.92	3.62	1.083	1.019-1.152
$AUC_{0-\tau}$	2292	1983	1.156	1.068-1.250
AUC_{0-1344}	2316	2002	1.157	1.072-1.249
$AUC_{0-\infty}$	2542	2158	1.178	1.080-1.284

Test= A single dose of 40 mg adalimumab, 100 mg/mL adalimumab formulation
Reference= A single dose of 40 mg adalimumab, currently marketed 50 mg/mL adalimumab formulation
a. Antilogarithm of the least squares means for logarithms
b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms
Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods (2.7.1), Table 19, page 28 and Table 7 of the CDTL review

6. Clinical Microbiology

See Product Quality Microbiology in Section 3.

7. Clinical/Statistical-Efficacy

The efficacy of currently approved 50 mg/mL adalimumab is well-established in its approved indications. As discussed in Section 5 above, compared to the 50 mg/mL formulation, the exposure of the 100 mg/mL formulation was slightly higher based on $AUC_{0-\infty}$ values. Therefore, the efficacy of the 100 mg/mL formulation could be presumed based on exposures that are equal or greater than exposures with the currently approved 50 mg/mL formulation. This is also based on the observation that immunogenicity for the 100 mg/mL formulation was similar or lower than for the 50 mg/ml (see Section 8 below). Therefore a difference in exposure with chronic treatment due to immunogenicity would not be expected.

However, the Applicant also conducted a small (100-patient), 24-week, randomized, double-blind trial comparing the PK, PD, safety, and immunogenicity of the 50 mg/mL and 100 mg/mL formulations in patients with RA (Study M13-390), followed by a 24-week open-label extension (88 patients) where all patients received the 100 mg/mL formulation (Study M13-692). Pre-specified protocol analyses were conducted to assess the difference between formulations at Weeks 12 and 24 in the framework of a 2-way analysis of covariance with classification by formulation and methotrexate (MTX) use, using the baseline efficacy measure as a covariate and including an effect for interaction between the formulation and methotrexate use. The study was not designed to demonstrate non-inferiority. Descriptively, results for the efficacy endpoints (including DAS28-CRP, HAQ-DI, ACR 20/50/70/90/100 responses, and SF-36)[1] were similar for the 100 mg/mL and the 50 mg/mL adalimumab formulations.

The DAS28-CRP results for the two formulations appeared to be different when stratified by MTX use: with the 50 mg/mL formulation, concomitant MTX use is known to result in higher exposure and better efficacy and this was also shown in Study M13-390, whereas with the 100 mg/mL formulation there did not appear to be as much of a difference in exposure or efficacy with or without MTX use. Although there was a statistically significant treatment-by-MTX-use interaction between the formulations for DAS28-CRP results at Week 12, a statistically significant difference was not observed at Week 24. Additionally, the numerical difference between groups observed in study M13-390 persisted in the open label extension study M13-692 even though all patients were receiving the 100 mg/mL adalimumab formulation, suggesting that the difference in results may not have been due to the formulation but due to some factor(s) specific to the group.

In summary, the efficacy of the 50 mg/mL formulation and the 100 mg/mL formulation would be expected to be similar based on similar/slightly higher exposures with the 100 mg/mL

[1] DAS28-CRP=Disease Activity Score (28-joints) using C-Reactive Protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; ACR 20/50/70/90/100=American College of Rheumatology Response Criteria-a composite index with numbers representing percent improvement; SF-36=Short Form-36 questions, a health status questionnaire.

formulation. Overall, this was supported by the results of the small study M13-390, in which efficacy appeared to be similar for both formulations. Results for the subgroups with or without concomitant MTX use in Study M13-390 are limited and definitive conclusions cannot be drawn.

8. Safety

As discussed in Section 5 above, compared to the 50 mg/mL formulation, the exposure of the 100 mg/mL formulation was slightly higher based on $AUC_{0-\infty}$ values. The main question arising from this difference is whether there is reason to expect any clinically significant differences in the safety profile of the 100 mg/mL formulation compared to the 50 mg/mL formulation.

In the original clinical program that supported approval of adalimumab for the treatment of RA, doses as high as 10mg/kg intravenous (IV) every other week (eow) were administered for up to 6 months, and 3mg/kg IV doses were administered eow for up to 2 years. In addition, there are clinical data from patients with RA treated with higher doses (up to 80 mg SC eow) and with higher doses in patients with psoriasis[2] and Crohn's disease[3]. In these studies in RA, psoriasis, and Crohn's disease, the overall safety profile was similar across a range of adalimumab doses. This suggests that the slightly higher exposure with the 100 mg/mL adalimumab formulation would not be expected to have a clinically significant impact on safety.

In addition, the 24-week Study M13-390 provides a descriptive comparison of safety of the 100 mg/mL and 50 mg/mL adalimumab formulations. As summarized in Table 3 below, the incidence of major safety events was generally similar for both formulations.

Table 3 Safety Overview, Study M13-390

	100 mg/mL N=50	**50 mg/mL N=50**
Deaths	0	0
Serious Adverse Events (SAE)	0	2 (4%)
Discontinuations due to AE	1 (2%)	2 (4%)
Common AE	31 (62%)	34 (68%)
Serious Infections	0	0
Infections	18 (36%)	20 (40%)
Injection Site Reactions	3 (6%)	2 (4%)

Source: Section 8 of the CDTL review

[2] Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55(4):598-606.

[3] Columbel JF, Sandborn WJ, Rutgeerts, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's Disease: the CHARM trial. Gastroenterology. 2007;132(1):52-65.

Immunogenicity was assessed in healthy subjects (Study M13-692 and Study M10-862) and RA patients (Studies M13-390 and extension study M13-692). As shown in Table 4 below, immunogenicity was generally similar between the 100 mg/mL and 50 mg/mL formulations. MTX reduced the rate of immunogenicity with both formulations. Five patients who were negative for anti-adalimumab antibodies (AAA) in M13-390 became AAA positive in Study M13-692.

Table 4: Incidence of Anti-Adalimumab Antibodies

Study	100 mg/mL	50 mg/mL
M12-159 (healthy)	1/24 (4%)	3/23 (13%)
M10-867 (healthy)	18/149 (12%)	23/151 (15%)
M13-390 (RA) Total With MTX Without MTX	 7/50 (14%) 1/27 (4%) 6/23 (26%)	 8/50 (16%) 1/29 (3%) 7/21 (33%)
M13-692 (RA, extension) Total With MTX Without MTX	 6/44 (14%) 2/23 (9%) 4/21 (19%)	(all patients switched to 100 mg/mL formulation) 8/44 (18%) 0/24 (0%) 8/20 (40%)

Source: Table 2.3.1.1_2 Clin Pharm review, page 18, and page 26/Table 14 of the CDTL review

In summary, the safety profile of the 100 mg/mL adalimumab formulation appears to be consistent with the known safety profile of the 50 mg/mL adalimumab formulation.

9. Advisory Committee Meeting

No issues were identified that would warrant discussion at an advisory committee meeting.

10. Pediatrics

Because this application did not include new active ingredients, indications, dosage forms, dosing regimens, or new routes of administration, this application is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- **Proprietary name**—no change to the currently approved, "Humira"
- **Physician labeling**

In determining the best approach to the labeling of high concentration (100 mg/mL) adalimumab, the Division presented the issues to the Biosimilar Review Committee (BRC) on March 26, 2015. Dr. Janet Woodcock attended the meeting as an ad hoc committee member. Other Agency stakeholders, including representatives from the Division of Dermatology and Dental Products, Division of Gastroenterology and Inborn Errors of Metabolism, Division of Medication Error Prevention and Analysis (DMEPA), and Office of Drug Evaluation 2 were invited to the meeting and also provided feedback on the most appropriate approach.

The meeting attendees agreed that it is difficult to justify separate labeling and different proprietary names for the currently approved Humira formulation and the proposed 100 mg/mL adalimumab formulation. The Applicant's primary data to support approval of the 40 mg/0.4 mL adalimumab formulation is the relative bioavailability data comparing the approved Humira to the proposed formulation. The minor PK/PD differences noted were not thought to be sufficient to suggest different safety or efficacy of the proposed product compared to the currently approved Humira. The majority of the safety and efficacy of the proposed formulation is derived from the Agency's previous finding of safety and efficacy of Humira. Thus, it was advised that it was reasonable to add the proposed formulation to the current Humira labeling and to use the same proprietary name (Humira) for both formulations.

Therefore, the proposed formulation will be added to the currently approved Humira label. The primary changes to the label would include the addition of information regarding the new the 40 mg/0.4 mL PFS to the dosage forms and strengths in Section 3 and a description of the formulation in Section 11.

- **Carton and immediate container labels**—no issues.
- **Patient labeling/Medication guide**—Minor edits were recommended by the Patient Labeling review team and were accepted by the Applicant.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on this supplemental application will be approval.

- **Risk Benefit Assessment**

The risk-benefit of the currently approved 50 mg/mL formulation of Humira (adalimumab) has been well established. The risk-benefit of the 100 mg/mL formulation of adalimumab relies on the established risk-benefit of the 50 mg/mL formulation. The bridge for this reliance is the relative bioavailability study demonstrating comparable exposure between the formulations. Although there is slight increase in $AUC_{0-\infty}$ with the 100 mg/mL formulation, this is not expected to result in a difference in risk or benefit, based on the known exposure-response relationships of adalimumab across the range of exposures previously evaluated in its clinical development program. Therefore, it can be concluded that the risk-benefit of the 100 mg/mL formulation of adalimumab is also acceptable.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)**

Humira does not have a current REMS, and none is recommended on the basis of this submission.

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

A single post-marketing commitment (PMC) is recommended by the Product Quality Microbiology review team, as follows:

> Submit hold time validation data from at least three commercial scale runs at (b) (4) to support the proposed drug product solution hold time of (b) (4) hours at (b) (4) C from the (b) (4). The three runs will include either drug product solution or a growth-promoting medium.
>
> Final Report Submission: 10/31/2016

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/s/

SARAH K YIM
11/15/2015