CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761024Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health
Addendum to the August 19, 2016 Review

Date: September 23, 2016 **Date consulted:** January 14, 2016

From: Miriam Dinatale, D.O., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Director
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Drug: ABP 501 (adalimumab-xxxx), subcutaneous injection

BLA: 761024

Applicant: Amgen, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indications: For the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps)

Materials Reviewed:

- DPMH consult request dated January 14, 2016, DARRTS Reference ID 3873993
- Applicant's submitted background package for ABP 501 (adalimumab-xxxx) BLA 761024.
- DPMH Review. Humira (adalimumab) Injection, BLA 125057. Jeanine Best, MSN, RN, PNP. March 13, 2013. DARRTS Reference ID 3275320.
- DPMH Review. Humira (adalimumab) Injection, BLA 125057. Miriam Dinatale, DO. March 25, 2014. DARRTS Reference ID 3476883.

- Division of Pediatric and Maternal Health review of 10th interim report of the adalimumab pregnancy registry report. IND 7627. Miriam Dinatale, D.O. November 3, 2014. DARRTS Reference ID 3650679
- DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672

Consult Question:
DPARP would like to seek DPMH "to provide comments and proposed revisions on the labeling sections that correspond to the new PLLR section of the package insert."

INTRODUCTION
The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 14, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of ABP 501 (adalimumab) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

DPMH completed their original ABP 501 memorandum on August 19, 2016. On September 14, 2016, DPARP requested the DPMH make minor edits to their memorandum, including replacing the term "adalimumab-(b) (4)" with "adalimumab-xxxx" throughout the memorandum. In this addendum, DPMH made minor revisions to the memorandum as requested by DPARP.

REGULATORY HISTORY
On November 25, 2015, Amgen, Inc. submitted a Biologics License Application (BLA) for ABP 501 (adalimumab-xxxx), BLA 761024, for the following proposed indications: treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps). Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). The biological reference product is Humira (adalimumab), which was approved in the US on December 31, 2002. Humira labeling, in the PLLR format, was updated on June 30, 2016. The reader is referred to the DPMH review by Miriam Dinatale, D.O. for further details.[1]

BACKGROUND
Adalimumab and Drug Characteristics
Adalimumab binds to TNF-alpha and blocks its interaction with p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF is increased in patients with RA, JIA, PsA, and AS. The exact mechanism of action of adalimumab is unknown. Adalimumab has a molecular weight of 148,000 Daltons and a mean terminal half-life of 2 weeks. [2]

[1] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672
[2] Humira (adalimumab) labeling. Section 12: Clinical Pharmacology. Drugs @FDA. Accessed 11/2/2015.

Current State of Labeling
Labeling for Humira, the biological reference product, was converted to the PLLR format on June 30, 2016 and included data from the RA portion of the Humira pregnancy exposure registry.

Pregnancy and Nursing Mothers Labeling
On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[3] also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[4] format to include information about the risks and benefits of using these products during pregnancy and lactation.

PREGNANCY
Nonclinical Experience
Current labeling provided by the applicant includes data from animal reproduction studies that were conducted for the initial approval of Humira in 2002. No additional nonclinical studies were submitted with this BLA. In perinatal development studies, there was no evidence of embryofetal toxicity in pregnant cynomolgus monkeys administered adalimumab during organogenesis at doses 373-times the maximum recommended human dose (MRHD). The reader is referred to the Nonclinical Review by Jianmeng Chen, M.D., Ph.D. for further details.

Applicant's Review of Published Literature
The applicant performed a literature review in PubMed and Ovid databases from January 2005 through March 2016 using the following search terms: "adalimumab" and "pregnancy" or "pregnant" to obtain information on adalimumab use during pregnancy. The results of the applicant's review of literature are provided below. In addition, Tables 1, 2 and 3 provided by the applicant include case reports regarding adalimumab use during pregnancy and are included in Appendix B of this review.

In a prospective cohort study conducted by the OTIS Collaborative Research Group (Chambers, *et al.*), 74 adalimumab-exposed with RA, 80 women with RA but with no adalimumab exposure, and 218 non-diseased women were enrolled. Women exposed to adalimumab had at least one dose of the medication in the first trimester, and approximately 43% used adalimumab in all three trimesters. The rate of major defects in the exposed, disease-matched, and non-diseased comparison groups was 5.6%, 7.8%, and 5.5%, respectively. A total of 234 infants (70% of the live born infants) were physically examined.

[3] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[4] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

There was no difference in the proportion of children with three or more minor abnormalities among three groups. In women with RA, the adalimumab-exposed group had a higher percentage of spontaneous abortions (SAB) compared to unexposed women (9% vs. 3.8%). The rate of SAB of clinically recognized pregnancies in the general population is between 15 and 20%. There was no statistically significant increase in the risk of spontaneous abortion following adalimumab exposure. The rate of spontaneous abortions, using an adjusted hazard ratio (HR), was 1.96 (95% CI, 0.47, 8.26) when comparing the adalimumab and disease-matched group and 3.79 (95% CI 1.01, 14.23) when comparing the adalimumab and non-diseased group. However, the number of events was small with seven events in the ADA-exposed cohort and three events in the RA unexposed cohort. The rate of preterm delivery and small-for-gestational age infants did not differ among the three groups. The authors concluded that pregnant women with RA who used adalimumab in the first trimester of pregnancy compared to women with RA who were not treated with adalimumab, did not appear to be at an increased risk for adverse fetal outcomes.

In a prospective observational study, (Zelinkova, *et al*.) the authors followed 31 pregnancies in 28 women with inflammatory bowel disease (IBD) between April 2006 and April 2011 who were treated with anti-TNF-α agents. Eleven women received adalimumab during 13 pregnancies. All thirteen patients discontinued adalimumab before gestational week 30; two patients suffered relapses of IBD. There were two miscarriages in the first trimester and no congenital abnormalities. Adalimumab was detected in five cord blood samples. The authors concluded that although anti-TNF therapy appears to be safe in pregnant women with quiescent IBD, anti-TNF drugs are detected in cord blood samples.[5]

In the ongoing Pregnancy IBD and Neonatal Outcomes (PIANO) study (Mahadevan, *et al*.), the authors provided data on the safety of adalimumab use in all three trimesters of pregnancy in women with IBD and data on infant immune development. One hundred seventy four infants who were exposed to adalimumab *in utero* (117 had adalimumab exposure during the third trimester), were compared to infants with no *in utero* adalimumab exposure. The infants were followed for one year. There was no difference in infection rates between infants exposed to biologics *in utero* compared to unexposed infants. The authors concluded that the study reinforces the safety of adalimumab use in the third trimester.[6]

In a 2011 registry report by The British Society for Rheumatology Biologics Register (Verstappen, *et al*.[7]), the authors published the outcomes of 130 pregnancies in women treated with anti-TNF-α agents. Of the 130 pregnancies, 26 pregnancies were exposed to adalimumab. The study did not report isolated adalimumab findings, but included findings observed in women exposed to anti-TNF-α agents in general. The following outcomes were observed:

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[5] Zelinkova, et al. Effects of Discontinuing Anti-Tumor Necrosis Factor Therapy During Pregnancy on the Course of Inflammatory Bowel Disease and Neonatal Exposure. Clinical Gastroenterology and Hepatology. 2013; 11: 318-321.

[6] Mahadevan, et al. 960 exposure to anti-TNF-alpha therapy in the third trimester of pregnancy is not associated with increased adverse outcomes:results from the PIANO registry. *Gastroenterology*. 2014;146(5):S170.

[7] Verstappen, et al. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2011;70:823-826.

- 88 live births
- 29 spontaneous abortions (no information about gestational age or fetal malformations)
- 10 elective terminations (no reason for termination was provided)
- one neonate death (perinatal hypoxia. The mother had been on etanercept)
- four intrauterine deaths (two deaths from two different sets of twins)
- four congenital abnormalities (congenital hip dislocation, pyloric stenosis winking jaw syndrome, strawberry birth mark)
- one full term infant with low birth weight

In a prospective 3-center study conducted between January 2007 and December 2012 (Bortlik, *et al*.), the authors reported on 41 pregnancies that were exposed to anti-TNF-α agents (infliximab: 31, adalimumab: 9). Of the nine patients exposed to adalimumab during pregnancy, eight pregnancies were exposed to adalimumab at conception, nine pregnancies were exposed during the first trimester, seven pregnancies were exposed during the second trimester, and three pregnancies were exposed during the third trimester. Of the nine patients exposed to adalimumab, one patient had an elective abortion due to personal circumstances. There were no congenital malformations in the patients exposed to adalimumab during pregnancy. The authors also noted that the rate of spontaneous abortions (12%) and low birth weight (3%) was not higher than the general population.[8]

In a report by the World Congress of Gastroenterology, the Organization for Teratology Information Specialists (OTIS) provided data on 38 women enrolled in a prospective study of adalimumab in pregnancy and 133 adalimumab-exposed pregnant women in a case series. The authors noted that rate of spontaneous abortion (5/38 [13%]), stillbirth (0 out of 38), and congenital malformation (2/33 [6.1%]) in the adalimumab-exposed group was similar to the disease- matched and general population when taking into account the reporting bias.[9]

In a letter to the editor (Jürgens, *et al*.), the authors described a case report of a 32 year-old female with Crohn's disease who was exposed to adalimumab during the first trimester of pregnancy. Adalimumab was discontinued at 7 weeks gestation. The mother delivered a healthy female infant. The authors also conducted a review of published literature and found 132 pregnancies that occurred in women treated with adalimumab during pregnancy. There were no cases of congenital abnormalities and no differences in the risk of spontaneous abortion and preterm delivery that were observed.[10]

[8] Bortlik, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-a therapy during pregnancy: three-center study. Scandinavian Journal of Gastroenterology. 2013; 48: 951-958.

[9] Mahadevan, et al. The London Position Statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: pregnancy and pediatrics. *Am J Gastroenterol.* 2011; 106:214-223.

[10] Jurgens, et al. Safety of adalimumab in Crohn's disease during pregnancy; case report and review of literature. Inflamm Bowel Dis. 2010; 16: 1634-1636.

In a review article (Kahn, *et al*.), the authors reviewed several case reports and case series[11,12] of adalimumab use in pregnant women and noted that there are no significant differences in the risk of spontaneous abortions or congenital malformations between women exposed to adalimumab during pregnancy compared to unexposed women.

DPMH's Review of Published Literature

DPMH performed a search of Micromedex[13] and in PubMed and Embase using the following search terms: "adalimumab" and "pregnancy" and "fetal malformations" or "miscarriage." In addition to the data reviewed by the applicant, DPMH reviewed additional published articles[14,15,16,17,18,19,20] in previous reviews of adalimumab. The reader is referred to previous DPMH reviews by Miriam Dinatale, D.O. for further details of published literature.[21,22]

Summary

There have been 669 adalimumab-exposed pregnancies reported in literature (adalimumab pregnancy registry, prospective and retrospective observational studies and case reports). Overall, maternal risks were not increased and fetal and infant risks, infection rates and immune development are similar to the rates seen in the disease-matched and general population. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and lack of control for disease activity or severity. There is no information specific to ABP 501 that would warrant different labeling for pregnancy.

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[11] Schnitzler, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis*. 2011;17:1846–1854.

[12] Weber-Schoendorfer, et al. Pregnancy outcome after TNF-a inhibitor therapy during the first trimester: A prospective multicentre cohort study. *Br J Clin Pharmacol.* 2015;80(4):727-739.

[13] www. Micromedexsolutions.com. Accessed 6/8/2016.

[14] Wallenius *et al*. Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. Acta Obstet Gynecol Scand epub ahead of print. 2013.

[15] Norgaard *et al* "Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study." *Journal of Internal Medicine*. 2010; 268: 329-337.

[16] Viktil et al. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150 000 pregnant women and expectant fathers. 2012 Scand J Rheumatol 41:196-201.

[17] Zelinkova A et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clinical Gastroenterology and Hepatology. 2013 11:318-321.

[18] Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol. 2014;43:78-84.

[19] Mahadevan, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterology Hepatology. 2013; 11(3): 286-92.

[20] Palmeira, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012; 2012: 985646.

[21] Division of Pediatric and Maternal Health review of 10th interim report of the adalimumab pregnancy registry report. IND 7627. Miriam Dinatale, D.O. November 3, 2014. DARRTS Reference ID 3650679

[22] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672

LACTATION

Applicant's Review of Published Literature

The applicant performed a literature review in PubMed and Ovid databases from January 2005 through March 2016 using the following search terms: "adalimumab" and "breastfeeding" or "lactation" to obtain information on adalimumab use during breastfeeding. A review of relevant published literature is provided below.

In a case report (Ben-Horin, *et al*.), a 26-year-old female with CD gave birth to a healthy term infant after receiving adalimumab until week 30 of gestation. The mother experienced a flare-up of CD at four weeks post-partum and restarted adalimumab (40mg) while continuing to breastfeed. Maternal blood and breast milk sample were obtained before and every two days for eight days after adalimumab administration. Sample collection stopped at day eight when the patient decided to stop breastfeeding (no reason provided). Following injection of adalimumab, adalimumab level rose in the maternal serum peaking at day three at 4300 ng/mL and declining after day three. Breast milk adalimumab levels were less than 1/100 (1%) of the corresponding maternal serum level. The milk drug level rose from undetectable (pre-adalimumab injection) to 31 ng/mL of post-injection day six. There were no reported adverse effects on the infant. The authors noted that small quantities of adalimumab would be present in breast milk and would be further broken down in the infant after ingestion. However, the authors noted that further studies would be needed to determine if even low levels of adalimumab would have an effect on an infant. [23]

DPMH's Review of Published Literature

In addition to the literature search performed by the applicant, DPMH performed a search of *Medications and Mother's Milk*[24], the Drugs and Lactation Database (LactMed),[25] PubMed, Embase and TERIS. The results of the literature search are described below.

In *Medication and Mother's Milk*, Dr. Thomas Hale, a breastfeeding expert, notes that IgG transfer into breast milk is highest in the first four days postpartum and is minimal afterwards. Immunoglobulins are transferred into breast milk by carrier protein, with IgA as the primary immunoglobulin seen in human milk. The transfer of IgG-like products is limited, and it is unlikely that adalimumab will be transferred into breast milk in clinically relevant amounts after the first week postpartum. However, data are limited.

LactMed notes that there are low levels of adalimumab in breast milk and no evidence of adverse effects of the drug on the breastfeeding infant. Since the molecular weight of adalimumab is large (148,000 Daltons), the amount of drug in the milk is likely to be low and

[23] Ben-Horin S, Yavzori M, Katz L et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol. 2010;8:475-6

[24] Hale, Thomas, Ph.D. Medications and Mother's Milk: A Manual of Lactational Pharmacology-2012, 15th edition. Hale Publishing, L.P.

[25] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

absorption is unlikely since the infants gastrointestinal tract destroys the drug. Since there is minimal information of adalimumab use during breastfeeding, LactMed recommends that caution should be used during breastfeeding.

As part of a multicenter prospective cohort study of pregnant woman with inflammatory bowel disease (IBD) and their offspring (PIANO Registry), breast milk samples were collected from patients on biologics (Infliximab (n=11), adalimumab (n=6), certolizumab (n=3)) at one, 12, 24 and 48 hours after drug administration. Data about the child's health and infections were obtained from mother's and from the child's pediatrician at 12, 24, 36 and 48 months of age. While infliximab was present in breast milk (90-591 ng/ml) between 24 and 48 hours after infusion, adalimumab and certolizumab were not detected in breast milk at any point in time. When comparing breastfed infants on biologics versus non-breastfed infants, there were no differences in infant development or rates of infection between the two groups.[26]

Reviewer comment:
The authors in the PIANO Registry collected breast milk samples only until 48 hours after adalimumab administration. Therefore, it is possible that the authors did not collect breast milk samples for an adequate duration of time and may have missed the appearance of adalimumab in breast milk.

In a case report (Fritzsche, *et al*.),[27] the authors reported on two patients who were treated with adalimumab 40mg for treatment of inflammatory bowel disease at unstated intervals. The detection limit of the assay for adalimumab in breast milk was 40ng/ml. The breast milk level of adalimumab was less than 1/1000 or 0.1% (4.83 ng/mL) of the corresponding maternal serum level in one patient and not detectable in the other patient. The reader is referred to the DPMH review by Miriam Dinatale, D.O for further details of the case report.[28]

Summary
Limited data from case reports in published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects (developmental delays or increase in infection) of adalimumab on the breastfed infant and no effects on milk production. Therefore the "Risk Summary" section of 8.2 will include the following statement:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [TRADENAME] and any potential adverse effects on the breastfed child from [TRADENAME] or from the underlying maternal condition.

[26] Matro, R. Detection of Biologic Agents in Breast Milk and Implication for Infection, Growth, and Development in Infants Born to Women with Inflammatory Bowel Disease: Results from the PIANO Registry. Gastroenterology. 2015. 148(4). Suppl 1.
[27] Fritzsche J , Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46:718-9
[28] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience

(b) (4)

Applicant's Review of Published Literature
The applicant performed a literature review in PubMed and Ovid databases from January 2005 through March 2016 using the following search terms: "adalimumab" and "fertility" to obtain information on adalimumab use and its effects on fertility. A review of relevant published literature is provided below.

Although clinical data is limited, adalimumab does not appear to affect female or male fertility. [29] In a retrospective study (Winger, E. and Reed, J.), 75 women with a history of recurrent SAB were evaluated. The patients were divided into three groups: 21 patients were treated with anticoagulants (heparin 5000 IU, Lovenox 30 or 40 mg , Clexane, or Arixtra), 37 patients were treated with anticoagulants plus intravenous immunoglobulin (IVIG at 400mg/kg) and 17 patients were treated with anticoagulants plus IVIG, and a TNF-α (Etanercept or adalimumab). The authors noted that in women with recurrent SAB, treatment with the addition of IVIG or a TNF- α inhibitor improved the live birth outcome compared to the group that was treated with an anticoagulant alone.[30]

DPMH's Review of Published Literature
In addition to the review of published literature performed by the applicant, DPMH also performed a literature review in PubMed and Embase using the key search words "adalimumab and fertility" and "adalimumab and sperm" Three relevant articles[31,32,33] were found and noted that exposure to anti-TNF therapy, including treatment with adalimumab, does not appear to adversely affect sperm quality or testicular function in male patients. The reader is referred to the DPMH review by Miriam Dinatale, D.O. for further details of the three published studies.[34]

Summary
Overall, it does not appear that adalimumab affects female or male fertility. Since there is no evidence that adalimumab impacts fertility, section 8.3, Females and Males of Reproductive Potential will be omitted from labeling.

[29] Grunewald S, Jank A. New systemic agents in dermatology with respect to fertility, pregnancy, and lactation. J Dtsch Dermatol Ges. 2015;13(4):277 -89.
[30] Winger, EE and Reed, JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. Am J Reprod Immunol. 2008; 60:8-16.
[31] Micu, et al. TNF-a inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology. 2014; 53(7):1250-5.
[32] Ramonda, et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014: 101(2): 359-365.
[33] Villiger, et al. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Annals of Rheumatic Disease. 2010. 69(10): 1842-4.
[34] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672.

CONCLUSIONS

ABP 501 (adalimumab-xxxx) labeling has been updated to comply with the PLLR. DPMH has the following recommendations for ABP 501 labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of ABP 501 (adalimumab-xxxx) labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections[35].
- **Lactation, Section 8.2**
  - The "Lactation" section of ABP 501 (adalimumab-xxxx) labeling was formatted in the PLLR format to include the "Risk Summary" section[36].

RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 in ABP 501 (adalimumab-xxxx) labeling for compliance with the PLLR (see below). See Appendix A for the applicant's proposed pregnancy and lactation labeling. DPMH refers to the final BLA action for final labeling.

[35] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[36] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

DPMH Proposed ABP 501 (adalimumab-xxxx) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Limited clinical data are available from the adalimumab pregnancy registry. Excluding lost-to-follow-up, data from the registry report an incidence of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations
Fetal/Neonatal adverse reactions
Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *[see Data]*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to [TRADENAME] *in utero [see use in Specific Populations (8.4)]*.

Data
Human Data
In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non- randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with adalimumab, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of adalimumab was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and

0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [TRADENAME] and any potential adverse effects on the breastfed child from [TRADENAME] or from the underlying maternal condition.

MEDICATION GUIDE

What should I tell my doctor before taking [TRADENAME]**?**

- are pregnant or plan to become pregnant. It is not known if HUMIRA will harm your unborn baby. [TRADENAME] should only be used during a pregnancy if needed.
- have a baby and you were using [TRADENAME] during your pregnancy. Tell your baby's doctor before your baby receives any vaccines.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use [TRADENAME]. You should not do both.

APPENDIX A – Applicant's Proposed ABP 501 (adalimumab-xxxx) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

(b) (4)

Clinical Considerations

(b) (4)

Data
Human Data

(b) (4)

Animal Data

(b) (4)

8.2 Lactation

(b) (4)

Appendix B: Applicant's Summary of Published Studies with Use of Adalimumab During Pregnancy. See Appendix C for references.

Table 1. Published IBD Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Vesga et al	CD	ADA	2005	P(T1-T3) and breast-feeding	Case Report (1)	C-section	Normal, healthy, 38.5 weeks
Mishkin et al	CD	ADA	2006	PC/P(T1-T3)	Case Report (1)	Vaginal	Normal, healthy, full term
Coburn et al	CD	ADA	2006	P(T2; T3)	Case Report (1)	Unknown	Normal, healthy, 38 weeks
Bosworth et al	CD	ADA	2007	PC/P(T1-T3)	Case Report (1)	C-section	Normal, health, 36 weeks
Ben-Horin et al	CD	ADA	2010	PC/P(T1-T3) and breast-feeding	Case Report (1)	Vaginal	Healthy, normal, full term; no adverse effects from breast-feeding
Jürgens et al	IBD	ADA	2010	PC/P(T1)	Case Report (1)	Vaginal	Healthy, full term
Abdul Wahab and Harkin	CD	ADA	2011	PC/P(T1-T3)	Case Report (1)	C-section	Twins, normal, healthy, full term
Sujikawa et al	CD	ADA	2013	P(T1-T3)	Case Report (1)	Unknown	Normal, healthy, full term
Julsgaard et al	CD	ADA	2013	P(T1-T2)	Case Report (1)	Unknown	Normal, healthy, full term
Bortlik et al	IBD	IFX/ADA[a]	2013	PC/P(T1-T3)	Prospective 3-center study (41 total; 32 [IFX]; 9 [ADA])	Unknown	34 live births; 28 full term; 6 preterm; 5 spontaneous abortions; 2 therapeutic abortions; 1 congenital abnormality (hip dysplasia). (ADA-only data not available)
Seirafi et al	IBD	IFX/ADA/CZP[a]	2011	PC/P(T1-T3)	Case series (85 women)	Unknown	6/85 were miscarriages, 47/85 were live births (30/85 ongoing), 8/49 were preterm, 3/49 were deaths (2 in utero/1 very premature),7/46 live births had neonatal complications (1 infection, 3 respiratory distress syndrome, 6 LBW <2500 g, 1 HELLP syndrome

Table 1. Published IBD Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Casanova et al	IBD	IFX/ADA/CZP[a]	2011	PC/P(T1-T3)	Case-controlled retrospective study (30 pregnancies in treated mothers vs. 110 unexposed IBD pregnancies)	Unknown	Prevalence of unfavorable delivery outcome (eg, spontaneous abortion, preterm delivery, low birth weight and abnormalities) were higher in the control group
Mahadevan et al	IBD	IFX/ADA/CZP[a]	2013	PC/P(T1-T3)	Case series (31 women)	15 vaginal; 16 C-section	All 33 children (2 sets of twins) were normal, healthy, full term
Casanova et al	IBD	IFX/ADA/CZP[a]	2013	PC/P(T1-T3)	Case series (66 pregnancies)	Unknown	55 normal, healthy full term; 4 preterm; 6 miscarriages; 1 congenital abnormality (several cardiac abnormalities)
Dunne et al	CD	IFX/ADA[a]	2011	PC/P(T1-T3)	15 case series (15 women; 3 ADA pregnancies)	Unknown	9 successful pregnancies at study end. All live births were healthy, but 5 LBW, with two sets of twins. No congenital abnormalities
Schnitzler et al	IBD	IFX/ADA[a]	2011	PC and/or P(T1) and/or P(T2)	Case-controlled study (35 women with 42 pregnancies (35 IFX + 7 ADA) vs. 101 pregnancies before IBD/ treatment and 56 matched pregnancies in healthy controls)	Unknown	10 abortions (1 trisomy 18, 1 elective), 1 stillbirth (umbilical strangulation), 32 live births: 8/32 premature, 6/32 LBW. All children were born healthy but 1 child with necrotizing enterocolitis died at 13 days of age (mother required treatment for severe asthma and CD during T3)

Table 1. Published IBD Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Machková et al	IBD	IFX/ADA[a]	2012	PC/P(T1-T3)	Case series (33 pregnancies in 31 women)	Unknown	5/33 pregnancies ongoing. 24/28 healthy children (4/24 preterm), 3/24 spontaneous abortions, and 1/24 provoked abortion
Zelinkova et al	IBD	IFX/ADA[a]	2013	PC/P(T1-T3) (T1-T2 ADA only)	Case series (31 pregnancies in 28 women)	Unknown	28 live births (27 normal, healthy, full term; 1 child born to a mother treated with concomitant methotrexate periconceptually had polydactyly); 3 miscarriages
Traussnigg et al	IBD	IFX/ADA[a]	2013	PC/P(T1-T3)	Case series (14 pregnancies in 13 women)	Unknown	13 normal, healthy, full term; 1 miscarriage
Habal	IBD	IFX/ADA[a]	2013	PC/P(T1-T3)	Prospective study (29 pregnancies in 21 women)	Unknown	27 normal, healthy, full term; 2 miscarriages
Mahadevan et al	IBD	ADA/IFX/CZP	2014	PC/P(T1-T3)	Prospective cohort study (1289 exposed to anti-TNF-α agents; 174 infants exposed to ADA; 117 exposed in T3)	Unknown	Anti-TNF-α results: 1039 live births. No significant difference in infection rates or immune developmental achievements of those exposed compared to unexposed

Adopted from Dessinioti et al, 2011; Nielsen et al, 2013; and Diav-Citrin et al, 2014.
ADA = Adalimumab; CD = Crohn's disease; CZP = Certolizumab; ETA = Etanercept; IBD = Irritable Bowel Disease; IFX = Infliximab; JIA = juvenile idiopathic arthritis; LBW = Low birth weight; P(T1-T3) P(T1-T3) = biologics administered in trimester 1 through 3; PC = Periconceptual (ie, use within 90 days before conception).
a: Independent data for ADA not available. Data reported for all anti-TNF-α agents.

Table 2. Published Rheumatology Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Hyrich et al	RA	ADA	2006	PC/P(T1)	Case Series (3 pregnancies)	Vaginal	2 live births, 1 miscarriage in first trimester, no major fetal abnormalities
Roux et al	RA	ADA	2007	PC	Case Report (1)	Vaginal	Normal, healthy, born at 32 weeks (healthy at 12 month follow-up)
Kraemer et al	Takayasu's arteritis	ADA	2008	P(T1)	Case Report (1)	C-section	Normal, healthy, 37 weeks gestation
Berthelot et al	RA and spondyl-arthropathy	ADA	2009	P(T1-T3)	Case Series (2 pregnancies)	1 vaginal; 1 C-section	1 infant born at 37 weeks, healthy; the other infant born at 38 weeks, healthy
Chambers et al	RA	ADA	2015	PC/P(T1-T3)	Case series (74 ADA, 80 DM, 218 ND)	Unknown	Total of 334 live births. Congenital abnormalities in 4, 6, and 12 births in ADA, DM, and ND, respectively
Verstappen et al	RA/PsA/JIA /AS/SLE/Still's disease	IFX/ADA/ETA[a]	2011	PC/P(T1-T3)	Case Series (130 total pregnancies [exposed to anti-TNF-α]; 26 ADA)	Unknown	88 live births (anti-TNF-α exposure); 29 spontaneous abortions; 10 terminations; 1 neonate death; 4 intrauterine deaths (2 were twins); 19 premature; 1 full term infant with LBW; and 4 congenital abnormalities (ADA-only data unavailable)

Adopted from Dessinioti et al, 2011; Nielsen et al, 2013; and Diav-Citrin et al, 2014.
ADA = Adalimumab; AS = ankylosing spondylitis; DM = Disease-matched; ETA = Etanercept; IFX = Infliximab; JIA = juvenile idiopathic arthritis; LBW = Low birth weight; ND = Nondiseased-matched; P(T1-T3) P(T1-T3) = biologics administered in trimester 1 through 3; PC = Periconceptual (ie, use within 90 days before conception); PsA = psoriatic arthritis; RA = Rheumatoid arthritis; SLE = Systemic lupus erythematosus.
a: Independent data for ADA not available. Data reported for all anti-TNF-α agents.

Table 3. Published Studies and Cases on the Use of Adalimumab During Pregnancy in Multiple Conditions and Infertility

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Winger et al	Infertility	ADA	2009	PC	Prospective study (47 pregnancies)	Unknown	33 live births
Johnson et al	Multiple (RA and CD)	ADA	2009	PC/P(T1-T3)	Case–control (85 women)	Unknown	71 live births; 13 miscarriages; 1 therapeutic abortion; 11 preterm. Rate of abortion in ADA-exposed group was 15.3% vs. 5.3% in DM controls; 7 major defects
Mahadevan and Miller et al	Multiple	ADA	2011	PC/P(T1-T3)	Case series (5 women)	2 vaginal; 3 C-sections	Healthy (1 infant developed pulmonary edema, but recovered fully)
Weber-Schoendorfer et al	Multiple	ADA/IFX	2011	P(T1)	Case series (85 pregnancies; 28 ADA-exposed pregnancies)	Unknown	24 live ADA births total; 2 ADA miscarriages; 2 ADA voluntary terminations; 4 ADA premature births; 1 ADA autosomal disease inherited
Weber-Schoendorfer et al	Multiple	IFX/ADA/CZP /GOL/ETA[a]	2015	P(T1)	Prospective cohort study (495 exposed to anti-TNF-α; 172 exposed to ADA)	Unknown	ADA data: 144 live births; 9 birth defects; 25 preterm; LBW tendency in the ADA-exposed group
Diav-Citrin et al	Multiple	IFX/ADA/ETA[a]	2014	P(T1-T3)	Prospective, comparative study (35 IFX; 25 ETA; 23 ADA; 86 DM untreated; 341 unexposed pregnancy controls)	43 vaginal; 22 C-section; 1 vacuum	Anti-TNF-α group: 67 live births; 9 miscarriages; 5 elective abortions; 1 stillbirth; 1 ectopic; 3 major abnormalities; 3 major non-genetic or cytogenic abnormalities; 1 congenital abnormality in ADA group

Table 3. Published Studies and Cases on the Use of Adalimumab During Pregnancy in Multiple Conditions and Infertility

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Slama et al	Multiple	IFX/ADA[a]	2010	PC/P(T1-T3)	Case series (289 pregnancies)	Unknown	No increased risk of adverse pregnancy outcome compared with unexposed IBD pregnancies
Julsgaard et al	Multiple	IFX/ADA[a]	2015	PC/P(T1-T3)	Case-controlled, prospective study (89 pregnancies)	Unknown	5 miscarriages, 3 preterm births, 3 LBW, and 2 congenital abnormalities

Adopted from Dessinioti et al, 2011; Nielsen et al, 2013; and Diav-Citrin et al, 2014.
ADA = Adalimumab; CZP = Certolizumab; DM = Disease-matched; ETA = Etanercept; GOL = golimumab; IFX = Infliximab; LBW = Low birth weight; P(T1-T3) P(T1-T3) = biologics administered in trimester 1 through 3; PC = Periconceptual (ie, use within 90 days before conception); RA = Rheumatoid arthritis.
a: Independent data for ADA not available. Data reported for all anti-TNF-α agents.

Appendix C: Applicant's References

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/s/

MIRIAM C DINATALE
09/23/2016

LYNNE P YAO
09/28/2016

FINAL LABEL AND LABELING REVIEW

Date:	September 22, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products
Through:	Jun Park, PhD, Quality Reviewer Division of Biotechnology Review and Research II
Application:	BLA 761024/0
Product:	Amjevita (adalimumab-atto*)
Applicant:	Amgen Inc.
Submission Dates:	November 25 2015; September 21, 2016

Executive Summary:

The PI, IFU, MG, container labels, and carton labeling for Amjevita (adalimumab-atto*) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. Labeling deficiencies were identified and resolved. The labels and labeling submitted on September 21, 2016 are acceptable.

Background and Summary Description:

The Applicant submitted a 351(k) BLA 761024 Amjevita (adalimumab-atto*) on November 25 2015 as a proposed biosimilar to US-licensed Humira (adalimumab). Table 1 lists the proposed characteristics of Amjevita (adalimumab-atto*). This review evaluates the Applicant's container labels and carton labeling submitted on November 25, 2015 (Application 761024 - Sequence 0001 - 0001 (1) 11/25/2015 ORIG-1 /Multiple Categories/Subcategories).

* Amjevita has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Subsequent to submission of the 351(k) BLA, the nonproprietary name for Amjevita was determined to be adalimumab-atto.

Table 1: Proposed Product Characteristics of Amjevita (adalimumab-atto*).

Proprietary Name:	Amjevita
Proper Name:	adalimumab-atto*
Indication:	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis
Dose:	20 mg to 160 mg depending on indication
Route of Administration:	Subcutaneous
Dosage Form:	Injection
Strength and Container-Closure:	20 mg/0.4 mL or 40 mg/0.8 mL prefilled syringe (PFS) 40 mg/0.8 mL autoinjector (AI)
Storage and Handling:	Refrigerate at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, AMJEVITA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. AMJEVITA should be discarded if not used within the 14-day period. Record the date when AMJEVITA is first removed from the refrigerator in the spaces provided on the carton. Do not store AMJEVITA in extreme heat or cold.

Materials Reviewed:

Container Labels

- PFS 20 mg/0.4 mL , PFS 40 mg/0.8 mL, AI 40 mg/0.8 mL

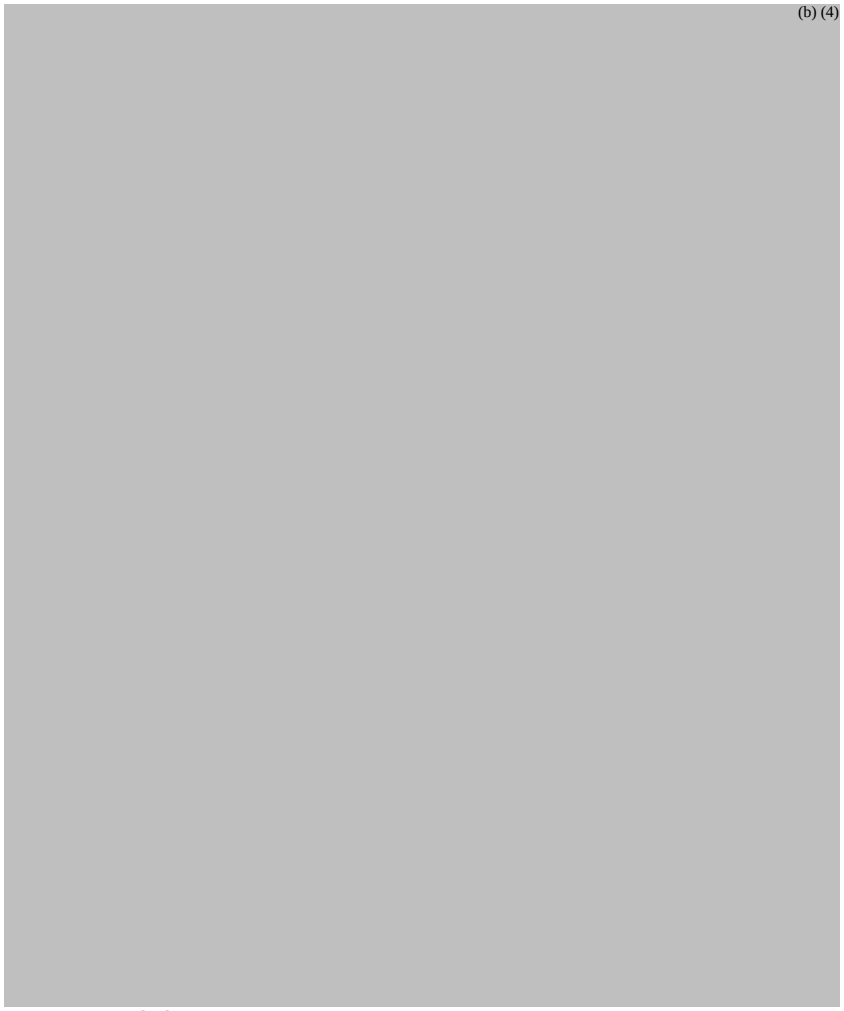
Carton Labeling

- PFS 20 mg/0.4 mL count-1
- PFS 40 mg/0.8 mL, 1-count, 2-count**, (b) (4)
- AI 40 mg/0.8 mL, 1-count, 2-count**, (b) (4)

Note: the Applicant decided not to market the (b) (4) count package configurations.

** Graphic not included in the images.

Start of Sponsor Material



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label; *the PFS and AI for this product have partial labels (see below). However, there is space on the label to allow for placement of some of the items recommended for the full label*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum

- the name (expressed either as the proper or common name); *conforms*. *However, we recommend adding the proprietary name*.

  OBP Requests:
  Update the trade name on the container labels and carton labeling to display Amjevita instead of Trade Name.
  Applicant revised as requested.

- the lot number or other lot identification; *conforms*.
- the name of the manufacturer; *conforms*.
- in addition, for multiple dose containers, the recommended individual dose. *conforms*.
- Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered

for its full length or circumference to permit inspection of the contents; *conforms*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Requests:
PFS
Reduce the prominence of the "Rx Only" statement by un-bolding and reducing the size of the font. As currently presented, it is more prominent than more relevant information such as the proper name.
Applicant revised as requested.

AI
Relocate the statement "SureClick Prefilled Autoinjector" below the strength statement.
Applicant revised as requested.

Relocate "Single-Use" to appear under the route of administration To make space, consider deleting the following information that is not required on the partial label per 21 CFR 610.60(c).

- U.S. license number No. 1080
- Storage information.

Applicant revised as requested.

Revise the light blue color font used for most of the information presented on this label to a darker color to improve contrast and legibility. As currently presented, the contrast between the light blue font and white background make the label difficult to read.
The Applicant provided a visual representation of how the label will appear on the blue colored pen. The colors are acceptable.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *does not conforms*.

OBP Requests:
PFS and AI

(b) (4)

only the actual net content (i.e. 20 mg/0.4 mL or 40 mg/0.8 mL) is required on the labels per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drugs Products.
Applicant revised as requested.

PFS
Revise the strength statement so that it is presented only once as "20 mg/0.4 mL" or 40 mg/0.8 mL" to prevent clutter and improve legibility on these small labels. For this single-dose injectable drug product, the strength per total volume should be the primary and prominent expression on the principal display panel (PDP) of the label. For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drugs Products.
Applicant revised as requested.

AI
Revise the strength statement so that it is presented only once as "40 mg/0.8 mL" to prevent clutter and improve legibility on these small labels. Consider relocating "Single-Use" from next to the strength statement to appear under the route of administration.
Applicant revised as requested.

K. 21 CFR 201.55 Statement of dosage; *not applicable*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

Start of Sponsor Material

(b) (4)

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

(b) (4)

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms.*

b) The name, addresses, and license number of manufacturer; *conforms. However, OBP recommends relocating the manufacturer information from the crowded PDP and ensuring the license number appears with the name and address*.

OBP Requests:
Relocate the manufacturer information from the crowded PDP to a side panel.
Applicant revised as requested.

Relocate the license number to appear with the manufacturer name and address.
Applicant revised as requested.

c) The lot number or other lot identification; *conforms*.

d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.

f) The number of containers, if more than one; *conforms*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *does not conform*.

OBP Request:
(b) (4)
, only the actual net content (i.e. 20 mg/0.4 mL or 40 mg/0.8 mL) is required on the labels per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drugs Products.
Applicant revised as requested.

Revise the strength statement that appears next to the (b) (4) image representing the prefilled syringe or autoinjector from (b) (4) to read "20 mg/0.4 mL" or "40 mg/0.8 mL".

On 9/15/2016, the Applicant provided revised labeling with the strength presentation appearing as:

40
mg/
0.8 mL

On 9/16/2016, we requested the following:
Revise the strength presentation on the carton labeling similar to other Amgen products such as Repatha (evolocumab), Blincyto (blinatumomab), and Neulasta Onpro (pegfilgrastim).

40
mg/0.8 mL

or

40 mg/
0.8 mL
Applicant revised as requested.

h) The recommended storage temperature; *conforms*. *However, we recommended improving the instructions*.

OBP Request:
Revise the patient/caregiver storage instructions on the side panel of the 1-count and 2-count cartons to read:

> Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If needed, Amjevita may be kept at room temperature up to 77°F (25°C) in the original carton and must be used within 14 days. (b) (4) the date removed from the refrigerator. ___/___/___

Note replacement (b) (4) with "___/___/___" to allow users to fill in the actual date.
Applicant revised as requested.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; *not applicable*.

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above); *conforms*. *However, we recommend placement on the PDP*.

  OBP Request:
  PFS
  Relocate the medication guide statement ("ATTENTION: Enclosed Medication Guide is required for each patient) to the principal display panel where the statement "Carton (b) (4): ..." is located.
  Applicant revised as requested.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Amjevita (adalimumab-atto*) is a monoclonal antibody and therefore is exempt*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *not applicable*.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Requests:
PFS and AI
As currently presented, "Injection" appears obstructed by the blue and yellow graphic next to the proper name "adalimumab-atto*". Revise the blue and yellow graphic so that "Injection" can appear in its customary presentation centered or left justified under the proper name.
Applicant revised as requested.

PFS
Consider revising the white font used on the side panels to a black font to improve contrast and legibility. As currently presented, the small size font and low contrast between the white font over blue background makes the information difficult to read.
Applicant revised as requested.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform*.

OBP Request:
(b) (4)
only the actual net content (i.e. 20 mg/0.4 mL or 40

mg/0.8 mL) is required on the labels per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drugs Products. *Applicant revised as requested*.

Revise the strength statement that appears next to the (b) (4) image representing the prefilled syringe or autoinjector from "(b) (4)" or "(b) (4)" to read "20 mg/0.4 mL" or "40 mg/0.8 mL".

On 9/15/2016, the Applicant provided revised labeling with the strength presentation appearing as:

40
mg/
0.8 mL

On 9/16/2016, we requested the following:
Revise the strength presentation on the carton labeling similar to other Amgen products such as Repatha (evolocumab), Blincyto (blinatumomab), and Neulasta Onpro (pegfilgrastim).

40
mg/0.8 mL

or

40 mg/
0.8 mL

Applicant revised as requested.

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *does not conform.*

OBP Request: Revise the list of ingredients to be consistent with the *Description and Composition of the Drug Product* submitted in the BLA. Additionally, list the names of the inactive ingredients in alphabetical order per USP, General Chapters: <1091> Labeling of Inactive Ingredients. For example:

Each single-use prefilled syringe delivers x mL containing adalimumab-atto* x mg, glacial acetic acid (x mg), polysorbate 80 (x mg), sodium hydroxide for pH adjustment, sucrose (x mg), and Water for Injection, USP.

Applicant revised as requested.

Additional Labeling Recommendations:

This section contains additional labeling recommendations based of CDER's Labeling preferences. The Applicant agreed to all these recommendations.

A. PFS and AI Carton Labeling
   1. Consider revising the schematic image of the prefilled syringe and Sureclick Autoinjector by utilizing a more accurate image or photo.

B. PFS Carton Labeling
   1. Delete the strength statement on the side panels or consider adding the proprietary name, proper name, and dosage form along with strength in the customary presentation.

   2. Relocate the statement "(b) (4): ..." to the side panel where the medication guide statement is located.

   3. We note that section 16 of the prescribing information details the different needle sizes for each configuration of the prefilled syringes along with the associated NDC. Add the needle size to the "Carton contents" statement. For example:

      Carton contents (1 prefilled syringe with 27 gauge needle, 1 package insert...

Conclusions:

The PI, IFU, MG, container labels, and carton labeling for Amjevita (adalimumab-atto*) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. Labeling deficiencies were identified and resolved. The labels and labeling submitted on September 21, 2016 are acceptable (see container labels and carton labeling below).

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIBRIL ABDUS-SAMAD
09/22/2016

JOEL T WELCH
09/22/2016

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
MEMORANDUM

Date: September 22, 2016

To: File

From: CDR Alan Stevens, Branch Chief

Subject: Consult for BLA 761024, ICC 1600028

Applicant	Amgen
Indication for Use	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease, Pediatric Crohn's Disease, Plaque Psoriasis (PsO), Ulcerative Colitis (UC)
Drug / Biologic Constituent	ABP501
Device Constituent	SureClick Autoinjector and prefilled syringe

Recommendation: Approve

Digital Signature Concurrence Table

Alan M. Stevens -S

Digitally signed by Alan M. Stevens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S
Date: 2016.09.22 15:13:17 -04'00'

Summary of Review

Dr. Lana Shiu provided a complete review of the device constituent parts of the ABP501combination product on March 2, 2016. This review is attached as Appendix A. Dr. Shiu's review covered the device design control documentation, including design requirements, verification and validation data.

The device constituent is the SureClick injector, produced for Amgen by (b) (4). Amgen has another BLA approved with a similar device constituent (BLA 103795, Enbrel).

The purpose of this summary review is to cover the Design Transfer information for the device and assure that essential performance requirements are transferred to the appropriate product in-process controls and release specifications.

Device Description and Specifications

The submission contains two device constituents for injection of ABP501:

prefilled syringe:

Note: CDRH reviewed the device data for the following presentations that were originally submitted. However, only the PFS with 29G needle will be marketed at this time.

ABP 501 is available in the following prefilled syringe (PFS) presentations:

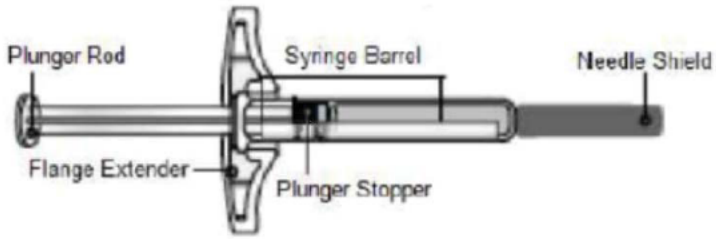
(b) (4)

☐40 mg (0.8 mL) PFS with a 29-gauge (29G) staked-in-place needle

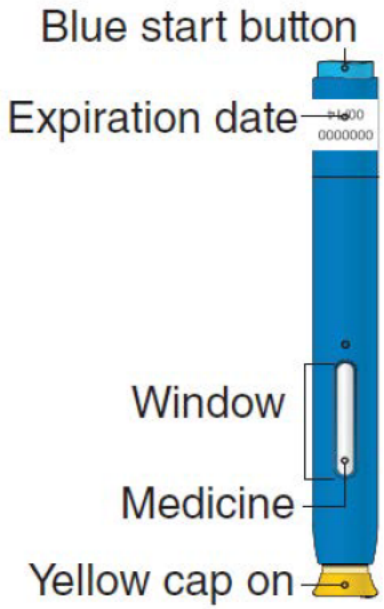
(b) (4)

☐20 mg (0.4 mL) PFS with a 29G staked-in-place needle

Figure 1. Prefilled Syringe Components



autoinjector:



Attribute	Specification
Deliverable Volume	(b) (4) mL
Injection time	(b) (4) seconds

Needle depth	(b) (4) mm
Activation Force	(b) (4) kgf

Design Verification and Validation

The verification and validation data are covered in Dr. Shiu's review memo (Appendix A).

Design Transfer Information - Release Specifications and In-Process Controls - Autoinjector
The device constituent release specifications for the product are contained in eCTD module 3.2.P.5

> The autoinjector (AI) contains a prefilled syringe (PFS). The PFS drug product is tested and released per the specification provided in 3.2.P.5.1 (Specification - PFS).
>
> The release specification for the AI with drug product is provided in Table 1.

Table 1. Autoinjector with Drug Product Specification

Parameter	Test Method	Acceptance Criteria
Device functionality	Injection time	(b) (4) seconds
	Deliverable volume	(b) (4) mL

An Information Request was issued to Amgen on July 29, 2016

> *We generally expect that the release specifications for autoinjectors would include the performance requirements deemed to be essential to the functioning of the device. These may include deliverable volume, injection time and needle extension length. The currently proposed release specifications include deliverable volume and injection time. The June 29, 2016, information amendment references design verification data covered in section 3.2.P.7, which we agree are adequate for the purposes of verifying the design requirements. However, this information is not adequate to assure that the release product meets its performance requirements. Modify the release specifications in Section 3.2.P.5 to include the needle extension length specification, or provide an explanation for how the in-process controls* (b) (4) *are adequate to assure that the finished product will meet the needle length extension specification.*

In a response dated August 2, 2016, Amgen agreed to establish in-process controls (IPC) (b) (4) . Amgen updated eCTD module 3.2P.3.3 to cover the additional IPC.

In-process Control	Details
(b) (4)	

	(b) (4)

Release Specifications – Prefilled Syringe

Table 1. Drug Product Release Specification

Parameter	Test Method	Acceptance Criteria
Appearance	Appearance	Liquid, practically free from particles
	Color	≤ (b) (4)
	Clarity	≤ Reference III
Identity	ABP 501 ELISA	Pass[a]
Purity	CEX-HPLC	Main peak: ≥ (b) (4)%
		Basic peaks: ≤ (b) (4)%
		Acidic peaks: ≤ (b) (4)%
	SE-HPLC	HMW: ≤ (b) (4)%
	rCE-SDS	Heavy chain + light chain: ≥ (b) (4)%
Adventitious agents	Bacterial endotoxins	≤ (b) (4) EU/mg
	Sterility	Pass[b]
Potency	Apoptosis inhibition bioassay	(b) (4)% relative potency
Quantity	Deliverable volume[c]	
	0.8 mL	Pass ((b) (4) mL)
	0.4 mL	Pass ((b) (4) mL)
General	Subvisible particles	≤ (b) (4) µm per container
		≤ (b) (4) µm per container
Functionality	Breakloose and extrusion	≤ (b) (4) N

[a] For ABP 501 ELISA, "Pass" is defined as an optical absorbance signal-to-noise ratio for each sample replicate ≥ (b) (4)
[b] "Pass" is equivalent to no growth.
[c] Deliverable volume is determined by real-time release testing (RTRT) through evaluation of (b) (4) (b) (4)

Conclusion

Based on the design verification / validation review provided by Dr. Shiu, and the additional IPC and release specification information documented in my review, I recommend that the device constituents are approvable.

APPENDIX A

DR. LANA SHIU – Review Memo

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 28, 2016

From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Sadaf Nabavian/Ladan Jafari
Division of Pulmonary and Rheumatology Product, Office of New Drugs, CDER

Via: Keith Marin
Combination Products Team Leaders, GHDB, DAGRID, CDRH

CDR Alan Stevens
Acting Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH
Subject: BLA 761024-ABP 501 Biosimilar to Humira (adalimumab) 50 mg/mL Injection (in 0.4ml and 0.8ml prefilled syringe presentation) /Applicant: Amgen
CDRH Tracking: ICC160028

Indication: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease, Pediatric Crohn's Disease, Plaque Psoriasis (PsO), Ulcerative Colitis (UC)
Consult Request: request for a collaborative review of the device component data submitted by Amgen for their proposed auto-injector and prefilled syringe as s single-use device.

Background: ABP 501 will be supplied as a sterile, preservative-free solution of ABP501 (TNF-alpha inhibitor) for subcutaneous administration. The drug will be supplied as either a single-use, 1 mL prefilled glass syringe or as a single-use, prefilled SureClick® autoinjector. Enclosed within the autoinjector is a single-use, 1 mL prefilled glass syringe with a (b) (4) stainless steel needle. ABP 501 will be dispensed at 0.4mL and 0.8mL of 50mg/mL concentration.
Amgen currently already has another TNF-alpha inhibitor (treating the similar patient population) on the market called Enbrel/Entanercept BLA103795. Amgen intends to use the same device constituent of PFS ((b) (4) **) and SureClick 1.5 autoinjector (**developed by (b) (4) - BLA 103795/S-5532 ***approved by FDA on 20 March 2015***) **to be fill with the current TNF-alpha inhibitor/ABP 501. The difference is the color scheme on the injector.**

BLA103795/S5532	**Enbrel/SureClick 1.5**	**ICC1400747**	**CDRH: Keith Marin/Ryan McGowan**

Component	Device Configurations	
	ABP 501 AI Commercial Configuration	Enbrel Updated SureClick AI Commercial Configuration[a]
		(b) (4)
Color shell	Blue	Teal
Color plunger rod		(b) (4)
Color needle cover	Yellow	Dark teal
Color cap	Yellow	White
Color activation button	Cool blue	Purple
Activation sequence	2	2
Needle cover stop	Protrudes 1 mm	Protrudes 1 mm

[a] The Enbrel commercial configuration was used in the human factors formative and summative studies.

☐ ABP 501 and Enbrel have similar user populations, including users with hand dexterity issues.
☐ The only difference between the Enbrel updated SureClick AI device and the ABP 501 AI device is the exterior color.
☐ ABP 501 AI has shorter injection time than the Enbrel updated SureClick AI due to (b) (4) .

PFS-Device Description:

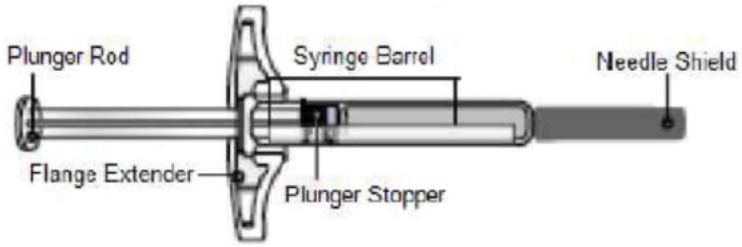
The ABP 501 PFS is a single-use, disposable, handheld drug delivery device. The PFS incorporates a rigid needle shield (RNS), which is a non-rigid rubber needle shield with a rigid plastic cover, and a flange extender (Figure 1). The PFS may have (b) (4) (29G) needle. (b) (4)

ABP 501 is available in the following prefilled syringe (PFS) presentations: (b) (4)

☐40 mg (0.8 mL) PFS with a 29-gauge (29G) staked-in-place needle (b) (4)

☐20 mg (0.4 mL) PFS with a 29G staked-in-place needle

Figure 1. Prefilled Syringe Components



Device Principle of Operation

This manual subcutaneous injection via prefilled syringe does not include fill level indicators or graduation marks because the product is a single dose, single use injection system. It is intended that the complete syringe volume will be injected and the empty syringe will be disposed.

Biocomaptibility-Prefilled syringe –Consulted to Dr. Bifeng Qian of INCB

Table 2. Biocompatibility Results – Plunger Rods and Flange Extender

Test	Test Method Reference	Acceptance Criteria	PFS Component	Result
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – In vitro methods	Cytotoxicity according to ISO 10993-5 Section 8.5	Plunger Rod (b) (4)	Pass
			Plunger Rod (b) (4)	Pass
			Flange Extender	Pass
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation	Sensitization according to ISO 10993-10 Section 7.5.6	Plunger Rod (b) (4)	Pass
			Plunger Rod (b) (4)	Pass
			Flange Extender	Pass
Irritation	ISO 10993-10: Tests for Sensitization and Irritation	Irritation according to ISO 10993-10 Section 6.4.7	Plunger Rod	Pass
			Plunger Rod (b) (4)	Pass
			Flange Extender	Pass

From: Qian, Bifeng
Sent: Monday, March 28, 2016 11:36 AM
To: Shiu, Lana
Cc: Murray III, Clarence; Claverie, Elizabeth F
Subject: RE: BLA 761024-Biocompatibility

Hi Lana,
Biocompatibility information provided in BLA 761024 for the (PFS configuration) (b) (4) prefilled syringe is deemed adequate.

Thank you,

BiFeng

PFS Description of Components and Materials of Construction

Component	Material	Drug Product Contacting (Fluid Path)	User Contacting
Barrel	(b) (4)	Yes	Yes
Needle		Yes	Yes
Plunger-stopper		Yes	No
Non-rigid needle shield		Yes	Yes
Needle shield outer plastic cover		No	Yes
Flange extender		No	Yes
Plunger rod		No	Yes

Component	Parameter	Specification	Test Method
Product contact components		(b) (4)	
Syringe barrel with staked needle	Material requirements		Manufacturer's certificate
	Barrel inner diameter		Measurement
	Minimum glaze-in diameter after flanging		Measurement
	Length (without needle shield)		Measurement
	Needle length		Measurement
	Needle gauge		Manufacturer's certificate
	(b) (4)		Manufacturer's certificate
			Manufacturer's certificate
			Manufacturer's certificate
Plunger-stopper	Material requirements		Manufacturer's certificate
			Manufacturer's certificate
	Outer diameter (b) (4) (b) (4)		Measurement
	Maximum trim outer diameter		Measurement
	Overall length		Measurement
Non-rigid needle shield	Material requirements		Manufacturer's certificate
			Tested

Component	Parameter	Specification	Test Method
Non-product contact components		(b) (4)	
Plunger rod	Material requirements		Manufacturer's certificate
	Overall length		Measurement
	Shaft diameter		Measurement
Rigid needle shield	Material requirements		Manufacturer's certificate
Flange extender	Material		Manufacturer's certificate
	Overall length		Measurement
	Inside diameter		Measurement

Table 1. Standards Applicable to PFS

Document Number	Year Published	Document Title
ISO 10993-1	2009	Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process
ISO 10993-5	2009	Biological Evaluation of Medical Devices – Part 5: Tests for in vitro cytotoxicity
ISO 10993-7	2008	Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals.
ISO 10993-10	2010	Biological Evaluation of Medical Devices – Part 10: Tests for irritation and skin sensitization
ISO 15223-1	2012	Medical Devices-Symbols to Be Used With Medical Device Labels, Labeling and Information to Be Supplied-Part 1: General Requirements
EN 1041	2008	Information supplied by the manufacturer of medical devices
IEC 62366	2007	Medical Devices – Application of Usability Engineering to Medical Devices
ISO 11040-4	2007	Prefilled Syringes – Part 4: Glass Barrels for injectables
ASTM D4169	2009	Standard Practice for Performance Testing of Shipping Containers and Systems.
ISO 14971	2007	Medical devices – Application of Risk Management to Medical Devices.
EN 556-1	2007	Sterilization of Medical Devices – Requirements for Medical Devices to be Designated "Sterile" – Part 1. Requirements for Terminally Sterilized Medical Devices.
ASTM F1980	2007	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
AAMI TIR16	2009	Microbiological Aspects of Ethylene Oxide Sterilization.
ISO 11135-1	2007	Sterilization of Health Care Products – Ethylene Oxide Part 1: Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices.
ISO 11137-1	2006	Sterilization of health care products – Radiation – Part 1: Requirements for development, validation, and routine control of sterilization process for medical devices.
ISO 11137-2	2013	Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose.

Document Number	Year Published	Document Title
ISO 11137-3	2006	Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects
ISO 11737-1	2006	Sterilization of Medical Devices - Microbiological Methods - Part 1: Determination of a Population of Microorganisms on Products.
ISO 11138-2	2006	Sterilization of health Care products – Biological indicators – Part 2: Biological Indicators for ethylene oxide sterilization processes
ASTM F1929	2012	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration.
ASTM F2096	2011	Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test).
ASTM F88/F88M	2009	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F1886-M	2009	Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection
FDA Guidance	2013	Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" Draft Guidance for Industry and FDA Staff
FDA Guidance	2013	Draft Guidance - Glass Syringes for Delivering Drug product and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4
FDA Guidance	2013	Guidance - Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

Bench Testing-Prefilled Syringe (PFS)

Summary of Functionality/Performance Verification Testing for 0.8 mL and 0.4 mL ABP 501 PFS

Test	Test Method Description	Acceptance Criteria (AC) & Confidence Interval (CI)	Test Article	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
BLE at operating temperature - standard (23°C ± 5°C)	Allow units to acclimate to standard temperature (23°C ± 5°C) for at least 15 minutes. Breakloose and extrude the drug at (b) (4) mm/min, using an Instron Material Tester	AC: Breakloose force and maximum extrusion force are both ≤ (b) (4) N CI: 95% Confidence/ 95% Reliability k ≥ (b) (4)	0.8 mL 29G	n = 30 mean / s / k Breakloose: (b) (4) Extrusion: (b) (4)	Pass	RPT-060840
			0.4 mL 29G	n = 30 mean / s / k Breakloose: (b) (4) Extrusion	Pass	

Test	Test Method Description	Acceptance Criteria (AC) & Confidence Interval (CI)	Test Article	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
BLE at operating temperature – cool (5°C ± 3°C)	Acclimate for four hours at 5°C ± 3°C. Breakloose and extrude the drug at (b) (4) mm/min, using an Instron Material Tester	AC: Breakloose force and maximum extrusion force are both ≤ (b) (4) N CI: 95% Confidence/ 95% Reliability k ≥ (b) (4)	(b) (4)		(b) (4)	RPT-060840
			0.8 mL 29G	n = 30 mean s k Breakloose (b) (4) Extrusion	Pass	
			(b) (4)			
			0.4 mL 29G	n = 30 mean s k Breakloose (b) (4) Extrusion	Pass	

Test	Test Method Description	Acceptance Criteria (AC) & Confidence Interval (CI)	Test Article	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
BLE at operating temperature - warm (40°C ± 2°C)	Acclimate for four hours at 40°C ± 2°C. Breakloose and extrude the drug at (b) (4) mm/min, using an Instron Material Tester	AC: Breakloose force and maximum extrusion force are both ≤ (b) (4) N CI: 95% Confidence/ 95% Reliability k ≥ (b) (4)	(b) (4)		(b) (4)	RPT-060840
			0.8 mL 29G	n = 30 mean s k Breakloose (b) (4) Extrusion	Pass	
			(b) (4)			
			0.4 mL 29G	n = 30 mean s k Breakloose (b) (4) Extrusion	Pass	

Test	Test Method Description	Acceptance Criteria (AC) & Confidence Interval (CI)	Test Article	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Deliverable volume (DV)	Extrude drug product at room temperature. Measure weight before and after and calculate volume by drug product density	AC: DV (b) (4) mL CI: 95% Confidence/ 95% Reliability k ≥ (b) (4)	(b) (4)	(b) (4)	(b) (4)	RPT-060839
			0.8 mL 29G	n = 30 mean s k (b) (4)	Pass	
		AC: DV (b) (4) mL CI: 95% Confidence/ 95% Reliability k ≥ (b) (4)	(b) (4)	(b) (4)	(b) (4)	
			0.4 mL 29G	n = 30 mean s k (b) (4)	Pass	
Packaging: Transportation Testing	Individual cartons were placed into approved shippers and subjected to ASTM D4169-09 distribution Cycle (b) (4) conditioning	Visual inspection for • No broken/cracked syringes • All needle shields are intact	(b) (4)	(b) (4)	(b) (4)	RPT-054677 TRPT-025517
			0.8 mL 29G 2 count	All units inspected remained assembled and free of damage. All needle shields were intact	Pass	
			0.4 mL 29G 1 count	All units inspected remained assembled and free of damage. All needle shields were intact	Pass	

Table 5. Breakloose and Extrusion Force Results

Test Condition	Test Article	Units Tested	Acceptance Criteria (AC) (N)	Mean (N)	Max (N)	Min (N)	SD (N)	Result	k Value AC	Actual k Value	Result
Standard Operating Conditions 23°C ± 5°C	(b) (4)	(b) (4)	Breakloose Force ≤ (b) (4)	(b) (4)			(b) (4)	(b) (4)	k_{act} ≥ (b) (4)		(b) (4)
	0.8 mL 29G	30						Pass		(b) (4)	Pass
	(b) (4)							(b) (4)			Pass
	0.4 mL 29G	30						Pass			Pass
	(b) (4)	Same as the units used in breakloose testing	Extrusion Force ≤ (b) (4)					(b) (4)			Pass
	0.8 mL 29G							Pass			Pass
	(b) (4)							(b) (4)			Pass
	0.4 mL 29G							Pass			Pass

Table 5. Breakloose and Extrusion Force Results

Test Condition	Test Article	Units Tested	Acceptance Criteria (N)	Mean (N)	Max (N)	Min (N)	SD (N)	Result	k Value AC	Actual k Value	Result
Warm 40°C ± 2°C	[redacted]	[redacted]	Breakloose Force ≤ [redacted]	[redacted]			[redacted]	[redacted]	$k_{act} \geq$ [redacted]	[redacted]	[redacted]
	0.8 mL 29G	30						Pass			Pass
	[redacted]	[redacted]						[redacted]			[redacted]
	0.4 mL 29G	30						Pass			Pass
	[redacted]	Same as the units used in breakloose testing	Extrusion Force ≤ [redacted]					[redacted]			[redacted]
	0.8 mL 29G							Pass			Pass
	[redacted]							[redacted]			[redacted]
	0.4 mL 29G							Pass			Pass

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Table 5. Breakloose and Extrusion Force Results

Test Condition	Test Article	Units Tested	Acceptance Criteria (N)	Mean (N)	Max (N)	Min (N)	SD (N)	Result	k Value AC	Actual k Value	Result
Cool Condition 5°C ± 3°C	[redacted]	[redacted]	Breakloose Force ≤ [redacted]	[redacted]			[redacted]	[redacted]	$k_{act} \geq$ [redacted]	[redacted]	[redacted]
	0.8 mL 29G	30						Pass			Pass
	[redacted]	[redacted]						[redacted]			[redacted]
	0.4 mL 29G	30						Pass			Pass
	[redacted]	Same as the units used in breakloose testing	Extrusion Force ≤ [redacted]					[redacted]			[redacted]
	0.8 mL 29G							Pass			Pass
	[redacted]							[redacted]			[redacted]
	0.4 mL 29G							Pass			Pass

Page 2 of 3

Table 6. Deliverable Volume Results

Test Article	Units Tested	AC (mL)	Mean (mL)	Max (mL)	Min (mL)	SD (mL)	Avg. within AC	All values within AC	k Value AC	Actual k Value	Actual k ≥ Target
[redacted]											[redacted]
0.8 mL 29G	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pass	Pass	$k_{act} \geq$ [redacted]	[redacted]	Pass
[redacted]											[redacted]
0.4 mL 29G	30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pass	Pass	$k_{act} \geq$ [redacted]	[redacted]	Pass

Autoinjector- Device Description:

Modified from the Enbrel SureClick 1.5 to change the outer appearance in terms of color so that patients can differentiate between Enbrel and ABP501.

	Enbrel SureClick 1.5 ([redacted] Project code 0051-010)	ABP501 SureClick 1.5 ([redacted] Project code 0051-026)
Colors of components:		
Front Shell	Teal (PMS [redacted])	Amgen Blue (PMS [redacted])
Rear Shell	Light Green (PMS [redacted])	Amgen Blue (PMS [redacted])
Activation Button	Purple (PMS [redacted])	Cool Blue (PMS [redacted])
Shield Remover/ Cap	White	Yellow (PMS [redacted])

The AI is a single-use, disposable, handheld, mechanical ([redacted]) injection device which consists of a PFS ([redacted] Type 1 glass prefilled glass syringe [redacted] with a 27-gauge needle) contained within 2 subassemblies. The prefilled syringe contains 0.8mL of ABP 501.

(b) (4)

Figure 1. Diagram of the Autoinjector System

Components	Fully Assembled
(b) (4)	

Description of Components and Materials of Construction – ABP 501 AI

(b) (4)

Component	Material	User Contacting
(b) (4)	(b) (4)	Yes
		Yes
		No
		No
		No
		No
		No
		No
		No

(b) (4)

Description of Components and Materials of Construction – ABP 501 AI

(b) (4)

Component	Material	User Contacting
(b) (4)	(b) (4)	Yes
		Yes
		Yes
		Yes
		Yes
		No

(b) (4)

Table 1. Standards Applicable to AI

Document Number	Version	Document Title
ASTM D4169	2009	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM F1980	2007	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices (reapproved in 2011)
EN 1041	2008	Information Supplied by the Manufacturer of Medical Devices
ISO 10993-1	2009	Biological Evaluation of Medical Devices-Part 1: Evaluation and Testing Within A Risk Management Process
ISO 10993-5	2009	Biological Evaluation of Medical Devices-Part 5: Tests for In Vitro Cytotoxicity
ISO 10993-10	2010	Biological Evaluation of Medical Devices-Part 10: Tests for Irritation and Skin Sensitization
ISO 11608-1	2012	Needle-based injection systems for medical use -- Requirements and test methods -- Part 1: Needle-based injection systems
ISO 15223-1	2012	Medical Devices-Symbols to Be Used With Medical Device Labels, Labeling and Information to Be Supplied-Part 1: General Requirements
ISO 23908	2011	Sharps Injury Protection-Requirements and Test Methods-Sharps Protection Features for Single-Use Hypodermic Needles, Introducers for Catheters and Needles Used for Blood Sampling
FDA Guidance	2013	Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products
FDA Guidance	2013	Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" Draft Guidance for Industry and FDA Staff

Biocompatibility-Autoinjector-MAF (b) (4): Reviewed by Dr. Bifeng Qian of INCB

The proposed autoinjector materials of construction and device function specifications remains unchanged from Enbrel SureClick 1.5 but color changes were instituted in order for the patient to differentiate the 2 drugs.

	Enbrel SureClick 1.5 ((b) (4) Project code 0051-010)	ABP501 SureClick 1.5 ((b) (4) Project code 0051-026)
Colors of components:		
Front Shell	Teal (PMS (b) (4))	Amgen Blue (PMS (b) (4))
Rear Shell	Light Green (PMS (b) (4))	Amgen Blue (PMS (b) (4))
Activation Button	Purple (PMS (b) (4))	Cool Blue (PMS (b) (4))
Shield Remover/ Cap	White	Yellow (PMS (b) (4))

AI Biocompatibility Testing – Skin Surface Contact Components

Test	Test Method Description	Acceptance Criteria	Test Results
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – In vitro methods	Cytotoxicity according to ISO 10993-5 Section 8.5	Pass
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation	Sensitization according to ISO 10993-10 Section 7.5.6	Pass
Irritation	ISO 10993-10: Tests for Sensitization and Irritation	Irritation according to ISO 10993-10 Section 6.4.7	Pass

From: Qian, Bifeng
Sent: Monday, March 28, 2016 11:36 AM
To: Shiu, Lana
Cc: (b) (4)
Subject: RE: MAF (b) (4)-BLA 761024-Biocompatibility questions

Hi Lana,

I have reviewed the provided two PDF documents. (b) (4) has provided the materials information as requested and revised their statement regarding the use of (b) (4). There are no pending biocompatibility deficiencies regarding the auto-injector (b) (4) SureClick (ABP501) proposed in (b) (4) 2661

Thank you,

BiFeng

From: (b) (4)
Sent: Thursday, March 24, 2016 6:34 PM
To: Shiu, Lana
Cc: Qian, Bifeng
Subject: RE: MAF (b) (4)-BLA 761024-Biocompatibility questions

Hello Lana,

Please find the response to the inquiries. Please let me know if you have any additional questions.

Best regards,

James

Please consider the environment before printing this email.

(b) (4)

From: (b) (4)
Sent: Thursday, March 24, 2016 8:52 AM

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Please respond and let us know if you can provide the requested information by COB Friday 3/18/2016. Thank you.

Lana Shiu, M.D.
Captain, U.S. Public Health
Senior Medical Advisor
General Hospital Device Branch
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

Bench Testing-Autoinejctor:

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Storage Temperature ISO 11608-1	Devices under test (DUT) were placed in a testing chamber set to 5°C ± 3°C for 96 hours, and then conditioned and tested for deliverable volume at 23°C ± 5°C as described in the test for Operating Temperature and Humidity	AC: Deliverable Volume (DV) mean (b) (4) mL CI: 95% Confidence/ 97.5% Reliability k ≥ (b) (4) AC: Visual defect: Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	n = 60[3] mean: (b) (4) mL; s: (b) (4) mL; k: (b) (4) No visual defects found	Pass	TRPT-026037

[3] The results provided support the ISO 11608-1 requirements for Storage Temperature and Operating Temperature and Humidity for standard condition.

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Test Condition	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Operating Temperature and Humidity ISO 11608-1	DUTs were placed in a testing chamber set to: Cool: 5°C ± 3°C Standard: 23°C ± 5°C, 50% ± 25% RH Warm: 40°C ± 2°C, 50% ± 10% RH for at least 4 hours prior to testing and then tested for deliverable volume under the same environmental conditions	AC: DV mean (b) (4) mL CI: 95% Confidence/ 97.5% Reliability k ≥ (b) (4) AC: Visual defects: Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	Cool	n = 60 mean: (b) (4) mL; s: (b) (4) mL; k: (b) (4) No visual defects found	Pass	TRPT-026037
			Standard[a]	n = 60 mean: (b) (4) mL; s: (b) (4) mL; k: (b) (4) No visual defects found	Pass	
			Warm	n = 60 mean: (b) (4) mL; s: (b) (4) mL; k: (b) (4) No visual defects found	Pass	

[a] The results provided support the ISO 11608-1 requirements for Storage Temperature and Operating Temperature and Humidity for standard condition.

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Test Condition	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Deliverable Volume and Injection Time post Transportation Shock and Vibration ISO 11608-1	DUTs were tested per ASTM D4169, then pre-conditioned at 23°C ± 5°C, 50% ± 25% RH for at least 4 hours and tested for deliverable volume and injection time at 23°C ± 5°C	AC: DV mean (b) (4) mL CI: 95%Confidence/ 95% Reliability k ≥ (b) (4) AC: Injection Time (IT) ≤ (b) (4) Accept = (b) (4) failure, Reject = (b) (4) failure	1-pack	n = 60 DV: mean (b) (4) mL; max NA; s (b) (4) mL; k (b) (4) IT: mean NA; max (b) (4) sec; s NA; k NA	Pass	TRPT-026034
			2-pack	n = 60 DV: mean (b) (4) mL; max NA; s (b) (4) mL; k (b) (4) IT: mean NA; max (b) (4) sec; s NA; k NA	Pass	

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Subassembly Shelf-Life	Device subassemblies were assembled and tested for function after accelerated storage conditions of 45°C ± 2°C and 50% ± 5% RH for (b) (4) weeks to simulate (b) (4) years	Shield remover removal force (b) (4) kgf Needle cover pre-injection force (b) (4) kgf Activation force (b) (4) kgf Needle extension (b) (4) mm Needle cover override force maximum displacement (b) (4) mm Separation force ≥ (b) (4) kgf	n=150 (T_0, $T_{0.5}$, T_1, T_2, and T_3) n=30 sampled per time point. See Section 3.1.4 Subassembly Shelf-Life for data	Pass	0051-026-TR-AATR-150305

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Needle Extension	DUT were placed in a fixture to measure the needle length exposed during injection (as measured from the front plane of the needle cover when the needle cover is fully compressed)	Needle extension (b) (4) mm Accept = (b) failure, Reject = (4) failure	n = 60 min: (b) (4) mm max: (b) (4) mm	Pass	0051-026-TR-DVTR-141217

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Needle Cover Override Force	A compressive force of (b) (4) kgf is applied to the extended needle cover of a post-activated post-removal DUT. The displacement of the needle cover is measured while under this compressive force	Extended needle cover is displaced ≤ (b) mm under compressive force of (b) kgf. Accept = (b) failure, Reject = (4) failure	n = 60 max = (b) (4) mm	Pass	0051-026-TR-DVTR-141217

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Shield Remover Removal Force	An axial tensile force is applied to the needle shield remover until it separates from the DUT. The resultant force is measured and recorded	Shield remover removal force (b) (4) kgf Accept = (b) failure, Reject = (4) failure	n = 60 min: (b) (4) kgf max: (b) (4) kgf	Pass	0051-026-TR-DVTR-141217

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Free-fall Test ISO 11608-1	DUTs were dropped in 3 different orientations from a height of 1 m onto a steel surface backed by wood, per ISO 11608-1. DUTs were then evaluated for visual defects and deliverable volume	AC: DV mean (b) (4) mL CI: 95%Confidence/ 95% Reliability k ≥ (b) (4) AC: Visual defects: Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	n = 30 mean: (b) (4) mL s: (b) (4) mL k: (b) (4) No visual defects found	Pass	TRPT-025993

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Vibration Test ISO 11608-1	DUTs were vibrated in 3 different orientations per ISO 11608-1. They were then evaluated for visual defects and deliverable volume	AC: DV mean (b) (4) mL CI: 95%Confidence/ 95% Reliability k ≥ (b) (4) AC: Visual defects: Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	n = 20 mean: (b) (4) mL; s: (b) (4) mL; k: (b) (4) No visual defects found	Pass	TRPT-025993

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Activation Force	DUTs were placed in a fixture and the activation force test was executed. The semi-automated test machine (SATM) measured the force necessary to activate the device	Activation force (b) (4) kgf Accept = (b) (4) ailure, Reject = ailure	n = 60 min: (b) (4) kgf; max: (b) (4) kgf	Pass	0051-026-TR-DVTR-141217

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Needle Cover Pre-Injection Force	DUTs were placed in a fixture and the pre-injection force test was executed. The SATM measured the force necessary to retract the needle cover to the pre-injection hard stop position	Needle cover pre-injection force (b) (4) kgf Accept = (b) (4) ailure, Reject = ailure	n = 60 min: (b) (4) kgf; max: (b) (4) kgf	Pass	0051-026-TR-DVTR-141217

Test	Test Method Description	Acceptance Criteria (AC) and Confidence Interval (CI)	Data Summary *s – Standard Deviation* *k – Tolerance Interval*	Test Results	Report Number
Separation Force	The SATM gradually increased the tensile force until reaching (b) kgf while measuring the relative movement between the front and rear halves	AC: (b) (4) (b) (4) Accept = (b) (4) failure, Reject = failure	n = 60 All devices tested showed no permanent separation	Pass	0051-026-TR-DVTR-141217

Storage Temperature

Sixty assembled AI units were stored at 5□C □□3□C for a minimum of 96 hours, and then placed in an environmental chamber at 23 □C □□5□C for at least 4 hours prior to testing.
The units were visually inspected and then tested at 23 □C□□□□5□C for dose accuracy.

Acceptance Criteria
All units must have a mean deliverable volume that is within the 2-sided dose accuracy requirements of (b) (4) mL to (b) (4) mL, with a k value greater than or equal to the target value of (b) (4).
All units must pass the following visual inspection acceptance criteria:
□□ All product markings on the devices under test (DUT) are legible (if applicable)
□□ No cracks in the body and/or components of the DUT that might impact safe functioning.
□□ No compromised assembly bonds, joint and alignments that might impact safe functioning.
□□ The drug product in the window is clear and colorless.
□□ The needle cap is present and securely attached.

Storage Temperature – Dose Accuracy and Visual Inspection Test Results

Test	Acceptance Criteria	Data Summary	Result
Dose Accuracy	DV mean (b) (4) mL k ≥ (b) (4)	Mean = (b) (4) mL s = (b) (4) k =	Pass
Visual Inspection	Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	No visible defects found	Pass

Operating Temperature and Humidity
180 AI units assembled with a 0.8 mL PFS were tested.
60 assembled AI units were used for each of the following 3 conditions (Cool, Standard, Warm)
□□ 5□C □□3□C for a minimum of 4 hours prior to testing at the same environmental conditions
□□ 23□C □□5□C and 50% □□25% RH for a minimum of 4hours prior to testing at the same environmental conditions
□□ 40□C □□2□C and 50% □10% RH for a minimum of 4 hours prior to testing at the same environmental conditions

Acceptance Criteria
All units must have a mean deliverable volume that is within the 2-sided dose accuracy requirements of (b) (4) mL to (b) (4) mL, with a k value greater than or equal to the target value of (b) (4).
All units must pass the following visual inspection acceptance criteria:
□□ All product markings on the DUT are legible (if applicable)
□□ No cracks in the body and/or components of the DUT that might impact safe functioning.
□□ No compromised assembly bonds, joint and alignments that might impact safe functioning.
□□ The drug product in the window is clear and colorless.
□□ The needle cap is present and securely attached.

Operating Temperature and Humidity – Dose Accuracy and Visual Inspection Test Results

Test Conditions	Acceptance Criteria	Data Summary	Result
Cool	DV mean (b) (4) mL k ≥ (b) (4)	Mean = (b) (4) mL s = (b) (4) mL k = (b) (4)	Pass
	Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	No visible defects found	Pass
Standard	DV mean (b) (4) mL k ≥ (b) (4)	Mean = (b) (4) mL s = (b) (4) mL k = (b) (4)	Pass
	Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	No visible defects found	Pass
Warm	DV mean (b) (4) mL k ≥ (b) (4)	Mean = (b) (4) mL s = (b) (4) mL k = (b) (4)	Pass
	Devices must be free of defects, markings, cracks, compromised bonds, and fractured syringes	No visible defects found	Pass

Deliverable Volume and Injection Time post Transportation Shock and Vibration

180 assembled AI units - 120 units packaged into 60 cartons (2 AI per carton) and 60 units packaged into 60 cartons (1 AI per carton) - were subjected to simulated transportation testing per ASTM D4169. For each packaging configuration (1-count and 2-count), 3 shippers containing 20 cartons each were used.

After the transportation testing and inspection, 120 of the assembled AI units were tested for functionality (deliverable volume and injection time). Sixty units from the 1-count configuration and 60 units from the 2-count configuration were placed in an environmental chamber at 23 □C□□□□5□C and 50 conditions.

Acceptance Criteria

All units must have a mean deliverable volume that is within the 2-sided dose accuracy requirements of (b) (4) mL to (b) (4) mL, with a k value greater than or equal to the target value of (b) (4). All units must complete delivery of the deliverable volume in less than (b) (4) seconds. All units must be free from damage.

Post Transportation Dose Accuracy and Injection Time Test Results

Test	Packaging Configuration	Acceptance Criteria	Data Summary	Result
Deliverable Volume	1-count	DV mean (b) (4) mL k ≥ (b) (4)	Mean = (b) (4) mL s = (b) (4) mL k = (b) (4)	Pass
	2-count	DV mean (b) (4) mL k ≥ (b) (4)	Mean = (b) (4) mL s = (b) (4) mL k = (b) (4)	Pass
Injection Time	1-count	≤ (b) (4) sec	Max = (b) (4) sec	Pass
	2-count	≤ (b) (4) sec	Max = (b) (4) sec	Pass

Subassembly Shelf-Life

30 assembled devices were tested per time point. A total of 480 subassemblies were used in this test.

480 subassemblies (240 front and 240 rear)—Sixty subassemblies of each AI presentation (30 front and 30 rear) were inspected, assembled, and tested. The resulting data were the T0 results. The remaining 420 subassemblies (210 front and 210 rear) were placed in an environmental chamber set to 45 □6%□R□□□C and 50% □ maximum o (b) (4) weeks to simulat (b) (4) years (b) (4) of shelf life at 25 □C. Sixty subassemb

were removed at predetermined intervals, inspected, and equilibrated for 1 hour at ambient conditions prior to being assembled and tested. (b) (4) Thus far, T0, T0.5, T1, T2, and T3 data have been collected.

Subassembly Shelf-Life: Visual Inspection Test Results

		Acceptance Criteria / Results	
Aging Time Point	Part	Damage Free	No significant defects
T_0	Rear Sub-assembly	Pass	Pass
	Front Sub-assembly	Pass	Pass
$T_{0.5}$	Rear Sub-assembly	Pass	Pass
	Front Sub-assembly	Pass	Pass
T_1	Rear Sub-assembly	Pass	Pass
	Front Sub-assembly	Pass	Pass
T_2	Rear Sub-assembly	Pass	Pass
	Front Sub-assembly	Pass	Pass
T_3	Rear Sub-assembly	Pass	Pass
	Front Sub-assembly	Pass	Pass

Subassembly Shelf-Life: Functionality Test Results

Test Name	Acceptance Criteria[a]	Value	T_0	$T_{0.5}$	T_1	T_2	T_3
Shield Remover Removal Force	(b) (4) kgf	Mean	(b) (4)				
		Max					
		Min					
		s					
Needle Cover Pre-Injection Force	(b) (4) kgf	Mean					
		Max					
		Min					
		s					
Activation Force	(b) (4) kgf	Mean					
		Max					
		Min					
		s					
Needle Extension	(b) (4) mm	Mean					
		Max					
		Min					
		s					
Needle cover override force	Max displacement (b) (4) mm with min. applied force of (b) (4) kgf	Mean					
		Max					
		Min					
		s					
Separation Force	≥ (b) (4) kgf	Average load					
		Max load					
		Min load					
		s					

Stability Testing - Autoinjector –Adequate –Precise dose volume and injection time ≤ (b) (4) seconds

Deliverable volume/dose accuracy and injection time for the autoinjector combination product are monitored as part of the drug stability program and samples are analyzed at the following time points 0, 6, 12, 24, 30, and 36 months. Results up to 18 months are available for the supporting stability lot.

Table 1. Stability Data for Drug Product (AI) Supporting Lot 0010181622 Stored at 5°C

Test Method	Acceptance Criteria	Time Point (Months) 0	3	6	9	12	18
rCE-SDS							
% HC + LC	≥ (b) (4)%						
% LMW	NA						
% LC	NA						
% MMW	NA						
% NGHC	NA						
% HC	NA						
% HMW	NA						
Apoptosis inhibition bioassay	(b) (4)% relative potency						
Subvisible particles							
≥ 10 µm	≤ (b) (4) per container						
≥ 25 µm	≤ (b) per container						
Injection time	≤ (b) seconds						
Deliverable volume	(b) (4) mL						

(b) (4)

Table 1. Stability Data for Drug Product (AI) Qualification Lot 1058067 Stored at 5°C

Test Method	Acceptance Criteria	Time Point (Months) 0	3	6
rCE-SDS				
% HC + LC	≥ (b) (4)%			
% LMW	NA			
% LC	NA			
% MMW	NA			
% NGHC	NA			
% HC	NA			
% HMW	NA			
Apoptosis inhibition bioassay	(b) (4)% relative potency			
Subvisible particles				
≥ 10 µm	≤ (b) (4) per container			
≥ 25 µm	≤ (b) per container			
Injection time	≤ (b) seconds			
Deliverable volume	(b) (4) mL			

(b) (4)

Table 1. Stability Data for Drug Product (AI) Supporting Lot 0010181622 Stored at 25°C

Test Method	Time Point (Months) 0	0.5	1	3	6
CEX-HPLC					
% Main + basic peaks					
% Acidic peaks					
% Main peak					
% Basic peaks					
SE-HPLC					
% Main peak					
% HMW					
% LMW					

(b) (4)

Table 1. Stability Data for Drug Product (AI) Qualification Lot 1058067 Stored at 25°C

	Time Point (Months)			
Test Method	0	0.5	1	3
rCE-SDS	(b) (4)			
% HC + LC				
% LMW				
% LC				
% MMW				
% NGHC				
% HC				
% HMW				
Apoptosis inhibition bioassay (% relative potency)				
Subvisible particles				
≥ 10 µm per container				
≥ 25 µm per container				
Injection time (seconds)				
Deliverable volume (mL)				

Table 2. Stability Data for Drug Product (AI) Qualification Lot 1058068 Stored at 25°C

	Time Point (Months)			
Test Method	0	0.5	1	3
Injection time (seconds)	(b) (4)			
Deliverable volume (mL)				

Table 3. Stability Data for Drug Product (AI) Qualification Lot 1058070 Stored at 25°C

	Time Point (Months)			
Test Method	0	0.5	1	3
Injection time (seconds)	(b) (4)			
Deliverable volume (mL)				

Table 1. Stability Data for Drug Product (AI) Supporting Lot 0010181622 Stored at 40°C

	Time Point (Months)					
Test Method	0	0.1	0.25	0.5	1	3
rCE-SDS	(b) (4)					
% HC + LC						
% LMW						
% LC						
% MMW						
% NGHC						
% HC						
% HMW						
Apoptosis inhibition bioassay (% relative potency)						
Subvisible particles						
≥ 10 µm per container						
≥ 25 µm per container						
Injection time (seconds)						
Deliverable volume (mL)						

Table 1. Stability Data for Drug Product (AI) Qualification Lot 1058067 Stored at 40°C

	Time Point (Months)					
Test Method	0	0.03	0.25	0.5	1	3
rCE-SDS						(b) (4)
% HC + LC						
% LMW						
% LC						
% MMW						
% NGHC						
% HC						
% HMW						
Apoptosis inhibition bioassay (% relative potency)						
Subvisible particles						
≥ 10 µm per container						
≥ 25 µm per container						
Injection time (seconds)						
Deliverable volume (mL)						

Table 2. Stability Data for Drug Product (AI) Qualification Lot 1058068 Stored at 40°C

	Time Point (Months)					
Test Method	0	0.03	0.25	0.5	1	3
Injection time (seconds)						(b) (4)
Deliverable volume (mL)						

Table 3. Stability Data for Drug Product (AI) Qualification Lot 1058070 Stored at 40°C

	Time Point (Months)					
Test Method	0	0.03	0.25	0.5	1	3
Injection time (seconds)						(b) (4)
Deliverable volume (mL)						

Table 1. Stability Data for Drug Product (AI) Lot 0010203184 Transport Study at 5°C

		Time Point (Months)			
Test Method	Acceptance Criteria	0	3	9	15
rCE-SDS					(b) (4)
% HC + LC	≥ (b) (4)%				
% LMW	NA				
% LC	NA				
% MMW	NA				
% NGHC	NA				
% HC	NA				
% HMW	NA				
Apoptosis inhibition bioassay	(b) (4)% relative potency				
Subvisible particles					
≥ 10 µm	≤ (b) (4) per container				
≥ 25 µm	≤ (b) per container				
Injection time	≤ (b) seconds				
Deliverable volume	(b) (4) mL				

Needle Testing-Bench

Bending and breaking of the staked needle is a primary container component quality attribute that is not impacted by the drug product solution.

Deflection and Force at Yield --simulate cannula end loading and damage modeling where a ½ inch needle fixed on one end is displaced downward at the needle tip and the force is applied until the yield point is achieved (point where material begins to deform irreversibly). 29G (b) (4) needle bent more easily, but the 29G (b) (4) needle can also be deflected further than the 27G needles before the material reaches the yield point.

Nominal Design/Span	Deflection at Yield	Force at Yield
(b) (4) 27G/0.5 inch	(b) (4) inch	(b) (4) N
29G/0.5 inch	inch	N

Needle Fatigue Testing Results-- needle fatigue experiment performed by repeatedly cycling through ± 50° bends which is an assessment of the needle for resistance to breakage. Each cannula was cycled until needle breakage, and the number of cycles was recorded. The 29G (b) (4) needle withstands more bending cycles before breakage than the 27G (b) (4) needle.

	Number of repeated bending (-50°/+50°)	
N=50	1 ml 27G 5 bevel (b) (4)	1 ml 29G 5 bevel (b) (4)
Average	(b) (4)	
Maximum		
Minimum		
Standard Deviation		

In-vitro testing of Needle Bending and Penetra Force- 29G needle required about (b) (4) N to bend the needle compared to abou (b) (4) N for the 27G needle. However, both values are well above the required force to p ate the pork skin (to simulate human skin). The measured values of about (b) (4) N for the 27G needle and about (b) (4) N for the 29G needle suggest that needle penetration occurs before the need ending force is reached, so any difference in needle bending forces for the 27G and 29G needles should not impact syringe performance under normal use.

Description	Needle Bending Force (N)	Penetration Force (N)
27G (Mean + Std Dev)	(b) (4)	(b) (4)
29G (Mean + Std Dev)		
Samples per syringe type	30	10

Impact of Bent Needles on Functionality-- 29G (b) (4) syringes were bent at 5 and 10 degrees and complete dispensing of the 0.8 mL drug product solution was achieved w/o impacting plunger stopper break out and gliding forces by the bent needles. Bent needles had no impact on the functionality of the prefilled syringes.

Ejection Volume and Break Out/Gliding Forces with Bent Needles in Humira PFS									
	No Needle Bend			10° Needle Bend			5° Needle Bend		
Statistical Summary	Dispense Volume, mL	Break Out Force, N	Glide Force, N	Dispense Volume, mL	Break Out Force, N	Glide Force, N	Dispense Volume, mL	Break Out Force, N	Glide Force, N
Average	(b) (4)								
Std. Dev									
Maximum									
Minimum									

Rigid Needle Shield Removal Force for Prefilled Syringe- 20 empty units of both the (b) (4) 29G and the (b) (4) 27G syringe systems were performed to determine the forces required to remove the rigid needle shield (RNS). The RNS removal forces were determined at (b) (4) mm/min and (b) (4) mm/min feed motion. Both syringe systems had RNS removal forces less than (b) (4) Newtons meeting the performance criteria. Noted is RNS removal forces were approximately two-fold higher for the (b) (4) 29G syringe system than the (b) (4) 27G system, mainly due to the different (b) (4) material used for the soft needle shield

.

Test Speed	(b) (4) mm/min		(b) (4) mm/min	
Type of Syringe	(b) (4) 27G ½in	(b) (4) 29G ½in	(b) (4) 27G ½in	(b) (4) 29G ½in
Specimen Number	Fmax [N]	Fmax [N]	Fmax [N]	Fmax [N]
1		(b) (4)		
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
Average: Maximum: Minimum: Std. Dev.:				

Rigid Needle Shield Removal Force filled with biologic product--Rigid needle shield removal forces of 11 batches of ABP501 Solution for Injection, 50 mg/mL, Pre-filled Syringe samples were tested after warming up to 25°C and 10 syringes for lots VVKC35/1 and 16286LX were tested at 5°C. All the pre-filled syringe batches for the various lots and storage conditions met the defined acceptance criterion for RNS removal force of equal to or less than (b) (4) N.

(b) (4)

Plunger Forces Testing Results-- filled with biologic product
The plunger stopper break out and gliding force (BOGF) functional testing was performed using force testing equipment on ABP501 50 mg/mL (b) (4) 29G ((b) (4) syringes. Pre-filled syringes with fill volumes of 0.4 mL and 0.8 mL were manufacture at 2 sites (b) (4)).

Since the viscosity of the (b) (4) drug product solution might contribute to the respective gliding force of the prefilled syringe, the viscosity of the 50 mg/mL (b) (4) drug product solutions was measured at 20° and 25°C.

Temperature	Viscosity of 50 mg/mL (b) (4) Drug Product Solution [mPa•s]	(b) (4)
20°C	(b) (4)	
25°C		

Average break out and maximum gliding force specifications of mean ≤ (b) (4) N and single values ≤ (b) (4) N were met. In fact, average break out forces and gliding forces for the (b) (4) lots were less than (b) (4) Newtons (N) for the ABP501 50 mg/mL Pre-filled (b) (4) 29G Syringes

Forces (N) [a] n = 30 syringes	Primary Stability Lots (b) (4)					
	40 mg/0.4 mL Primary Stability Lot 11-005150	80 mg/0.8 mL Primary Stability Lot 11-005152	40 mg/0.4 mL Primary Stability Lot 11-005156	80 mg/0.8 mL Primary Stability Lot 11-005158	40 mg/0.4 mL Primary Stability Lot 11-005163	80 mg/0.8 mL Primary Stability Lot 11-005165
Break-out	(b) (4)					
Maximum Gliding						

Forces (N) [a] n=10 syringes	Demonstration and Engineering Lots (b) (4)			
	40 mg/0.4 mL Eng Lot 16163A6	80 mg/0.8 mL Eng Lot 16164A6	80 mg/0.8 mL Eng Lot 17106A6	40 mg/0.4 mL Demo Lot 20037A6
Break-out Beginning	(b) (4)			
Break-out Middle				
Break-out End				
Maximum Gliding Beginning				
Maximum Gliding Middle				
Maximum Gliding End				

a Velocity at (b) (4) mm/min

Table 1. Stability Data for Drug Product Lot 0010192968 Transport Study at 5°C

Test Method	Acceptance Criteria	Time Point (Months) 0	9
Breakloose and extrusion			
Breakloose*	≤ (b) (4) N	(b) (4)	
Extrusion*	≤ N		
Sterility	Pass	NS	Pass
CCI	Pass	NS	Pass

Page 3 of 3

Table 2. Stability Data for Drug Product Lot 0010192968 Transport Study at 5°C (Untreated Control)

Test Method	Acceptance Criteria	Time Point (Months) 0	9
Breakloose and extrusion			
Breakloose*	≤ (b) (4) N	(b) (4)	
Extrusion*	≤ N		
Sterility	Pass	NS	Pass
CCI	Pass	NS	Pass

Plunger Forces Testing Results-- filled with biologic product-Accelerated Aging
Stability Data for Batch 16164A6

Test	Shelf Life Specification	Duration	Storage Condition (°C / %RH)

		of Testing	+5	+25/60	+40/75
Pharmaceutical Tests, Measurement of Forces	Individual values ≤ (b) (4) N	Initial			(b) (4)
		1			
		3			
		6			
		9			
		12			
		18			
		24			
		36			

P Planned

NP Not Planned

Test	Shelf Life Specification	Duration of Testing (month)	Storage Condition (°C / %RH)		
			+5	+25/60	+40/75
Pharmaceutical Tests, Measurement of Forces (continued)	Average values ≤ (b) (4) N	Initial			(b) (4)
		1			
		3			
		6			
		9			
		12			
		18			
		24			
		36			

Stability Data for Batch 16286LXX

Test	Shelf Life Specification	Duration of Testing	Storage Condition (°C / %RH)		
			+5	+25/60	+40/75
Pharmaceutical tests, Measurement of forces	Individual values: ≤ (b) (4) N	Initial			(b) (4)
		1			
		3			
		6			
		9			
		12			
		18			
		24			
		36			
	Average values: ≤ (b) (4) N	Initial			
		1			
		3			

		(b) (4)			

P Planned

NP Not Planned

Dose accuracy-***consistent/repeatable dispensing of the drug volume from the PFS***

(b) (4) Volume in Container testing is performed as part of batch release testing, and the measured volume must be not less than the labeled volume. Results from this testing are provided in Table 5 of the "Batch Analyses (b) (4)" document in Module 3.2.P.5.4, demonstrating consistent dispensing of the labeled drug volume from the PFS.

Leakage – ***confirmation that syringe does not leak through the plunger while functioning***

Results from Volume in Container testing demonstrate that the labeled volume is expelled through the needle from the (b) (4) syringe, providing confirmation that leakage is not observed through the plunger during dispensing. Volume in Container testing results are provided in Table 5 of the "Batch Analyses (b) (4)" document in Module 3.2.P.5.4. Additionally, container closure integrity (CCI) shows that the plunger does not leak during storage. CCI stability data are summarized on page 26 of the "Stability Summary and Conclusions (b) (4) " document in Module 3.2.P.8.1, indicating no leakage was detected for any of the batches at any time points at all test conditions (CCI stability data tables for individual batches are provided in Module 3.2.P.8.3).

Shipping Study--**ASTM D4169**- Performance Testing of Shipping Containers and Systems
--ASTM D999 – Standard Methods for Vibration Testing of Shipping Containers

Shipping study was conducted to demonstrate the suitability of the primary packaging during air and ground transport. (b) (4) After the syringes are shipped by air, they are delivered to the final destination by ground transportation subjecting the 50 mg/mL ABP501 prefilled syringe to drop and shake movements.

After air shipment and drop/shake, the syringes were visually inspected and then analyzed for container closure integrity (sterility maintenance assessment), stopper movement (alternative sterility assessment), and syringe plunger force (syringe functionality).

Shipping Study Results:
**Stopper position measurement in (b) (4) syringes showed minimal movement during air shipment (b) (4) mm). The stopper movement measured satisfied the acceptance criteria (< (b) (4) mm).
** Ground transport simulation using drop/shake vibration testing did not affect the container closure integrity of the syringes as there was no blue color visible in the solution after syringes were submerged in methylene blue solution.

** All plunger forces were not affected by transport and showed maximum gliding forces (b) (4) N for all lots tested.

(b) (4)

***CDRH Question 1*: Summarize all of the device-malfunctions, device failures or medication errors/adverse events related to device malfunctions/failures during your bioequivalence or clinical trials. Detail the circumstances of use that resulted in these malfunctions/failures along with the root cause analysis and any mitigation steps that have been consequently instituted.**

IR response 1: There were no device-malfunctions, device failures or medication errors/adverse events related to device malfunctions/failures during the conduct of clinical studies 20110217, 20120262 and 20120263 in which the ABP 501 pre filled syringe (PFS) was used.

***CDRH Question 2:* Indicate whether or not auto-injectors (AIs) were used in your PK studies or clinical studies and if there were any failures/malfunctions/medication errors related to the AIs.**

IR response 2: Auto-injectors (AIs) were not used in the ABP 501 pharmacokinetic (PK) or clinical studies and therefore no failures/malfunctions/medication errors related to the AIs are provided in this response.

CDRH Recommendation: Amgen is using the SureClick 1.5 Autoinjector (same device approved in 3/2015 under BLA 103795/S5532) to deliver ABP 501 (b) (4)

BLA103795/S5532	**Enbrel/SureClick 1.5**	**ICC1400747 completed by GHDB**

The sponsor has provided comprehensive device functional testing for the prefilled syringe combination product as well as for the autoinjector product.

The prefilled syringe is able to meet the Break Loose Extrusion Force specification of < (b) (4) N while delivering precise volume ((b) (4) ml) of drug under temperatures and post-transport study.

The autoinjector configuration of the product is able to maintain the performance specification of delivering precise drug volume ((b) (4) ml) in less than (b) (4) seconds of injection time under various temperatures and in transport study.

Device information provided for the prefilled syringe and autoinjector is deemed adequate. No further deficiency questions.

Digital Signature Concurrence Table	
Reviewer Sign-Off	**Lana Shiu, M.D.**

Branch Chief Sign-Off	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
09/22/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer,
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: John Alexander, M.D., M.P.H., Deputy Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Pulmonary and Rheumatology Products (DPARP)

Drug: ABP 501

Application Number: BLA 761024

Sponsor: Amgen, Inc.

Proposed Indications: Treatment of:

1) Rheumatoid Arthritis (RA) in adults
2) Juvenile Idiopathic Arthritis (JIA) in patients 4 years and older
3) Psoriatic Arthritis (PsA) in adults
4) Ankylosing Spondylitis (AS) in adults
5) Crohn's Disease (CD) in adults
6) Ulcerative Colitis (UC) in adults
7) Plaque Psoriasis (PsO) in adults

Proposed dosage forms & route of administration: Single-use pre-filled syringes with 20 mg/0.4 mL and 40 mg/0.8 mL; 40 mg/0.8 mL solution in a single-use prefilled autoinjector; subcutaneous injection

Proposed Pediatric Dosing Regimen:
Juvenile Idiopathic Arthritis (JIA):

- 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week
- ≥ 30 kg (66 lbs): 40 mg every other week

Consult Request: DPARP requests Division of Pediatric and Maternal Health (DPMH) participation in the labeling discussions, and assistance in preparation for the Pediatric Review Committee.

Materials Reviewed:

- Division of Pediatric Maternal Health (DPMH) consult request
- Sponsor's proposed labeling for ABP 501 (July 26, 2016)
- Prior DPMH review for ABP 501 (IND 111714) dated December 30, 2014
- Pediatric Study Plan for ABP 501 (BLA 761024) dated November 25, 2015
- Current Humira (adalimumab) labeling (June 30, 2016)

Consult and Regulatory Background:
Amgen, Inc. is developing ABP 501 as a proposed biosimilar to Humira (adalimumab). Humira (adalimumab) is a tumor necrosis factor (TNF) blocker licensed by AbbVie, Inc. and was first approved in 2002. Adalimumab is a monoclonal antibody that binds specifically to TNF-alpha ligands and blocks interaction with cell surface TNF receptors. TNF is a cytokine involved in inflammatory and immune responses, and elevated TNF levels also play a role in pathology of anti-inflammatory diseases.[1]

The sponsor submitted a BLA for ABP 501 on November 25, 2015. Under the Pediatric Research and 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 an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because non-interchangeable biosimilar products, such as ABP 501, are considered to have new active ingredients, ABP 501 is subject to PREA and Amgen is expected to address PREA for the indications for which it is seeking licensure. The Agency issued an advice letter on September 14, 2015 (b) (4) However, no further correspondence was noted in DARRTS prior to the filing of the BLA. Therefore, while the sponsor did not reach final agreement with the Agency on their iPSP prior to filing their BLA, they did provide a proposal in the BLA submission (b) (4) PARP requests DPMH-Pediatrics team assistance in providing labeling recommendations for pediatric use, and preparing for the Pediatric Review Committee (PeRC) meeting.

[1] Current Humira (adalimumab) labeling (June 30, 2016)

Pediatric Plan:
The pediatric plan was deemed acceptable for filing of the BLA and is summarized in the table below. (See the prior DPMH consult review for ABP 501 (IND 111714) dated December 30, 2014 for further discussion on the pediatric development plan.)

Indication	Age	Pediatric Studies Plan
Polyarticular Juvenile Idiopathic Arthritis	Birth to < 2 years	Partial waiver requested
	2 to < 4 years	Deferral requested (b) (4)
	4 to 17 years	Extrapolation requested
Psoriatic Arthritis	Birth to 17 years	Full waiver requested
Ankylosing Spondylitis	Birth to 17 years	Full waiver requested
Pediatric Crohn's Disease	Birth to < 6 years	Partial waiver requested
	6 to 17 years	Deferral requested (b) (4)
Pediatric Ulcerative Colitis	Birth to < 5 years	Partial waiver requested
	5 to 17 years	Deferral requested (b) (4)
Plaque Psoriasis	Birth to 17 years	Full waiver requested

The sponsor also noted that they will provide 20-mg/0.4-mL and 40-mg/0.8-mL prefilled syringes with their initial BLA. These presentations are appropriate to treat the proposed indication of JIA patients 4 years and older. (b) (4)

DPMH Review of Labeling:
The DPMH-Maternal Health team will provide labeling recommendations for pregnancy and lactation (subsections 8.1 and 8.2) in a separate review.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

See Appendix 1 for Applicant's Relevant Proposed Labeling dated July 26, 2016.

Discussion on Pediatric Labeling Recommendations:
Of the pediatric indications approved for Humira, ABP 501 will only receive pediatric approval for JIA patients 4 years and older, (b) (4) Therefore, labeling for ABP 501 should only include pediatric information regarding JIA for patients 4 years and older. Amgen is seeking licensure for presentations that are appropriate for use in JIA patients 4 years and older. (b) (4) No necessary safety information has been excluded. Therefore, the proposed language related to pediatric use in JIA patients 4 years and older throughout labeling is appropriate. However, in subsection 8.4, the statement regarding safety and efficacy should be limited to this product, (b) (4) .

Conclusion:
DPMH agrees with the proposed pediatric development plans as outlined above. Postmarketing requirements should be issued under PREA to provide an assessment of ABP 501 for (1) Pediatric UC in patients 5 to 17 years of age, (2) Pediatric CD in patients 6 to 17 years of age, and (3) JIA in patients 2 to 4 years of age, and to develop an age-appropriate presentation for pediatric patients (b) (4) weighting less than 15 kg.

DPMH reviewed the sponsor's draft labeling and participated in the internal meetings held in August, 2016. DPMH provided labeling recommendations for the pediatric population per 21 CFR 201.57(c)(9)(iv). The following recommendations are based on labeling discussions between the review team and DPMH. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

DPMH Recommended Labeling for ABP 501:

8.4 Pediatric Use

Safety and efficacy of [insert biosimilar product tradename] in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) have has not been established. Due to its inhibition of TNFα, adalimumab products administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to adalimumab *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations (8.1)]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including adalimumab products *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, adalimumab was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies (14.2)]*. Adalimumab products have not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of adalimumab in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions (6.1)]*.

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERICA D RADDEN
09/22/2016

JOHN J ALEXANDER
09/22/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 761024
Product Name:	ABP 501 (adalimumab-atto; Amjevita)
PMR/PMC Description:	Assessment of adalimumab-atto for the treatment of juvenile idiopathic arthritis (JIA) in patients ages 2 to <4 years of age.

PMR/PMC Schedule Milestones:

Final Report Submission:	September 2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR is to address PREA requirements for adalimumab-atto for the treatment of JIA in patients 2 to <4 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Amgen can fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Clinical studies may not be needed.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Amgen can fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Clinical studies may not be needed.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 761024
Product Name:	ABP 501 (Adalimumab-xxxx; Amjevita)
PMR/PMC Description:	Assessment of adalimumab-atto for the treatment of pediatric Crohn's disease in patients 6 to 17 years of age.

PMR/PMC Schedule Milestones:

Final Report Submission:	September 2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR is to address PREA requirements for adalimumab-atto for the treatment of pediatric CD in patients 6 to 17 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Amgen can fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Clinical studies may not be needed.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Amgen can fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Clinical studies may not be needed.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 761024
Product Name:	ABP 501 (adalimumab-atto; Amjevita)
PMR/PMC Description:	Assessment of adalimumab-atto for the treatment of pediatric ulcerative colitis in patients 5 years to 17 years of age.

PMR/PMC Schedule Milestones:

Final Report Submission:	December 2020

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

(b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR is to address PREA requirements for adalimumab-atto for the treatment of pediatric UC in patients 5 to 17 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Amgen can fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Clinical studies may not be needed.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Amgen can fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-licensed Humira to ABP 501. Clinical studies may not be needed.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # BLA 761024
Product Name: ABP 501 (adalimumab-atto; Amjevita)

PMR/PMC Description: Develop a presentation that can be used to accurately administer adalimumab-atto to pediatric patients who weigh less than 15 kg.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	September 2021
Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☒ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

As currently presented, Amjevita prefilled syringe with needle safety device and autoinjector presentations are not designed to allow for the direct administration of doses less than 20 mg, which impacts children who weigh less than 15 kg. A presentation is required for accurate weight-based dosing of patients (b) (4) who weigh less than 15 kg.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR is to develop a presentation that can be used to directly and accurately administer adalimumab-atto to pediatric patients who weigh less than 15 kg.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor will need to develop the new presentation of Amjevita to ensure that the appropriate dose is accurately administered to children weighing less than 15 kg. The specific type of study(ies) will depend on the presentation chosen by the Sponsor.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)

Studies to be determined based on the presentation developed, which may include stability testing and/or other CMC-related studies.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # BLA 761024
Product Name: ABP 501 / Injection

PMC #1 Description: Perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	07/31/2017
	Other:	MM/DD/YYYY

PMC #2 Description:

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☐ Improvements to methods
   ☒ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

This study is a confirmatory study to evaluate the potential for changes in quality attributes under routine shipping conditions.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☐ Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☒ Other

   Describe the agreed-upon study:

Perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs?
   ☒ Are the objectives clear from the description of the PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(Signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # BLA 761024
Product Name: ABP 501 / Injection

PMC #1 Description: Perform supplemental method validation and introduce a non-reduced CE-SDS test into the integrated control strategy for drug substance manufacture. Submit the analytical procedure, validation report, the proposed acceptance criterion, and the data used to set the acceptance criterion will be provided in a CBE-0 supplement.

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2016
	Other:	MM/DD/YYYY

PMC #2 Description:

PMC Schedule Milestones:		
	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other:	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☒ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

The non-reduced CD-SDS (nrCE-SDS) was qualified for the purposes of inclusion in the analytical similarity assessment. Amgen has committed to establish nrCE-SDS as a test in the integrated control strategy to evaluate and allow for trending of drug substance during routine manufacturing operations.

2. Describe the particular review issue and the goal of the study.

Perform additional method validation in order to comply with ICHQ2 expectations and introduce the method into the integrated control strategy for drug substance with an in-process acceptance criterion.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

Perform additional method validation in order to comply with ICHQ2 expectations and introduce the method into the integrated control strategy for drug substance.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(Signature line for BLAs only)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
09/21/2016

MEMORANDUM

NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 15, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761024
Product Name and Strength:	Amjevita (adalimumab-atto) Injection 20 mg/0.4 mL Prefilled Syringe (PFS) 40 mg/0.8 mL Prefilled Syringe (PFS) 40 mg/0.8 mL Autoinjector (AI)
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen
Submission Date:	August 12, 2016 and September 13, 2016
OSE RCM #:	2016-1872
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD
OMEPRM:	Kellie Taylor, PharmD, MPH

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the suffixes proposed by Amgen for the nonproprietary name and communicates our recommendation for the nonproprietary name.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Amgen's Amjevita product is necessary to distinguish this proposed product from Humira (adalimumab). As explained in FDA's draft Guidance for Industry, Nonproprietary Naming of Biological Products ("draft guidance"), FDA expects that a nonproprietary name for Amjevita that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance. FDA advised Amgen to provide proposed suffixes in accordance with the principles that are described in Section V of the draft guidance[a]. FDA has not finalized a policy on the nonproprietary naming of biological products. Accordingly, we reviewed Amgen's proposed suffixes against the criteria described in the draft guidance.

2.1 INITIAL ASSESSMENT OF AMGEN'S PROPOSED SUFFIXES

On August 12, 2016, Amgen submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of their product. We evaluated the proposed suffixes in the order of the preference listed by the Applicant.

The proposed suffixes were not recommended for approval given that the suffixes included common medical abbreviations that may present a risk for errors due to such inclusions. Additionally, the suffix *-atto* returned live trademarks from USPTO.

On September 7, 2016, the FDA communicated these findings to Amgen via an advice letter[b]. Subsequently, the FDA held a teleconference with Amgen on September 9, 2016 to discuss our findings and determine a path forward[c].

2.2 AMGEN'S RECONSIDERATION REQUEST ASSESSMENT

On September 13, 2016 Amgen submitted a reconsideration request for their proposed suffixes.

The ensuing paragraphs outline Amgen's arguments that are applicable to the concerns FDA previously identified with -atto, Amgen's preferred suffix for ABP 501, followed by DMEPA's assessment in italics.

1. Evaluation of complete suffix. Amgen believes it is not reasonable to assume that a subset of the suffix would be read as a stand-alone medicine. They argue that if that was the standard of evaluation, then the root names and trade names that include a pair of letters that constitute a meaningful abbreviation would be unacceptable as presenting excessive risk of medication error. Thus, any assessment performed specifically on the suffix should consider all four letters.

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[a] FDA draft guidance for industry on Nonproprietary Naming of Biological Products (August 2015). When final, this guidance will represent FDA's current thinking on this topic. 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

[b] Taylor, K. General Advice Letter. Silver Spring (MD): FDA, CDER, OSE, OMEPRM (US); 2016 SEP 07. BLA 761024.

[c] Harris, S. Memorandum of Meeting Minutes. Silver Spring (MD): FDA, CDER, OSE (US); 2016 SEP 13. BLA 761024.

DMEPA Response: We concur that, given the facts here regarding the abbreviations identified within the -atto suffix, that it is unlikely that a subset of letters within the -atto suffix would be misread as a stand-alone medicine when considering the expected use of this product.

2. Amgen argues that the majority of the concerns raised by FDA are based on similarities between 2-letter subsets of the suffix from a large database of medical abbreviations. Amgen argues that in order for such similarities to lead to a medication error, all of the following would need to occur:
    a. Only 2 letters of the suffix portion of the complete proper name would be read, recognized, or recalled;
    b. These 2 letters would be misinterpreted to mean another product; and
    c. This would lead to administration of a drug other than adalimumab-xxxx.

    With regards to points a. and b. Amgen argues that this risk in not greater than the risk with proprietary/non-proprietary names if applied to the same standard (i.e. overlapping of subsets of letters within the proprietary name with medical abbreviations).

    With regards to point c. Amgen argues that is critical to consider the plausibility of a medical intervention occurring as a result of the potential misreading or misinterpretation of the proper name. As an example they noted that our evaluation identified (b) (4) as an abbreviation for (b) (4) and they argue that neither of these are drug names and therefore the probability of this misinterpretation resulting in a medication error is negligible. Of note is the fact that Amgen "understands" that certain suffixes or subsets could be found unacceptable if it constituted a conflict with a medical term implying potential treatment with adalimumab such as –mtx or –qbd, that could potentially be misinterpreted to mean a particular use of the product.

    DMEPA response: DMEPA has considered the failure modes and effects analysis presented by Amgen regarding the potential for subsets in –atto to lead to confusion, and concluded that the overlap of 2-letter or 3-letter subsets of –atto with the medical abbreviations FDA previously identified is unlikely to be a source of error for ABP 501.

3. With regard to the four registered trademarks that are similar to the suffix –atto, Amgen argues that "the goods/services of the parties are completely different, are intended for different relevant consumers and travel in different channels of trade such that confusion as to the source of the goods/services would not be likely. The goods in these registrations are not of the kind that would be prescribed by medical professionals or distributed in pharmacies and, therefore, there would be no risk of medical error or mistaken prescription."

    DMEPA response: DMEPA notes that Amgen has evaluated registered trademarks for potential conflicts and provided justification for why the suffix "atto" would not create confusion.

3 CONCLUSION

Based on our analysis of the information submitted by the Applicant in support of the nonproprietary name reconsideration request for -atto, we conclude that the proposed suffix is acceptable for ABP 501. We have reconsidered the safety concerns outlined in our previous assessment and find that the information and analysis provided by Amgen allays our concerns with the –atto suffix.

Because our previous assessment for the suffix –atto did not identify any other issues that would render the name unacceptable, we now find this suffix acceptable.

FDA's determination does not constitute or reflect a decision on a general naming policy for biological products, including biosimilars. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance[a]. As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biological products established by FDA. Were the name to change, FDA intends to work with Amgen to minimize the impact this would have to its manufacture and distribution of this product, should it be licensed.

3.1 RECOMMENDATIONS FOR AMGEN

We find the nonproprietary name, adalimumab-atto, conditionally acceptable for your proposed product. Adalimumab-atto will be the proper name designated in the license should your 351(k) BLA be approved. You should revise your proposed labels and labeling accordingly.

FDA's comments on the nonproprietary name for this product do not constitute or reflect a decision on a general naming policy for biosimilar products. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

[a] FDA has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars (see Docket No. FDA-2014-P-0077). The citizen petitions submitted by the Generic Pharmaceutical Association and Novartis request that FDA require biosimilar products to be identified by the same nonproprietary name as their reference products (see Docket Nos. FDA-2013-P-1153 and FDA-2013-P-1398). Although FDA is designating a proper name that contains a distinguishing suffix for Amjevita, FDA is continuing to consider the issues raised by these citizen petitions, the comments submitted to the corresponding public dockets, and comments submitted to the dockets for the draft guidance for industry, "Nonproprietary Naming of Biological Products" (August 2015) and the proposed rule, "Designation of Official Names and Proper Names for Certain Biological Products" (80 FR 52224), with respect to establishing a general naming convention for biological products.

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/s/

CARLOS M MENA-GRILLASCA
09/15/2016

LUBNA A MERCHANT
09/15/2016

KELLIE A TAYLOR
09/15/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 31, 2016

To: Sadaf Nabavian, Pharm.D., Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

Subject: BLA # 761024 – ABP-TRADENAME (adalimumab-xxxx) injection, for subcutaneous use

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OPDP acknowledges receipt of DPARP's consult request dated January 14, 2016, requesting review of the proposed Package Insert (PI), Carton/Container Labeling, Medication Guide (MG), and Instructions for Use (IFU) for ABP-TRADENAME (adalimumab-xxxx) injection, for subcutaneous use.

Reference is made to DPARP's email to OPDP on August 9, 2016, conveying that a labeling review for the proposed PI is not expected for this cycle. Therefore, OPDP will not provide comments regarding the proposed PI for this application during this review cycle. OPDP requests that DPARP submit a new consult request during the subsequent review cycle.

OPDP has reviewed the proposed Carton/Container labeling that was sent from DPARP to OPDP on August 22, 2016. OPDP has no comments at this time on the proposed Carton/Container labeling.

Please note that comments on the proposed MG and IFU were provided on August 23, 2016, under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

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08/31/2016

Clinical Inspection Summary

Date	August 24, 2016
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Susan D. Thompson, M.D., Acting Branch Chief for Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	DDDP\Team Leader\Gordana Diglisic DDDP\Medical Officer\Denise Cook DDDP\Project Manager\Cristina Attinello DPARP\Team Leader\Nikolay Nikolov DPARP\Medical Officer\Keith Hull DPARP\Project Manager\Sadaf Nabavian
NDA/BLA #	BLA 761024
Applicant	Amgen, Inc.
Drug	(b) (4) (ABP 501)
NME (Yes/No)	BLA (biosimilar to adalimumab)
Therapeutic Classification	Standard Review
Proposed Indication(s)	Treatment of moderate to severe plaque psoriasis
Consultation Request Date	January 14, 2016
Summary Goal Date	August 25, 2016
Action Goal Date	September 25, 2016
PDUFA Date	September 25, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Gooderham and Raman were inspected in support of this BLA, in addition to an inspection of the sponsor, Amgen. The final classification of these inspections was No Action Indicated (NAI).

Based on the results of these inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this BLA to support the use of (b) (4) for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, adult Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis. Two clinical studies were submitted in support of this biosimilar BLA; one study in subjects with psoriasis and the second in subjects with rheumatoid arthritis. This Clinical Inspection Summary includes inspections related to the psoriasis study and the BLA sponsor. The Clinical Inspection Summary covering inspections related to the rheumatoid arthritis study was finalized in DARRTS on July 15, 2016.

Protocol 20120263, entitled "A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of ABP 501 Compared with Adalimumab in Subjects with Moderate to Severe Plaque Psoriasis" was inspected in support of this application. This study was conducted at 49 centers in six countries (Australia, Canada, France, Germany, Hungary, and Poland). A total of 350 subjects were randomized and analyzed (175 subjects per treatment group) in the full analysis set.

The primary objective of this study was to evaluate the efficacy of ABP 501 in subjects with moderate to severe plaque psoriasis, as measured by the Psoriasis Area and Severity Index (PASI) percent improvement from baseline, compared with adalimumab.

Randomization was stratified based on prior biologic use for psoriasis and geographic region. Subjects were randomized 1:1 to either the test article (ABP 501) or the comparator, adalimumab. At Week 16, subjects with a PASI 50 response continued on study for up to 52 weeks. These subjects were either continued on ABP 501, or, for those subjects initially randomized to adalimumab, were re-randomized at 1:1 to either ABP 501 or adalimumab. Final efficacy assessments were conducted at Week 50 with an End-of-Study Visit at Week 52.

The primary endpoint was the PASI percent improvement from baseline at Week 16. According to the sponsor, the 95% CI was within the predefined equivalence margin of (-15, 15), thus demonstrating the clinical equivalence of ABP 501 and adalimumab.

The sites of Drs. Gooderham and Raman were selected because no U.S. sites were involved in the study, and they represented relatively large enrollments for the study.

3. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
16002 Melinda J. Gooderham, M.D. SKiN Centre for Dermatology 775 Monaghan Road Peterborough, ON K9J 5K2 Canada and SKiN Centre for Dermatology 743 Lansdowne Street West Peterborough, ON K9J 1Z2 Canada	201202063/ 14	23-25 May 2016	NAI
16010 Mani Raman, M.D. The Centre for Dermatology 312 Highway 7 East Richmond Hill, ON L4B 1A5 CANADA	201202063/ 12	16-19 May 2016	NAI

Amgen One Amgen Center Drive Thousand Oaks, CA	Study #20120262 (rheumatoid arthritis) and Study #20120263 (psoriasis)	11-13 Apr 2016	NAI

Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Melinda J. Gooderham, M.D.

At this site for Protocol 20120263, 17 subjects were screened, 14 subjects were enrolled, two subjects withdrew consent because of lack of efficacy, and 12 subjects completed the study.

Review of the records for all 17 screened subjects included, but was not limited to, training logs, delegation logs, IRB correspondence and approvals, sponsor and monitoring correspondence, laboratory qualifications, screening and enrollment logs, inclusion/exclusion criteria, subject randomization, primary and secondary efficacy endpoints, protocol deviations, adverse events, concomitant medications, and test article accountability and storage.

Informed consent forms were completed appropriately by all subjects prior to any study-related testing. The source documents and Case Report Forms (CRFs) matched the information contained in the line listings.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Mani Raman, M.D.

At this site for Protocol 20120263, 13 subjects were screened, 12 subjects were randomized, two subjects withdrew consent for lack of efficacy, and 10 subjects completed the study

Review of the records for all 13 screened subjects included, but was not limited to, training logs, delegation logs, IRB correspondence and approvals, sponsor and monitor correspondence, financial disclosure, laboratory qualifications, inclusion/exclusion criteria, subject randomization, screening and enrollment logs, protocol deviations, primary and

secondary efficacy endpoints, adverse events, concomitant medications, and test article accountability and storage.

Informed consent forms were completed appropriately by all subjects prior to any study-related testing. The source documents and Case Report Forms (CRFs) matched the information contained in the line listings.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Amgen

At this site for Protocols 20120262 and 20120263, an inspection of the sponsor, Amgen, was conducted and focused on the following clinical investigators: Drs. Klimiuk, Racewicz, Brzezicki, Greenwald, Gooderham, and Raman. A separate CIS was issued covering the studies under Protocol 20120262 conducted by Drs. Klimiuk, Racewicz, Brzezicki, and Greenwald.

The inspection reviewed the following which included, but were not limited to, membership and activities of the external independent Data Monitoring Committee (DMC), presence of product complaints (none), adverse event reporting practices, the Trial Master File (TMF) (including FDA Form 1572s, IRB approvals, the informed consent form template for each study, lists of subjects enrolled in each study, lists of investigators and sub-investigators, and the submission histories of the two protocols and communications with FDA), sponsor organization, SOPs, transfer of responsibilities to (b) (4) , listings of outside service vendors, registration of studies in Clinicaltrials.gov, site recruitment questionnaires, monitor selection, financial disclosure, test article sourcing, manufacturing, transport, and disposition, trial document handling, storage, and disposition, and Interactive Voice/Web Response System (IXRS) structure and usage.

Amgen's procedures required 100% data verification of information entered into the Case Report Forms. (b) (4) was responsible for monitoring the studies conducted by the investigators identified above.

A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\BLA 761024
DPARP\Division Director\Badrul Chowdhury
DPARP\Team Leader\Nikolay Nikolov
DPARP\Medical Officer\Keith Hull
DPARP\Project Manager\Sadaf Nabavian
DDDP\Division Director\Kendall Marcus
DDDP\Team Leader\Gordana Diglisic
DDDP\Medical Officer\Denise Cook
DDDP\Project Manager\Cristina Attinello
OSI\DCCE\Division Director\Ni Khin
OSI\ DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\ DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\ DCCE\GCPAB\Reviewer\Roy Blay
OSI\ DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
08/24/2016

JANICE K POHLMAN
08/24/2016

SUSAN D THOMPSON
08/24/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 23, 2016
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (nonproprietary name):	[ABP-TRADENAME] (adalimumab-xxxx[1])
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761024
Applicant:	Amgen, Inc.

[1] A four letter suffix for the nonproprietary name for [ABP-TRADENAME] has not been determined. FDA is using "-xxxx" as a placeholder for the suffix. "-xxxx" is not intended to be included in the final printed labels and labeling.

1 INTRODUCTION

On November 25, 2015, Amgen, Inc. submitted for the Agency's review a 351(k) Biologics License Application (BLA) for [ABP-TRADENAME] (adalimumab-xxxx) injection, for subcutaneous use. Amgen, Inc. seeks approval for [ABP-TRADENAME] (adalimumab-xxxx) as a biosimilar product to the single reference biologic product HUMIRA (adalimumab) injection, for subcutaneous use, licensed under BLA 125057 by AbbVie, Inc. The Applicant has proposed the same indications for [ABP-TRADENAME] (adalimumab-xxxx) as the approved single reference product HUMIRA (b) (4) , for the treatment of the following:

- **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.
- **Juvenile Idiopathic Arthritis (JIA)**: Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- **Psoriatic Arthritis (PsA)**: Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS)**: Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (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.
- **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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on January 14, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for [ABP-TRADENAME] (adalimumab-xxxx) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review was completed on August 9, 2016.

2 MATERIAL REVIEWED

- Draft [ABP-TRADENAME] (adalimumab-xxxx) injection, for subcutaneous use MG and IFU received on November 25, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 9, 2016.
- Draft [ABP-TRADENAME] (adalimumab-xxxx) injection, for subcutaneous use Prescribing Information (PI) received on November 25, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 9, 2016.
- Approved HUMIRA (adalimumab) injection, for subcutaneous use comparator labeling dated June 30, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10 and 11 respectively.

In our collaborative review of the MG and IFU we have:

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the presentation of information in the MG is consistent with the format of the approved MG for the reference product where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
08/23/2016

ADEWALE A ADELEYE
08/23/2016

MARCIA B WILLIAMS
08/23/2016

LASHAWN M GRIFFITHS
08/23/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: August 18, 2016 **Date consulted:** January 14, 2016

From: Miriam Dinatale, D.O., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Director
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Drug: ABP 501 (adalimumab (b) (4), subcutaneous injection

BLA: 761024

Applicant: Amgen, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indications: For the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing arthritis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps)

Materials Reviewed:

- DPMH consult request dated January 14, 2016, DARRTS Reference ID 3873993
- Applicant's submitted background package for ABP 501 (adalimumab) BLA 761024.
- DPMH Review. Humira (adalimumab) Injection, BLA 125057. Jeanine Best, MSN, RN, PNP. March 13, 2013. DARRTS Reference ID 3275320.
- DPMH Review. Humira (adalimumab) Injection, BLA 125057. Miriam Dinatale, DO. March 25, 2014. DARRTS Reference ID 3476883.
- Division of Pediatric and Maternal Health review of 10th interim report of the adalimumab pregnancy registry report. IND 7627. Miriam Dinatale, D.O. November 3, 2014. DARRTS Reference ID 3650679

- DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672

Consult Question:
DPARP would like to seek DPMH "to provide comments and proposed revisions on the labeling sections that correspond to the new PLLR section of the package insert."

INTRODUCTION
The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 14, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of ABP 501 (adalimumab) to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY
On November 25, 2015, Amgen, Inc. submitted a Biologics License Application (BLA) for ABP 501 (adalimumab-(b) (4) BLA 761024, for the following proposed indications: treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing arthritis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis (Ps). Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). The biological reference product is Humira (adalimumab), which was approved in the US on December 31, 2002. Humira labeling, in the PLLR format, was updated on June 30, 2016. The reader is referred to the DPMH review by Miriam Dinatale, D.O. for further details.[1]

BACKGROUND
Adalimumab and Drug Characteristics
Adalimumab binds to TNF-alpha and blocks its interaction with p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF is increased in patients with RA, JIA, PsA, and AS. The exact mechanism of action of adalimumab is unknown. Adalimumab has a molecular weight of 148,000 Daltons and a mean terminal half-life of 2 weeks. [2]

Current State of Labeling
Labeling for Humira, the biological reference product, was converted to the PLLR format on June 30, 2016 and included data from the RA portion of the Humira pregnancy. Since the results of the Humira Pregnancy Registry are published in literature, information from the Humira pregnancy registry will be included in ABP 501 labeling.

Pregnancy and Nursing Mothers Labeling
On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[3] also known as

[1] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672
[2] Humira (adalimumab) labeling. Section 12: Clinical Pharmacology. Drugs @FDA. Accessed 11/2/2015.
[3] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[4] format to include information about the risks and benefits of using these products during pregnancy and lactation.

PREGNANCY

Nonclinical Experience

Current labeling provided by the applicant includes data from animal reproduction studies that were conducted for the initial approval of Humira in 2002. No additional nonclinical studies were submitted with this BLA. In perinatal development studies, there was no evidence of embryofetal toxicity in pregnant cynomolgus monkeys administered adalimumab during organogenesis at doses 373-times the maximum recommended human dose (MRHD). The reader is referred to the Nonclinical Review by Jianmeng Chen, M.D., Ph.D. for further details.

Applicant's Review of Published Literature

The applicant performed a literature review in PubMed and Ovid databases from January 2005 through March 2016 using the following search terms: "adalimumab" and "pregnancy" or "pregnant" to obtain information on adalimumab use during pregnancy. The results of the applicant's review of literature are provided below. In addition, Tables 1, 2 and 3 provided by the applicant include case reports regarding adalimumab use during pregnancy and are included in Appendix B of this review.

In a prospective cohort study conducted by the OTIS Collaborative Research Group (Chambers, *et al.*), 74 adalimumab-exposed with RA, 80 women with RA but with no adalimumab exposure, and 218 non-diseased women were enrolled. Women exposed to adalimumab had at least one dose of the medication in the first trimester, and approximately 43% used adalimumab in all three trimesters. The rate of major defects in the exposed, disease-matched, and non-diseased comparison groups was 5.6%, 7.8%, and 5.5%, respectively. A total of 234 infants (70% of the live born infants) were physically examined. There was no difference in the proportion of children with three or more minor abnormalities among three groups. In women with RA, the adalimumab-exposed group had a higher percentage of spontaneous abortions (SAB) compared to unexposed women (9% vs. 3.8%). The rate of SAB of clinically recognized pregnancies in the general population is between 15 and 20%. There was no statistically significant increase in the risk of spontaneous abortion following adalimumab exposure. The rate of spontaneous abortions, using an adjusted hazard ratio (HR), was 1.96 (95% CI, 0.47, 8.26) when comparing the adalimumab and disease-matched group and 3.79 (95% CI 1.01, 14.23) when comparing the adalimumab and non-diseased group. However, the number of events was small with seven events in the ADA-exposed cohort and three events in the RA unexposed cohort. The rate of preterm

[4] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

delivery and small-for-gestational age infants did not differ among the three groups. The authors concluded that pregnant women with RA who used adalimumab in the first trimester of pregnancy compared to women with RA who were not treated with adalimumab, did not appear to be at an increased risk for adverse fetal outcomes.

In a prospective observational study, (Zelinkova, *et al*.) the authors followed 31 pregnancies in 28 women with inflammatory bowel disease (IBD) between April 2006 and April 2011 who were treated with anti-TNF-α agents. Eleven women received adalimumab during 13 pregnancies. All thirteen patients discontinued adalimumab before gestational week 30; two patients suffered relapses of IBD. There were two miscarriages in the first trimester and no congenital abnormalities. Adalimumab was detected in five cord blood samples. The authors concluded that although anti-TNF therapy appears to be safe in pregnant women with quiescent IBD, anti-TNF drugs are detected in cord blood samples.[5]

In the ongoing Pregnancy IBD and Neonatal Outcomes (PIANO) study (Mahadevan, *et al*.), the authors provided data on the safety of adalimumab use in all three trimesters of pregnancy in women with IBD and data on infant immune development. One hundred seventy four infants who were exposed to adalimumab *in utero* (117 had adalimumab exposure during the third trimester), were compared to infants with no *in utero* adalimumab exposure. The infants were followed for one year. There was no difference in infection rates between infants exposed to biologics *in utero* compared to unexposed infants. The authors concluded that the study reinforces the safety of adalimumab use in the third trimester.[6]

In a 2011 registry report by The British Society for Rheumatology Biologics Register (Verstappen, *et al*.[7]), the authors published the outcomes of 130 pregnancies in women treated with anti-TNF-α agents. Of the 130 pregnancies, 26 pregnancies were exposed to adalimumab. The study did not report isolated adalimumab findings, but included findings observed in women exposed to anti-TNF-α agents in general. The following outcomes were observed:

- 88 live births
- 29 spontaneous abortions (no information about gestational age or fetal malformations)
- 10 elective terminations (no reason for termination was provided)
- one neonate death (perinatal hypoxia. The mother had been on etanercept)
- four intrauterine deaths (two deaths from two different sets of twins)
- four congenital abnormalities (congenital hip dislocation, pyloric stenosis winking jaw syndrome, strawberry birth mark)
- one full term infant with low birth weight

[5] Zelinkova, et al. Effects of Discontinuing Anti-Tumor Necrosis Factor Therapy During Pregnancy on the Course of Inflammatory Bowel Disease and Neonatal Exposure. Clinical Gastroenterology and Hepatology. 2013; 11: 318-321.

[6] Mahadevan, et al. 960 exposure to anti-TNF-alpha therapy in the third trimester of pregnancy is not associated with increased adverse outcomes:results from the PIANO registry. *Gastroenterology*. 2014;146(5):S170.

[7] Verstappen, et al. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2011;70:823-826.

In a prospective 3-center study conducted between January 2007 and December 2012 (Bortlik, *et al*.), the authors reported on 41 pregnancies that were exposed to anti-TNF-α agents (infliximab: 31, adalimumab: 9). Of the nine patients exposed to adalimumab during pregnancy, eight pregnancies were exposed to adalimumab at conception, nine pregnancies were exposed during the first trimester, seven pregnancies were exposed during the second trimester, and three pregnancies were exposed during the third trimester. Of the nine patients exposed to adalimumab, one patient had an elective abortion due to personal circumstances. There were no congenital malformations in the patients exposed to adalimumab during pregnancy. The authors also noted that the rate of spontaneous abortions (12%) and low birth weight (3%) was not higher than the general population.[8]

In a report by the World Congress of Gastroenterology, the Organization for Teratology Information Specialists (OTIS) provided data on 38 women enrolled in a prospective study of adalimumab in pregnancy and 133 adalimumab-exposed pregnant women in a case series. The authors noted that rate of spontaneous abortion (5/38 [13%]), stillbirth (0 out of 38), and congenital malformation (2/33 [6.1%]) in the adalimumab-exposed group was similar to the disease- matched and general population when taking into account the reporting bias.[9]

In a letter to the editor (Jürgens, *et al*.), the authors described a case report of a 32 year-old female with Crohn's disease who was exposed to adalimumab during the first trimester of pregnancy. Adalimumab was discontinued at 7 weeks gestation. The mother delivered a healthy female infant. The authors also conducted a review of published literature and found 132 pregnancies that occurred in women treated with adalimumab during pregnancy. There were no cases of congenital abnormalities and no differences in the risk of spontaneous abortion and preterm delivery that were observed.[10]

In a review article (Kahn, *et al*.), the authors reviewed several case reports and case series[11,12] of adalimumab use in pregnant women and noted that there are no significant differences in the risk of spontaneous abortions or congenital malformations between women exposed to adalimumab during pregnancy compared to unexposed women.

DPMH's Review of Published Literature

DPMH performed a search of Micromedex[13] and in PubMed and Embase using the following search terms: "adalimumab" and "pregnancy" and "fetal malformations" or "miscarriage."

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[8] Bortlik, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-a therapy during pregnancy: three-center study. Scandinavian Journal of Gastroenterology. 2013; 48: 951-958.

[9] Mahadevan, et al. The London Position Statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: pregnancy and pediatrics. *Am J Gastroenterol.* 2011; 106:214-223.

[10] Jurgens, et al. Safety of adalimumab in Crohn's disease during pregnancy; case report and review of literature. Inflamm Bowel Dis. 2010; 16: 1634-1636.

[11] Schnitzler, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis*. 2011;17:1846–1854.

[12] Weber-Schoendorfer, et al. Pregnancy outcome after TNF-a inhibitor therapy during the first trimester: A prospective multicentre cohort study. *Br J Clin Pharmacol.* 2015;80(4):727-739.

[13] www. Micromedexsolutions.com. Accessed 6/8/2016.

In addition to the data reviewed by the applicant, DPMH reviewed additional published articles[14,15,16,17,18,19,20] in previous reviews of adalimumab. The reader is referred to previous DPMH reviews by Miriam Dinatale, D.O. for further details of published literature.[21,22]

Summary

There have been 669 adalimumab-exposed pregnancies reported in literature (adalimumab pregnancy registry, prospective and retrospective observational studies and case reports). Overall, maternal risks were not increased and fetal and infant risks, infection rates and immune development are similar to the rates seen in the disease-matched and general population. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and lack of control for disease activity or severity. There is no information specific to ABP 501 that would warrant different labeling for pregnancy.

LACTATION

Applicant's Review of Published Literature

The applicant performed a literature review in PubMed and Ovid databases from January 2005 through March 2016 using the following search terms: "adalimumab" and "breastfeeding" or "lactation" to obtain information on adalimumab use during breastfeeding. A review of relevant published literature is provided below.

In a case report (Ben-Horin, *et al*.), a 26-year-old female with CD gave birth to a healthy term infant after receiving adalimumab until week 30 of gestation. The mother experienced a flare-up of CD at four weeks post-partum and restarted adalimumab (40mg) while continuing to breastfeed. Maternal blood and breast milk sample were obtained before and every two days for eight days after adalimumab administration. Sample collection stopped at day eight when the patient decided to stop breastfeeding (no reason provided). Following injection of adalimumab, adalimumab level rose in the maternal serum peaking at day three at 4300 ng/mL and declining after day three. Breast milk adalimumab levels were less than 1/100

[14] Wallenius *et al*. Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. Acta Obstet Gynecol Scand epub ahead of print. 2013.
[15] Norgaard *et al* "Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study." *Journal of Internal Medicine*. 2010; 268: 329-337.
[16] Viktil et al. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150 000 pregnant women and expectant fathers. 2012 Scand J Rheumatol 41:196-201.
[17] Zelinkova A et al. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clinical Gastroenterology and Hepatology. 2013 11:318-321.
[18] Diav-Citrin O, Otcheretianski-Volodarsky A, Shechtman S, et al. Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. Reprod Toxicol. 2014;43:78-84.
[19] Mahadevan, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterology Hepatology. 2013; 11(3): 286-92.
[20] Palmeira, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012; 2012: 985646.
[21] Division of Pediatric and Maternal Health review of 10th interim report of the adalimumab pregnancy registry report. IND 7627. Miriam Dinatale, D.O. November 3, 2014. DARRTS Reference ID 3650679
[22] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672

(1%) of the corresponding maternal serum level. The milk drug level rose from undetectable (pre-adalimumab injection) to 31 ng/mL of post-injection day six. There were no reported adverse effects on the infant. The authors noted that small quantities of adalimumab would be present in breast milk and would be further broken down in the infant after ingestion. However, the authors noted that further studies would be needed to determine if even low levels of adalimumab would have an effect on an infant. [23]

DPMH's Review of Published Literature

In addition to the literature search performed by the applicant, DPMH performed a search of *Medications and Mother's Milk*[24], the Drugs and Lactation Database (LactMed),[25] PubMed, Embase and TERIS. The results of the literature search are described below.

In *Medication and Mother's Milk*, Dr. Thomas Hale, a breastfeeding expert, notes that IgG transfer into breast milk is highest in the first four days postpartum and is minimal afterwards. Immunoglobulins are transferred into breast milk by carrier protein, with IgA as the primary immunoglobulin seen in human milk. The transfer of IgG-like products is limited, and it is unlikely that adalimumab will be transferred into breast milk in clinically relevant amounts after the first week postpartum. However, data are limited.

LactMed notes that there are low levels of adalimumab in breast milk and no evidence of adverse effects of the drug on the breastfeeding infant. Since the molecular weight of adalimumab is large (148,000 Daltons), the amount of drug in the milk is likely to be low and absorption is unlikely since the infants gastrointestinal tract destroys the drug. Since there is minimal information of adalimumab use during breastfeeding, LactMed recommends that caution should be used during breastfeeding.

As part of a multicenter prospective cohort study of pregnant woman with inflammatory bowel disease (IBD) and their offspring (PIANO Registry), breast milk samples were collected from patients on biologics (Infliximab (n=11), adalimumab (n=6), certolizumab (n=3)) at one, 12, 24 and 48 hours after drug administration. Data about the child's health and infections were obtained from mother's and from the child's pediatrician at 12, 24, 36 and 48 months of age. While infliximab was present in breast milk (90-591 ng/ml) between 24 and 48 hours after infusion, adalimumab and certolizumab were not detected in breast milk at any point in time. When comparing breastfed infants on biologics versus non-

[23] Ben-Horin S, Yavzori M, Katz L et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol. 2010;8:475-6

[24] Hale, Thomas, Ph.D. Medications and Mother's Milk: A Manual of Lactational Pharmacology-2012, 15th edition. Hale Publishing, L.P.

[25] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

breastfed infants, there were no differences in infant development or rates of infection between the two groups.[26]

Reviewer comment:
The authors in the PIANO Registry collected breast milk samples only until 48 hours after adalimumab administration. Therefore, it is possible that the authors did not collect breast milk samples for an adequate duration of time and may have missed the appearance of adalimumab in breast milk.

In a case report (Fritzsche, *et al*.),[27] the authors reported on two patients who were treated with adalimumab 40mg for treatment of inflammatory bowel disease at unstated intervals. The detection limit of the assay for adalimumab in breast milk was 40ng/ml. The breast milk level of adalimumab was less than 1/1000 or 0.1% (4.83 ng/mL) of the corresponding maternal serum level in one patient and not detectable in the other patient. The reader is referred to the DPMH review by Miriam Dinatale, D.O for further details of the case report.[28]

Summary
Limited data from case reports in published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects (developmental delays or increase in infection) of adalimumab on the breastfed infant and no effects on milk production. Therefore the "Risk Summary" section of 8.2 will include the following statement:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [TRADENAME] and any potential adverse effects on the breastfed child from [TRADENAME] or from the underlying maternal condition.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience

(b) (4)

Applicant's Review of Published Literature
The applicant performed a literature review in PubMed and Ovid databases from January 2005 through March 2016 using the following search terms: "adalimumab" and "fertility" to obtain information on adalimumab use and its effects on fertility. A review of relevant published literature is provided below.

[26] Matro, R. Detection of Biologic Agents in Breast Milk and Implication for Infection, Growth, and Development in Infants Born to Women with Inflammatory Bowel Disease: Results from the PIANO Registry. Gastroenterology. 2015. 148(4). Suppl 1.
[27] Fritzsche J , Pilch A, Mury D et al. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46:718-9
[28] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672

Although clinical data is limited, adalimumab does not appear to affect female or male fertility.[29] In a retrospective study (Winger, E. and Reed, J.), 75 women with a history of recurrent SAB were evaluated. The patients were divided into three groups: 21 patients were treated with anticoagulants (heparin 5000 IU, Lovenox 30 or 40 mg , Clexane, or Arixtra), 37 patients were treated with anticoagulants plus intravenous immunoglobulin (IVIG at 400mg/kg) and 17 patients were treated with anticoagulants plus IVIG, and a TNF-α (Etanercept or adalimumab). The authors noted that in women with recurrent SAB, treatment with the addition of IVIG or a TNF- α inhibitor improved the live birth outcome compared to the group that was treated with an anticoagulant alone.[30]

DPMH's Review of Published Literature

In addition to the review of published literature performed by the applicant, DPMH also performed a literature review in PubMed and Embase using the key search words "adalimumab and fertility" and "adalimumab and sperm" Three relevant articles[31,32,33] were found and noted that exposure to anti-TNF therapy, including treatment with adalimumab, does not appear to adversely affect sperm quality or testicular function in male patients. The reader is referred to the DPMH review by Miriam Dinatale, D.O. for further details of the three published studies.[34]

Summary

Overall, it does not appear that adalimumab affects female or male fertility. Since there is no evidence that adalimumab impacts fertility, section 8.3, Females and Males of Reproductive Potential will be omitted from labeling.

CONCLUSIONS

ABP 501 (adalimumab) labeling has been updated to comply with the PLLR. DPMH has the following recommendations for Humira labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of ABP 501 (adalimumab) labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections[35].

[29] Grunewald S, Jank A. New systemic agents in dermatology with respect to fertility, pregnancy, and lactation. J Dtsch Dermatol Ges. 2015;13(4):277 -89.

[30] Winger, EE and Reed, JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. Am J Reprod Immunol. 2008; 60:8-16.

[31] Micu, et al. TNF-a inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology. 2014; 53(7):1250-5.

[32] Ramonda, et al. Influence of tumor necrosis factor α inhibitors on testicular function and semen in spondyloarthritis patients. Fertil Steril. 2014: 101(2): 359-365.

[33] Villiger, et al. Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Annals of Rheumatic Disease. 2010. 69(10): 1842-4.

[34] DPMH Review. Humira (adalimumab) Injection. BLA 125057/S-397. Miriam Dinatale, D.O. March 24, 2016. DARRTS Reference ID 3904672.

[35] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Lactation, Section 8.2**
  - The "Lactation" section of ABP 501 (adalimumab) labeling was formatted in the PLLR format to include the "Risk Summary" section[36].

RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 in ABP 501 (adalimumab) labeling for compliance with the PLLR (see below). See Appendix A for the applicant's proposed pregnancy and lactation labeling. DPMH refers to the final NDA action for final labeling.

[36] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

DPMH Proposed ABP 501 (adalimumab) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Limited clinical data are available from the adalimumab pregnancy registry. Excluding lost-to-follow-up, data from the registry report an incidence of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations
Fetal/Neonatal adverse reactions
Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *[see Data]*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see use in Specific Populations (8.4)]*.

Data
Human Data
In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non- randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with adalimumab, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of adalimumab was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 μg/mL in cord blood, 4.28-17.7 μg/mL in infant serum, and

0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data
In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation
Risk Summary
Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

MEDICATION GUIDE

What should I tell my doctor before taking HUMIRA?
- are pregnant or plan to become pregnant. It is not known if HUMIRA will harm your unborn baby. HUMIRA should only be used during a pregnancy if needed.
- have a baby and you were using HUMIRA during your pregnancy. Tell your baby's doctor before your baby receives any vaccines.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use HUMIRA. You should not do both.

APPENDIX A – Applicant's Proposed ABP 501 (adalimumab) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

(b) (4)

Clinical Considerations

(b) (4)

Data
Human Data

(b) (4)

Animal Data

(b) (4)

8.2 Lactation

(b) (4)

Appendix B: Applicant's Summary of Published Studies with Use of Adalimumab During Pregnancy. See Appendix C for references.

Table 1. Published IBD Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Vesga et al	CD	ADA	2005	P(T1-T3) and breast-feeding	Case Report (1)	C-section	Normal, healthy, 38.5 weeks
Mishkin et al	CD	ADA	2006	PC/P(T1-T3)	Case Report (1)	Vaginal	Normal, healthy, full term
Coburn et al	CD	ADA	2006	P(T2; T3)	Case Report (1)	Unknown	Normal, healthy, 38 weeks
Bosworth et al	CD	ADA	2007	PC/P(T1-T3)	Case Report (1)	C-section	Normal, health, 36 weeks
Ben-Horin et al	CD	ADA	2010	PC/P(T1-T3) and breast-feeding	Case Report (1)	Vaginal	Healthy, normal, full term; no adverse effects from breast-feeding
Jürgens et al	IBD	ADA	2010	PC/P(T1)	Case Report (1)	Vaginal	Healthy, full term
Abdul Wahab and Harkin	CD	ADA	2011	PC/P(T1-T3)	Case Report (1)	C-section	Twins, normal, healthy, full term
Sujikawa et al	CD	ADA	2013	P(T1-T3)	Case Report (1)	Unknown	Normal, healthy, full term
Julsgaard et al	CD	ADA	2013	P(T1-T2)	Case Report (1)	Unknown	Normal, healthy, full term
Bortlik et al	IBD	IFX/ADA[a]	2013	PC/P(T1-T3)	Prospective 3-center study (41 total; 32 [IFX]; 9 [ADA])	Unknown	34 live births; 28 full term; 6 preterm; 5 spontaneous abortions; 2 therapeutic abortions; 1 congenital abnormality (hip dysplasia). (ADA-only data not available)
Seirafi et al	IBD	IFX/ADA/CZP[a]	2011	PC/P(T1-T3)	Case series (85 women)	Unknown	6/85 were miscarriages, 47/85 were live births (30/85 ongoing), 8/49 were preterm, 3/49 were deaths (2 in utero/1 very premature),7/46 live births had neonatal complications (1 infection, 3 respiratory distress syndrome, 6 LBW <2500 g, 1 HELLP syndrome

Table 1. Published IBD Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Casanova et al	IBD	IFX/ADA/CZP[a]	2011	PC/P(T1-T3)	Case-controlled retrospective study (30 pregnancies in treated mothers vs. 110 unexposed IBD pregnancies)	Unknown	Prevalence of unfavorable delivery outcome (eg, spontaneous abortion, preterm delivery, low birth weight and abnormalities) were higher in the control group
Mahadevan et al	IBD	IFX/ADA/CZP[a]	2013	PC/P(T1-T3)	Case series (31 women)	15 vaginal; 16 C-section	All 33 children (2 sets of twins) were normal, healthy, full term
Casanova et al	IBD	IFX/ADA/CZP[a]	2013	PC/P(T1-T3)	Case series (66 pregnancies)	Unknown	55 normal, healthy full term; 4 preterm; 6 miscarriages; 1 congenital abnormality (several cardiac abnormalities)
Dunne et al	CD	IFX/ADA[a]	2011	PC/P(T1-T3)	15 case series (15 women; 3 ADA pregnancies)	Unknown	9 successful pregnancies at study end. All live births were healthy, but 5 LBW, with two sets of twins. No congenital abnormalities
Schnitzler et al	IBD	IFX/ADA[a]	2011	PC and/or P(T1) and/or P(T2)	Case-controlled study (35 women with 42 pregnancies (35 IFX + 7 ADA) vs. 101 pregnancies before IBD/ treatment and 56 matched pregnancies in healthy controls)	Unknown	10 abortions (1 trisomy 18, 1 elective), 1 stillbirth (umbilical strangulation), 32 live births: 8/32 premature, 6/32 LBW. All children were born healthy but 1 child with necrotizing enterocolitis died at 13 days of age (mother required treatment for severe asthma and CD during T3)

Table 1. Published IBD Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Machková et al	IBD	IFX/ADA[a]	2012	PC/P(T1-T3)	Case series (33 pregnancies in 31 women)	Unknown	5/33 pregnancies ongoing. 24/28 healthy children (4/24 preterm), 3/24 spontaneous abortions, and 1/24 provoked abortion
Zelinkova et al	IBD	IFX/ADA[a]	2013	PC/P(T1-T3) (T1-T2 ADA only)	Case series (31 pregnancies in 28 women)	Unknown	28 live births (27 normal, healthy, full term; 1 child born to a mother treated with concomitant methotrexate periconceptually had polydactyly); 3 miscarriages
Traussnigg et al	IBD	IFX/ADA[a]	2013	PC/P(T1-T3)	Case series (14 pregnancies in 13 women)	Unknown	13 normal, healthy, full term; 1 miscarriage
Habal	IBD	IFX/ADA[a]	2013	PC/P(T1-T3)	Prospective study (29 pregnancies in 21 women)	Unknown	27 normal, healthy, full term; 2 miscarriages
Mahadevan et al	IBD	ADA/IFX/CZP	2014	PC/P(T1-T3)	Prospective cohort study (1289 exposed to anti-TNF-α agents; 174 infants exposed to ADA; 117 exposed in T3)	Unknown	Anti-TNF-α results: 1039 live births. No significant difference in infection rates or immune developmental achievements of those exposed compared to unexposed

Adopted from Dessinioti et al, 2011; Nielsen et al, 2013; and Diav-Citrin et al, 2014.
ADA = Adalimumab; CD = Crohn's disease; CZP = Certolizumab; ETA = Etanercept; IBD = Irritable Bowel Disease; IFX = Infliximab; JIA = juvenile idiopathic arthritis; LBW = Low birth weight; P(T1-T3) P(T1-T3) = biologics administered in trimester 1 through 3; PC = Periconceptual (ie, use within 90 days before conception).
a: Independent data for ADA not available. Data reported for all anti-TNF-α agents.

Table 2. Published Rheumatology Studies and Cases on the Use of Adalimumab During Pregnancy

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Hyrich et al	RA	ADA	2006	PC/P(T1)	Case Series (3 pregnancies)	Vaginal	2 live births, 1 miscarriage in first trimester, no major fetal abnormalities
Roux et al	RA	ADA	2007	PC	Case Report (1)	Vaginal	Normal, healthy, born at 32 weeks (healthy at 12 month follow-up)
Kraemer et al	Takayasu's arteritis	ADA	2008	P(T1)	Case Report (1)	C-section	Normal, healthy, 37 weeks gestation
Berthelot et al	RA and spondyl-arthropathy	ADA	2009	P(T1-T3)	Case Series (2 pregnancies)	1 vaginal; 1 C-section	1 infant born at 37 weeks, healthy; the other infant born at 38 weeks, healthy
Chambers et al	RA	ADA	2015	PC/P(T1-T3)	Case series (74 ADA, 80 DM, 218 ND)	Unknown	Total of 334 live births. Congenital abnormalities in 4, 6, and 12 births in ADA, DM, and ND, respectively
Verstappen et al	RA/PsA/JIA /AS/SLE/Still's disease	IFX/ADA/ETA[a]	2011	PC/P(T1-T3)	Case Series (130 total pregnancies [exposed to anti-TNF-α]; 26 ADA)	Unknown	88 live births (anti-TNF-α exposure); 29 spontaneous abortions; 10 terminations; 1 neonate death; 4 intrauterine deaths (2 were twins); 19 premature; 1 full term infant with LBW; and 4 congenital abnormalities (ADA-only data unavailable)

Adopted from Dessinioti et al, 2011; Nielsen et al, 2013; and Diav-Citrin et al, 2014.
ADA = Adalimumab; AS = ankylosing spondylitis; DM = Disease-matched; ETA = Etanercept; IFX = Infliximab; JIA = juvenile idiopathic arthritis; LBW = Low birth weight; ND = Nondiseased-matched; P(T1-T3) P(T1-T3) = biologics administered in trimester 1 through 3; PC = Periconceptual (ie, use within 90 days before conception); PsA = psoriatic arthritis; RA = Rheumatoid arthritis; SLE = Systemic lupus erythematosus.
a: Independent data for ADA not available. Data reported for all anti-TNF-α agents.

Table 3. Published Studies and Cases on the Use of Adalimumab During Pregnancy in Multiple Conditions and Infertility

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Winger et al	Infertility	ADA	2009	PC	Prospective study (47 pregnancies)	Unknown	33 live births
Johnson et al	Multiple (RA and CD)	ADA	2009	PC/P(T1-T3)	Case–control (85 women)	Unknown	71 live births; 13 miscarriages; 1 therapeutic abortion; 11 preterm. Rate of abortion in ADA-exposed group was 15.3% vs. 5.3% in DM controls; 7 major defects
Mahadevan and Miller et al	Multiple	ADA	2011	PC/P(T1-T3)	Case series (5 women)	2 vaginal; 3 C-sections	Healthy (1 infant developed pulmonary edema, but recovered fully)
Weber-Schoendorfer et al	Multiple	ADA/IFX	2011	P(T1)	Case series (85 pregnancies; 28 ADA-exposed pregnancies)	Unknown	24 live ADA births total; 2 ADA miscarriages; 2 ADA voluntary terminations; 4 ADA premature births; 1 ADA autosomal disease inherited
Weber-Schoendorfer et al	Multiple	IFX/ADA/CZP /GOL/ETA[a]	2015	P(T1)	Prospective cohort study (495 exposed to anti-TNF-α; 172 exposed to ADA)	Unknown	ADA data: 144 live births; 9 birth defects; 25 preterm; LBW tendency in the ADA-exposed group
Diav-Citrin et al	Multiple	IFX/ADA/ETA[a]	2014	P(T1-T3)	Prospective, comparative study (35 IFX; 25 ETA; 23 ADA; 86 DM untreated; 341 unexposed pregnancy controls)	43 vaginal; 22 C-section; 1 vacuum	Anti-TNF-α group: 67 live births; 9 miscarriages; 5 elective abortions; 1 stillbirth; 1 ectopic; 3 major abnormalities; 3 major non-genetic or cytogenic abnormalities; 1 congenital abnormality in ADA group

Table 3. Published Studies and Cases on the Use of Adalimumab During Pregnancy in Multiple Conditions and Infertility

Author	Condition	Anti-TNF-α Type	Year	Stage of Pregnancy	Study Type (N)	Delivery Mode	Pregnancy Outcome
Slama et al	Multiple	IFX/ADA[a]	2010	PC/P(T1-T3)	Case series (289 pregnancies)	Unknown	No increased risk of adverse pregnancy outcome compared with unexposed IBD pregnancies
Julsgaard et al	Multiple	IFX/ADA[a]	2015	PC/P(T1-T3)	Case-controlled, prospective study (89 pregnancies)	Unknown	5 miscarriages, 3 preterm births, 3 LBW, and 2 congenital abnormalities

Adopted from Dessinioti et al, 2011; Nielsen et al, 2013; and Diav-Citrin et al, 2014.
ADA = Adalimumab; CZP = Certolizumab; DM = Disease-matched; ETA = Etanercept; GOL = golimumab; IFX = Infliximab; LBW = Low birth weight; P(T1-T3) P(T1-T3) = biologics administered in trimester 1 through 3; PC = Periconceptual (ie, use within 90 days before conception); RA = Rheumatoid arthritis.
a: Independent data for ADA not available. Data reported for all anti-TNF-α agents.

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/s/

MIRIAM C DINATALE
08/19/2016

JOHN J ALEXANDER
08/19/2016
Signing for Dr. Yao

HUMAN FACTORS, LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 9, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761024
Product Name and Strength:	Amjevita (ABP 501)* Injection 20 mg/0.4 mL Prefilled Syringe (PFS) 40 mg/0.8 mL Prefilled Syringe (PFS) 40 mg/0.8 mL Autoinjector (AI)
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Amgen
Submission Date:	November 25, 2015
OSE RCM #:	2016-159
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD
OMEPRM Deputy Director:	Kellie Taylor, PharmD, MPH

*Amjevita has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for Amjevita has not yet been determined, ABP 501 is used throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

This review evaluates the applicant's Human Factors evaluation, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Amjevita[1] (ABP 501)* injection (BLA 761024) for areas of vulnerability that could lead to medication errors. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested this review to inform their evaluation of the 351k submission for Amjevita. The reference product, US-licensed Humira (BLA 125057), was approved in December 31, 2002.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)#	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
#We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Amjevita (ABP 501)* injection, BLA 761024.

The applicant is proposing the same indications (b) (4), dosing, and route of administration as the reference product, US-licensed Humira (BLA 125057). Amgen proposes to market a 20 mg and 40 mg pre-filled syringe (PFS) and a 40 mg autoinjector (AI). (b) (4) We note that the review team is considering a Post Marketing Requirement to introduce a presentation that could service pediatric patients (b) (4) under Pediatric Research Equity Act (PREA), and we defer to the review team's decision on this.

[1] Proposed proprietary name found conditionally acceptable by DMEPA in the IND.

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With regard to the proposed autoinjector, the applicant relies upon the human factors study data gathered for the modified Enbrel SureClick pen platform. The BLA for Enbrel (etanercept) is held by Immunex Corporation and the Enbrel Sureclick pen platform was approved as part of BLA 103795 on November 2, 1998. We note that Immunex Corporation is an Amgen company. During the BDP Type 2 meeting held on January 29, 2014, the Agency agreed that the patient population tested using the modified Enbrel SureClick is considered representative and applicable to all indications pursued for ABP 501 AI, including Crohn's disease and ulcerative colitis. Because the modified Enbrel SureClick human factor study included the representative RA, PsA, AS, and PsO users, as a scientific matter, DMEPA finds that the modified Enbrel Sureclick autoinjector human factors validation data referenced in this submission can be appropriately relied on to support the development of the Amjevita autoinjector.

Given that the applicant is relying on data in the Enbrel SureClick application, we would, as a scientific matter, expect that the device specific steps on Amjevita SureClick's IFU closely follow that of Enbrel's IFU. Product specific information on Amjevita SureClick's IFU must follow US-licensed Humira's IFU. However, in our review, we identified that there are some minor differences between the Instructions for Use for Enbrel SureClick and US-licensed Humira autoinjector and the Amjevita SureClick IFU. Therefore, we will provide recommendations to the Amjevita SureClick IFU to follow all device specific steps from Enbrel IFU and product specific information from US-licensed Humira IFU or ask that the sponsor provide a scientific justification to support the variation.

Although the proposed pre-filled syringes for Amjevita resemble the pre-filled syringes for US-licensed Humira (i.e. both are single-use, 1 mL prefilled glass syringes with a fixed (b) (4) 29 gauge, ½ inch needle), Amgen performed a HF studies for their proposed PFS. Fifty-eight of the 61 participants performed all of the essential steps successfully. A total of four use errors were committed on essential steps by three participants (participant #30 committed two use errors). All three participants were self-trained patients. Two use errors involved pushing the plunger rod down prior to inserting the needle into the skin pad (incomplete dose). One use error involved removing the needle from the skin pad before the plunger rod was pushed completely down (incomplete dose). The remaining use error involved not disposing of the device without needle stick injury (we note that although the applicant classified this as a use error, the participant did not get a needle stick but failed to properly dispose the PFS). Root cause analysis revealed that:

- One self-trained, injection-experienced participant pushed the plunger rod down prior to inserting the needle into the skin pad, resulting in a loss of drug product. During root cause debriefing, the participant stated that he committed the same use error during the first time he self-injected with Humira since he was not sure how hard he had to push on the plunger to inject the drug. The participant stated that because this was the first time he used this specific device, he was not confident about what he was doing (i.e. he was not sure how much pressure to exert to push down the plunger rod). The participant stated he would not contact his doctor because there was "not much fluid expelled onto the skin pad" and he was confident that he would not repeat the same mistake on any future injections with a PFS.
- One self-trained, injection-naïve participant committed two errors. First, she pushed the plunger rod down prior to inserting the needle into the skin pad, resulting in a loss of drug product. The participant realized the error, and then continued to fully insert the needle into the skin pad while also pushing the plunger rod down. The participant stated that she "wasn't sure how far to stick the needle in, or how much to inject even though it [the IFU] says to use it all", which led her to push the plunger rod down too soon. Furthermore, this participant began slowly removing the needle from the skin pad before the plunger rod was pushed completely down. This resulted in liquid again squirting onto the skin pad. The participant indicated that she understood what had occurred and stated "when I saw it all over the skin pad, a squirt, I realized I took it out too fast so I didn't get a full dose." During root cause debriefing for both use errors,

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the participant stated that as a result of her unfamiliarity with injection devices, she was a little bit uncomfortable during the injection task. However, she was also expecting further training, citing the IFU statement: "It is important you do not try to give yourself the injection unless you have received training from your doctor or healthcare provider."

- The third participant failed to discard the PFS into the sharps container. The participant placed the used PFS back into the packaging and into the refrigerator. The participant stated he did not put the PFS into the sharps container because he did not "want to trash up our room". At home, he would put used devices into the sharps container. Per the applicant, this was deemed a test artifact.

We consider these use errors to be self-correcting with continued use as the participants realized they had committed an error. In addition, there were multiple use-errors on non-essential tasks (e.g. checking expiration date, inspection the drug appearance, inspection for damage, checking the drug name, clean injection site, waiting 15-30 minutes to reach room temperature, and pinching the injection site). See Appendix C for more details. However, we note that these are known use errors for injectable products administered via PFS and no new risks were identified. Therefore, we find the HF validation for the proposed PFS acceptable.

We note that the strength statement is shown based on the net quantity (i.e. 20 mg/0.4 mL and 40 mg/0.8 mL) (b) (4)

We also note that the statement "single-use" is used throughout the labels and labeling. However, we defer to Office of Biological Products (OBP) labeling reviewers for the determination of the appropriate package type term on labels and labeling. In addition, the container labels and carton labeling can be improved to increase the visibility of the proper name, NDC number, and the color contrast of the strength statement (20 mg/0.4 mL PFS).

Finally, we acknowledge that there is one outstanding item (i.e. nonproprietary name for this product) that is still under consideration and therefore we defer any comments on this aspect of the labeling at this time.

4 CONCLUSION & RECOMMENDATIONS

Our review identified areas for improvement with regards to the visual display of the strength on the container labels and carton labeling of the proposed product, (b) (4) . Additionally, we identified other aspects of the labels and labeling that should be revised to improve readability of important information and promote the safe use of the product. We provide recommendations for Amgen in Section 4.1 below, prior to approval of BLA 761024.

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4.1 RECOMMENDATIONS FOR AMGEN

A. General Comments (All container labels and labeling)

1. Ensure the presentation of the proper name is at least ½ the size of the trade name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). As currently presented, the trade name placeholder and proper names are not commensurate in prominence due to the larger font size used for the trade name placeholder.
2. [redacted] (b) (4) only the actual net content (i.e. 20 mg/0.4 mL or 40 mg/0.8 mL) is required on the labels.
3. Increase the prominence of the middle digits of the NDC numbers by increasing their size in comparison to the remaining digits in the NDC and by bolding (for example: xxxxx-**XXX**-xx). The similarity of the product code numbers has led to selecting and dispensing errors. The middle digits of the NDC number are traditionally used by healthcare providers to check the correct product, strength, and formulation.

B. Container Labels (Prefilled syringe: 20 mg/0.4 mL and 40 mg/0.8 mL)

1. Revise the strength statement so that it is presented only once as "20 mg/0.4 mL" or 40 mg/0.8 mL" to prevent clutter and improve legibility on these small labels.
2. Reduce the prominence of the "Rx Only" statement by un-bolding and reducing the size of the font. As currently presented it is more prominent than more relevant information such as the proper name.

C. Container Label (Prefilled syringe: 20 mg/0.4 mL)

1. Revise the color scheme presentation for the strength statements (i.e. font color over color blocking) to increase contrast and legibility. As currently presented, the contrast between the light blue font and the orange color blocking is difficult to read.

D. Container Labels (SureClick Autoinjector)

1. Revise the light blue color font used for most of the information presented on this label to a darker color to improve contrast and legibility. As currently presented, the contrast between the light blue font and white background make the label difficult to read.
2. Revise the strength statement so that it is presented only once as "40 mg/0.8 mL" to prevent clutter and improve legibility on these small labels.
3. Relocate the statement "SureClick Prefilled Autoinjector" below the strength statement.

E. Carton labeling (All package sizes; Prefilled syringe: 20 mg/0.4 mL and 40 mg/0.8 mL mg; SureClick Autoinjector)

1. Revise the strength statement that appears next to the [redacted] (b) (4) image representing the dosage form (i.e. prefilled syringe and autoinjector) from "[redacted] (b) (4)" to read "20 mg/0.4 mL" or "40 mg/0.8 mL).
2. Revise the storage statement on the Principal Display Panel to read "Store refrigerated at…".

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F. Carton Labeling (Prefilled syringe: 20 mg/0.4 mL carton of 1; 40 mg/0.8 mL carton of 1 and carton of 2)

1. Relocate the medication guide statement ("ATTENTION: Enclosed Medication Guide is required for each patient) to the principal display panel where the statement "Carton (b) (4):…" is located.
2. Relocate the statement "Carton (b) (4):…" to the side panel where the medication guide statement is located.

G. Carton Labeling (Prefilled syringe: 40 mg/0.8 mL; SureClick autoinjector: 40 mg/0.8 mL)

1. Consider revising the white font used on the side panels to a black font to improve contrast and legibility. As currently presented the small size font and low contrast between the white font over blue background makes the information difficult to read.

H. SureClick Autoinjector Instructions for Use

In reviewing your IFU, which is supported by validation data in the Enbrel BLA, we noted that your proposed IFU has certain differences from the Enbrel IFU. We outline these differences below to harmonize this IFU with the validated Enbrel IFU for your consideration. In addition, we recommend that certain product specific information that would be expected to be relevant to the safe use of your biosimilar product be harmonized with the IFU of the reference product, US-licensed Humira. If you determine that some of these recommendations are not supportable for ABP 501, we recommend that you provide justification in your response to our comments.

1. Step 1 – D
    a. Include the statement "Do not fan or blow on the clean area" after the statement "Clean your injection site with an alcohol wipe. Let your skin dry."
    b. Include the statement "Choose a different injection site each time you give yourself an injection." preceding the "If you want to use the same injection site….".
    c. Revise the statement "If you want to use the same injection site…" to read "If you want to use the same injection site, make sure it is not the same spot on the injection site you used the last time."
    d. Include a last bullet statement that reads "Do not inject through your clothes."
2. Step 3 – H
    a. Revise the zoomed image depicting the autoinjector pressed against the skin with the statement "Push Down" to use the same image as your Enbrel SureClick IFU. We find the image and text on the Enbrel SureClick IFU is clearer.

I. Prefilled Syringe IFU

1. See comments H.1.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Amjevita that Amgen submitted on November 25, 2015, and the reference product.

Table 2. Relevant Product Information for Amjevita and the Reference Product

Product Name	Amjevita	US-licensed Humira
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	ABP 501*	adalimumab
Indication	• Rheumatoid Arthritis (RA) • Juvenile Idiopathic Arthritis (JIA) in patients aged 4 years and older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Adult Crohn's disease • Ulcerative Colitis • Plaque Psoriasis (PsO)	• Rheumatoid Arthritis (RA) • Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years and older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Adult Crohn's disease • Pediatric Crohn's disease • Ulcerative Colitis • Plaque Psoriasis (PsO) • Hidradenitis Supporativa
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection, solution	Injection, solution
Strength/How Supplied	40 mg/0.8 mL SureClick autoinjector 40 mg/0.8 mL PFS 20 mg/0.4 mL PFS	40 mg/0.8 mL Humira Pen 40 mg/0.4 mL Humira Pen 40 mg/0.8 mL PFS 40 mg/0.4 mL PFS 20 mg/0.4 mL PFS 10 mg/0.2 mL PFS 40 mg/0.8 mL vial for institutional use only
Dose and Frequency	Humira is administered by subcutaneous injection. • Adult RA 40 mg every week or every other week • Adult PsA, and AS 40 mg every other week • JIA 15 kg to < 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week • Adult Crohn's disease and Ulcerative Colitis Day 1: 160 mg	Humira is administered by subcutaneous injection. • Adult RA 40 mg every week or every other week • Adult PsA, and AS 40 mg every other week • JIA 10 kg to < 15 kg: 10 mg every other week 15 kg to < 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week • Adult Crohn's disease and Ulcerative

*Amjevita has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for Amjevita has not yet been determined, ABP 501 is used throughout this review in place of the nonproprietary name for this product.

	Day 15: 80 mg Day 29: 40 mg every other week • Crohn's disease Day 1: 80 mg Day 15: 40 mg every other week • Adult PsO Initial dose: 80 mg Then: 40 mg every other week stating one week after initial dose	Colitis Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week • Pediatric Crohn's disease 17 kg to < 40 kg: Day 1: 80 mg Day 15: 40 mg Day 29: 20 mg every other week ≥ 40 kg: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week • Adult PsO Initial dose: 80 mg Then: 40 mg every other week stating one week after initial dose • Adult HS Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every week
Storage	Refrigerated at 36° to 46°F (2° to 8°C). If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.	Refrigerated at 36° to 46°F (2° to 8°C). If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.

*Amjevita has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for Amjevita has not yet been determined, ABP 501 is used throughout this review in place of the nonproprietary name for this product.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 6, 2016 we searched the L:drive using the term, Amjevita, (b) (4) and ABP 501, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[1], and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. PREFILLED SYRINGE HUMAN FACTORS STUDY

Objectives

The first objective of this study was to validate, through objective and subjective evidence, that the intended user population can demonstrate proficiency with the following essential steps:

- Remove device from packaging
- Remove needle cover
- Place injection needle on injection site surface and pierce the skin (simulation with skin pad)
- Depress the syringe plunger rod, to empty the entire drug product
- Remove device from injection site without needle-stick injury
- Dispose of device without needle-stick injury

The second objective of this study was to assess performance of these tasks under learning decay conditions.

Intended User Population, Intended Use and Use Environments

The ABP 501 PFS intended user population includes HCPs, caregivers, and patients. The ABP 501 PFS is a single-use, disposable device intended to administer a fixed dose of ABP 501 drug product into the subcutaneous tissue (abdomen or thigh) of patients for the treatment of Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis, Juvenile Idiopathic Arthritis, Crohn's Disease, or Ulcerative Colitis. It is intended for use by patients and caregivers in a non-healthcare environment or by HCPs in a clinical setting. HCPs were not included in this study, as PFS devices are routinely used during their professional and on-the job training activities.

Device Configurations

ABP 501 PFS will be commercially available in 0.4 mL fill volume for 20 mg dose, and 0.8 mL fill volume for 40 mg dose. For this study, a PFS with 0.8 mL fill volume was used. This syringe contained a large fill volume that would take longer to extrude than smaller dosages, and thus could potentially present the most challenging scenario for users. This would be especially true for people with any substantial hand dexterity issues.

ABP 501 PFS will be available with (b) (4) a 29G needle and have rigid needle shields. A PFS with 29G needle was used in the study (b) (4)

Packaging Configurations

[1] McMillan, T. Human Factors Protocol Review for ABP 501 (IND 111714). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 10. RCM No.: Insert RCM 2014-1806.

This study evaluated the two-pack packaging configuration for ABP 501 PFS. Packaging configurations for ABP 501 PFS vary by the number of devices in a carton. The larger package (two-pack) was used for this study because it was considered the most challenging usage scenario; specifically, users had to first determine the correct number of syringes to use for the simulated drug administration.

Participant Demographics

The study sample consisted of 61 participants from two user groups: 1) Patient participants (n=30) and 2) Caregiver participants (n=31). See Table 1 for participant demographic information.

Table 1: Demographics

Demographics	Recruited Participants	
Average Age	**Patients (n=30)** – 46.3 years old **Caregivers (n=31)** – 47.2 years old **Total (n=61)** – 46.1 years old (range: 22-72)	
Gender	37 Female, 24 Male	
Hand Dominance	52 Right, 9 Left	
Average Years Since Diagnosis (Patients Only)	12 years (Range: 1-50)	
Injection Experience	**Patients** 15 naïve, 15 experienced **Caregivers** 16 naïve, 15 experienced	
	Level	**Frequency**
Hand Dysfunction (Patients Only)	Moderate Minor None	12 3 15
	Level	**Frequency**
Education	Less than High School High School Some College Bachelors Graduate Degree	1 5 20 25 10

- 15 patient participants were diagnosed with Crohn's disease or Ulcerative Colitis,
- 15 patient participants were diagnosed with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, or Plaque Psoriasis,
- 12 patient participants were over the age of 55, and
- 11 patient participants had experience with injecting Humira.

Table 2 below shows a breakdown of patient participants by injection experience, Humira experience and hand dysfunction.

Table 2: Patient Participant Breakdown

Patient participant	Hand Dysfunction	No Hand Dysfunction	Total
Injection-Naïve	7	8	15
Injection-Experienced	5 Humira experienced	6 Humira experienced	11
	3 Humira inexperienced	1 Humira inexperienced	4
Total	15	15	30

Learning Decay (Loss of Information Retention) Evaluation

To assess learning decay across training type (i.e. self-trained or moderator-trained), all users waited at least 60 minutes after training to perform device administration tasks. During the 60-minute wait period, participants stayed in a room in the research facility and engaged in an activity, such as reading; however, they did not leave the research facility. When participants returned to perform device administration tasks, they received no further training; however, they were informed that the IFU was available for reference during the testing.

Test Conditions

Self-trained: Half of patient participants (n = 15) and half of caregiver participants (n = 16) were self-trained using the IFU. All participants prepared and administered injections using an ABP 501 PFS 2-Pack Box. Patient participants performed the injection into an injection pad. Caregiver participants performed the injection into an injection pad attached to a medical mannequin.

Moderator-trained: The remaining patient participants (n = 15) and caregiver participants (n = 15) received a moderator-led training (i.e., moderator reading from a script covering key points from the IFU). After training, all participants prepared and administered an injection using an ABP 501 PFS 2-Pack Box. Patient participants performed the injection into an injection pad. Caregiver participants performed the injection into an injection pad attached to a medical mannequin.

Results

Key Results

According to the ABP 501 PFS Summative Study Protocol [Ref. 1], “Essential” steps are defined as the tasks necessary for successful use of the device for its intended purpose. For the ABP system, this includes the tasks necessary to enable study participants to successfully administer a complete dose.

A total of 4 essential step use errors were committed by 3 different participants. Fifty-eight participants (95%) performed all of the essential steps without committing any use errors. Note: one participant did successfully administer a complete dose, but did not properly dispose of the PFS.

Table 4 below lists each essential step and the corresponding performance rate by distinct user group (i.e., patient vs. caregiver) and training condition (i.e., moderator trained vs. self-trained). Performance rate is defined as the percentage of participants that completed a given essential step without any related use error during the session. For self-trained participants, three out of sixty-one participants committed a total of four essential step use errors. For moderator trained

participants, zero essential step use errors were committed. Performance was essentially equivalent between the patient participant and caregiver participant groups.

Table 4: Performance Rate for Essential Steps (All Groups)

Essential Steps	Overall	Moderator Trained			Self-Trained		
		Patients *(n=15)*	Caregivers *(n=15)*	Total *(n=30)*	Patients *(n=15)*	Caregivers *(n=16)*	Total *(n=31)*
Remove device from packaging	100% 61/61	100% 15/15	100% 15/15	100% 30/30	100% 15/15	100% 16/16	100% 31/31
Remove needle cover	100% 61/61	100% 15/15	100% 15/15	100% 30/30	100% 15/15	100% 16/16	100% 31/31
Place injection needle on injection site surface and pierce the skin	100% 61/61	100% 15/15	100% 15/15	100% 30/30	100% 15/15	100% 16/16	100% 31/31
Depress the syringe plunger rod to empty the entire drug product	**97% 59/61**	100% 15/15	100% 15/15	100% 30/30	87% 13/15	100% 16/16	**94% 29/31**
Remove device from injection site without needle-stick injury	100% 59/59*	100% 15/15	100% 15/15	100% 30/30	100% 13/13*	100% 16/16	100% 29/29*
Dispose of device without needle stick injury	**98% 59/59***	100% 15/15	100% 15/15	100% 30/30	**100% 12/13****	100% 16/16	**100% 28/29***

*Note: those participants who had committed a use error on an essential step are not included in the performance rate calculation after their initial use error.

** Note: no participant got a needle stick during disposal of the device; one participant did not properly dispose the PFS.

Table 6 shows that there were a total of 4 essential step use errors committed by 3 participants (participant #30 committed 2 use errors). All 3 participants were self-trained patients.

Table 6: Number of Essential Step Use Errors by Group/Condition

Essential Steps	Moderator-Trained (n=30)			Self-Trained (n=31)		
	Patients	Caregivers	Total	Patients	Caregivers	Total
Remove device from packaging	0	0	0	0	0	0
Remove needle cover	0	0	0	0	0	0
Place injection needle on injection site surface and pierce the skin	0	0	0	0	0	0
Depress the syringe plunger rod to empty the entire drug product	0	0	0	3	0	**3**
Remove device from injection site without needle-stick injury	0	0	0	0	0	0
Dispose of device without needle stick injury*	0	0	0	1	0	1
Total	0	0	**0**	3	0	**4**

* Note: no participant got a needle stick during disposal of the device; one participant did not properly dispose the PFS.

According to the ABP 501 PFS Summative Study Protocol [Ref. 1], "Steps Associated with Potential Use Errors with Severity of at least 5 " are defined as steps associated with potential use errors that could result in one or more harmful events that carry a severity rating of at least 5 as per the User Risk Assessment [Ref. 2]. A total of 70 use errors were committed by 42 participants occurred during such steps in the study (for the root causes see section 10.3.1).

Table 5: Performance Rate for Steps Associated with Potential Use Errors with Severity of at least 5 (All Groups)

Steps Associated with Potential Use Errors with Severity of 5 or higher	Moderator-Trained			Self-Trained		
	Patients *(n=15)*	Caregivers *(n=15)*	Total *(n=30)*	Patients *(n=15)*	Caregivers *(n=16)*	Total *(n=31)*
Inspect Drug Appearance	87% 13/15	80% 12/15	83% **25/30**	73% 11/15	100% 16/16	87% **27/31**
Inspect for damage	73% 11/15	87% 13/15	80% **24/30**	67% 10/15	94% 15/16	81% **25/31**
Check Expiration Date	60% 9/15	33% 5/15	47% **14/30**	33% 5/15	44% 7/16	39% **12/31**
Wash hands	100% 15/15	100% 15/15	100% 30/30	87% 13/15	94% 15/16	90% **28/31**
Clean site with alcohol wipe	73% 11/15	93% 14/15	83% **25/30**	87% 13/15	81% 13/16	84% **26/31**
Do Not recap PFS prior to injection	100% 15/15	100% 15/15	100% 30/30	93% 14/15	100% 16/16	97% **30/31**

Table 7 shows that 42 participants committed a total of 70 use errors on a step associated with potential use errors with a severity of at least 5. Note that 35 of these 70 (50%) use errors were failures to check the expiry date. Twenty-one moderator-trained participants (10 patients, 11 caregivers) committed 32 of these 70 use errors, while 21 self-trained participants (11 patients, 11 caregivers) committed the other 38 use errors. There was 1 close call committed by 1 moderator-trained caregiver participant; no operational difficulties were observed for these steps.

Table 7: Observed Number of Use Errors for Steps Associated with Potential Use Errors with Severity of at least 5

Steps Associated with Potential Use Errors with Severity of at Least 5	Moderator-Trained (n=30)			Self-Trained (n=31)		
	Patients	Caregivers	Total	Patients	Caregivers	Total
Inspect Drug Appearance	2	3	**5**	4	0	**4**
Inspect for Damage	4	2	**6**	5	1	**6**
Check Expiration Date	6	10	**16**	10	9	**19**
Wash hands	0	0	**0**	2	1	**3**
Clean site with alcohol wipe	4	1	**5**	2	3	**5**
Do Not recap PFS prior to injection	0	0	**0**	1	0	**1**
Totals	16	16	**32**	24	14	**38**

Table 8 shows that 51 participants committed a total of 76 use errors with a severity of 3 or less. A difference between moderator-trained and self-trained participants was observed, with

22 moderator-trained participants (12 patients, 10 caregiver participants) committing 29 of the 76 use errors, and 29 self-trained participants (15 patients, 14 caregivers) committing 47 use errors.

Table 8: Observed Number of Use Errors for Steps Associated with Severity of 3 or Less

Steps Associated with Potential Use Errors with Severity of 3 or Less	Moderator-Trained (n=30)			Self-Trained (n=31)		
	Patients	Caregivers	Total	Patients	Caregivers	Total
Retrieve Carton from Refrigerator	0	0	**0**	0	0	**0**
Check Drug Name on PFS	7	7	**14**	12	8	**20**
Wait 15-30 Minutes	6	5	**11**	5	7	**12**
Pinch Injection Site	1	2	**3**	5	3	**8**
Prepare Injection	0	0	**0**	1	1	**2**
Insert Needle	0	0	**0**	1	0	**1**
Recap PFS after Injection (Do not)	0	1	**1**	3	1	**4**
Examine Injection Site	0	0	**0**	0	0	**0**
Total	14	15	29	27	20	**47**

Summary Conclusions

The vast majority (95%) of participants were able to successfully complete the essential steps needed for an injection without committing any use-errors. (Note: one participant did successfully administer a complete dose, but did not properly dispose of the PFS).

Participants did not experience any issues with the fundamental design of the ABP 501 PFS that would interfere with safe and effective performance. Participants in the moderator-trained group (0 use errors) performed better than those in the self-trained group (4 use errors) with respect to essential steps.

42 participants committed a total of 70 use errors for steps associated with potential for a use error with a severity rating of 5 or higher as per the User Risk Assessment (Ref. 1). 50% of these use errors were failures to check the expiry date. No meaningful difference between the moderator and self-trained groups was observed.

Overall, the feedback for both the ABP 501 PFS and IFU were positive. Participants felt comfortable using the device, they were able to follow the flow of the IFU, and they felt that the information in the IFU was easy to understand. All participants were also able to comprehend the information, specifically the caution and warning statements, presented in the IFU.

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following ABP 501 labels and labeling submitted by Amgen on November 25,, 2015.

- Container label
- Carton labeling
- Prescribing Information (not pictured)
- Instructions for Use (not pictured)

G.2 Label and Labeling Images (not to scale)

(b) (4)

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/s/

CARLOS M MENA-GRILLASCA
08/09/2016

MISHALE P MISTRY
08/11/2016

LUBNA A MERCHANT
08/11/2016

LUBNA A MERCHANT on behalf of KELLIE A TAYLOR
08/11/2016

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 27, 2016

TO: Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs (OND)

FROM: Mohsen Rajabi, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Directory
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Amended Review of EIRs for ICON Early Phase Services, San Antonio, TX, USA and Bio-Kinetic Europe Ltd., Belfast, UK covering BLA 761024 (ABP 501), sponsored by Amgen, Inc., USA.

Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of pharmacokinetic study 20110217 at ICON Early Phase Services, San Antonio, TX, USA and Bio-Kinetic Europe Ltd., Belfast, UK. The evaluation of the inspection at Bio-Kinetic Europe Ltd., Belfast, UK was provided to OND on 7/21/2016 and the recommendation was to accept the data. This memo provides the evaluation of the inspection conducted at ICON Clinical Pharmacology, Omaha, NE, USA. At the conclusion of the inspection, no significant deficiencies were observed and no Form FDA 483 was issued. The final classification is No Action Indicated (NAI). After review of the inspectional findings, I recommend that the clinical data from ICON Clinical Pharmacology be accepted for further agency review.

Study Number: 20110217

Study Title: "A Randomized, Single-blind, Single Dose, 3-Arm, Parallel-Group Study to Determine the Pharmacokinetic Equivalence of ABP 501 and Adalimumab (Humira ®) in healthy Adult Subjects"

Study Dates: July 3, 2012 – October 26 2012

The inspection of the clinical study records at ICON Early Phase Services, San Antonio, TX, USA was conducted by ORA investigator Joel Martinez from March 28 to April 4, 2016.
Please note that the study was conducted at ICON's facility in Omaha, Nebraska. However, the ICON facility in Omaha has closed, therefore the study records and reserve samples were transferred to the San Antonio ICON facility where the inspection was conducted.

The inspection included a thorough review of the study records, protocols, SOPs, subject consent form, Independent Ethics Committee (IEC) documentation, adverse events reporting, enrolled subject records, drug accountability, record retention, as well as interviews and discussions with the firm's management and staff. The reserve samples were collected at the site by ORA investigator and shipped to DPA in St. Louis, MO.

No significant deficiencies were observed and no Form FDA 483 was issued at the conclusion of the inspection.
OSIS evaluation for inspection conducted at Bio-Kinetic Europe Ltd., Belfast, UK was provided to DPARP in a memo dated 7/21/2016 with a recommendation of acceptance of clinical data generated at Bio-Kinetic.

Recommendations:
After reviewing the EIR and inspectional findings, the data from the audited study were found to be reliable. Therefore, I recommend that the clinical data generated at ICON Early Phase Services for study 20110217, be accepted for further agency review.

Mohsen Rajabi, Ph.D.
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

NAI – ICON Early Phase Services, San Antonio, TX, USA
(FEI# 3007158681)

NAI – Bio-Kinetic Europe Ltd., Belfast, UK
(FEI# 3007420390)

CC:
OTS/OSIS/Kassim/Taylor/Kadavil/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Rajabi
OTS/OSIS/DGDBE/Cho/Skelly/Choi
CDER/OND/ODEII/Chowdhury
ORAHQ/OMPTO/DMPTI/Turner/Arline/Montemurro/Colon

Draft: MR 07/26/2016
Edit: GB 7/26/2016 AD 7/27/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical Site/BLA 761024

BE File #s: 7103
FACTS: 11620248

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/s/

MOHSEN RAJABI ABHARI
07/27/2016

ARINDAM DASGUPTA
07/27/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 27, 2016

TO: Badrul Chowdhury, MD., Ph.D.
Director
Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation II (ODEII)
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Visiting Associate
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Young Moon Choi, Ph.D.
Acting Deputy Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering BLA 761024 and NDA (b) (4) for an analytical inspection at (b) (4)

Recommendations:

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) conducted an inspection that included evaluating the following analytical studies at (b) (4) . We recommend that the analytical portion of studies 20110217 (BLA 761024) and (b) (4) be accepted for further Agency (FDA) review.

Application	Study	Study Site	Sponsor	Recommend
BLA 761024	20110217	[redacted]	Amgen, Inc.	**Acceptable**
[redacted]				

Study 20110217: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel-Group Study to Determine the Pharmacokinetic Equivalence of ABP 501 and Adalimumab (Humira®) in Healthy Adult Subjects"

Study Dates: 07/03/2012 - 10/26/2012

Study [redacted]

Study Dates: [redacted]

Inspection:

ORA investigator Karen L. Kosar and OSIS investigators Michael F. Skelly and Xiaohan Cai audited the analytical portion of study 20110217 (BLA 761024) at [redacted] during [redacted]. The audit included a thorough review of method validation and study records, examination of facility, equipment, and interviews and discussions with [redacted] management and staff. Following the inspection, no Form FDA 483 was issued at [redacted].

[redacted] transferred a method for measuring adalimumab in serum from Amgen. However, [redacted] did not have access to characterization information for the capture and detection antibody reagents. Thus, we could not establish whether the assay measured only free adalimumab or also antibody-bound adalimumab. However, it is

unlikely that many samples from this single-dose study contained rheumatoid factor, reactive antibodies, etc. In addition, we could not determine the potential reasons why the initial lot of ABP 501 was approximately 10% less potent in the assay as compared to Humira. Later lots of ABP 501 were equipotent with Humira.

(b)(4)

Conclusion:

Following evaluation of the inspectional findings, these reviewers conclude that data from the audited studies at (b)(4) are reliable and thus recommend that the analytical portion of studies 20110217 and (b)(4) be accepted for further Agency (FDA) review.

Xiaohan Cai, Ph.D.
OSIS, DGDBE

Michael F. Skelly, Ph.D.
OSIS, DGDBE

Final Site Classification:

NAI – (b)(4)
FEI: (b)(4)

cc:

OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Cho/Choi/Skelly/Au/Cai
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

ORA/(b)(4)-DO/ Matthias/Kosar

Draft: XHC 7/24/2016
Edit: MFS 7/25/2016, SA 7/25/2016, YMC 7/27/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL SITES/(b)(4)/BLA 761024_ABP 501 (Biosimilar to Adalimumab)

OSI files# (b)(4)

FACTS: (b)(4)

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/s/

XIAOHAN CAI
07/27/2016

MICHAEL F SKELLY
07/27/2016

YOUNG M CHOI
07/27/2016

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 18, 2016

TO: Badrul Chowdhury, M.D., Ph.D
Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs (OND)

FROM: Amanda Lewin, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Directory
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for Bio-Kinetic Europe Ltd., Belfast, UK covering BLA 761024 (ABP 501), sponsored by Amgen, Inc., USA.

Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of pharmacokinetic study 20110217 at Bio-Kinetic Europe Ltd., Belfast, UK. At the conclusion of the inspection, no significant deficiencies were observed and no Form FDA 483 was issued. The final classification for Bio-Kinetic Europe Ltd. is No Action Indicated (NAI). After review of the inspectional findings, I recommend that the data from the clinical portion of Study 20110217 be accepted for further agency review.

Study Number: 20110217
Study Title: "A Randomized, Single-blind, Single Dose, 3-Arm, Parallel-Group Study to Determine the Pharmacokinetic Equivalence of ABP 501 and Adalimumab (Humira ®) in healthy Adult Subjects"
Study Dates: July 3, 2012 – October 26 2012

The inspection of the clinical portion of study 20110217 was conducted by ORA Investigator Dawn Olenjack at Bio-Kinetic Europe, Ltd., Belfast, UK from June 6 – 10, 2016.

The inspection included a thorough review and examination of facilities and equipment, personnel records, training program, study responsibility and authority, protocols, SOPs, subject consent, electronic records, Independent Ethics Committee (IEC) documentation, enrolled subject records, specimen handling and integrity, test article storage and accountability, data audit of the positive Anti-Drug Antibody (ADA) results, record retention, as well as interviews and discussions with the firm's management and staff. The reserve samples were collected at the site by ORA investigator and shipped to DPA in St. Louis, MO.

No significant deficiencies were observed and no Form FDA 483 was issued to the clinical site at the conclusion of the inspection.

Conclusion:

After evaluation of the EIR and inspectional findings, the data from the audited study were found to be reliable. Thus, this reviewer recommends that the data from study 20110217, performed at Biokinetic Europe Ltd., Belfast, UK, be accepted for further agency review.

Amanda Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Final Classification:
NAI – Bio-Kinetic Europe Ltd., Belfast, UK.
(FEI# 3007420390)

CC:
OTS/OSIS/Kassim/Taylor/Kadavil/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Skelly/Choi
CDER/OND/ODEII/Chowdhury
ORAHQ/OMPTO/DMPTI/Turner/Arline/Montemurro/Colon

Draft: AEL 07/14/2016

Edit: GB 7/15/2016; CB 7/19/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical Site/Biokinetic Europe Ltd., Belfast, UK/BLA 761024 /Review (EIR Cover)

BE File #s: 7103
FACTS: 11620248

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/s/

AMANDA E LEWIN
07/21/2016

GOPA BISWAS
07/21/2016

CHARLES R BONAPACE
07/21/2016

CLINICAL INSPECTION SUMMARY

Date	July 13, 2016
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D. Team Leader, for Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief
To	Keith Hull M.D., Ph.D., Medical Officer Nikolay Nikolov, M.D.., Clinical Team Leader Sadaf Nabavian, Regulatory Project Manager
BLA	761024
Applicant	Amgen, Inc.
Drug	Adalimumab [ABP 501], Biosimilar to U.S.-licensed Humira®
NME	Biosimilar
Therapeutic Classification	351(k) Biosimilar
Proposed Indication/s	Rheumatoid arthritis, juvenile idiopathic arthritis, adult Crohn's disease, ulcerative colitis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis
Consultation Request Date	February 26, 2016
Summary Goal Date	July 25, 2016
Action Goal Date	September 25, 2016
PDUFA Date	September 25, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For BLA 761024, four clinical sites (Drs. Klimiuk, Racewicz, Brzezicki, and Greenwald) were selected for audit and inspection. The sponsor (Amgen, Inc.) was also inspected. The final classification, for the inspections of Drs. Klimiuk, Racewicz, Brzezicki, and Amgen, is No Action Indicated (NAI).The preliminary classification for the inspection of Dr. Greenwald is No Action Indicated (NAI) based on communications with the field investigator. The study data derived from these clinical sites and sponsor are considered reliable in support of the requested indication.

2. BACKGROUND

ABP 501 is proposed as a biosimilar to Humira® (adalimumab), an anti-TNFα monoclonal antibody. ABP 501 and adalimumab (U.S. and EU) have comparable binding affinity for TNFαs. ABP 501 and adalimumab also show comparable *in vitro* binding to the Fc neonatal receptor (FcRn) and Fc gamma receptor Type III (FcγRIII), and comparable antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) activity *in vitro*.

For the current submission, the sponsor is seeking adalimumab biosimilar approval for the following indications: rheumatoid arthritis, juvenile idiopathic arthritis, adult Crohn's disease, ulcerative colitis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.

A single randomized clinical trial was submitted in support of the applicant's BLA. Study 20120262 was the clinical trial submitted to support the rheumatoid arthritis indication. A single domestic and three foreign clinical sites were selected for inspection by DPARP.

Study 20120262
Study 20120262 was a randomized, double-blind, active-controlled study in patients with rheumatoid arthritis (RA) who had an inadequate response to methotrexate. Subjects were randomized to receive either adalimumab (ABP 501) 40 mg subcutaneous (SC) every 2 weeks or adalimumab 40 mg SC every 2 weeks in a blinded fashion until Week 22. The primary efficacy endpoint was ACR 20 (American College of Rheumatology 20% improvement criteria response assessed at week 24).

This study was conducted at 92 centers in 12 countries. A total of 526 subjects (264 subjects in the ABP 501 arm and 262 subjects in the adalimumab arm) were enrolled and randomized in this study and received at least 1 dose of investigational product. The first study subject was enrolled in October 24, 2013 and the last study subject completed in November 19, 2014.

3. RESULTS (by site):

Name of CI, Address	**Site #, Protocol #, and # of Subjects**	**Inspection Date**	**Classification**
Piotr Adrian Klimiuk, M.D., Ph.D. Gabinet Internistcyzno-Reumatologiczny Ulica Legionowa 3 15-099 Bialystok, Poland	Site 48013 Study Protocol 20120262 Subjects n=21 enrolled subjects	May 16 to 19, 2016	NAI
Artur Racewicz, M.D., Ph.D. Zdrowie Osteo-Medic Ulica Wiejska 81 15-351 Bialystok, Poland	Site 48001 Study Protocol 20120262 Subjects n=30 enrolled subjects	May 9 to 12, 2016	NAI
Jan Brzezicki, M.D., Ph.D. Centrum Kliniczno-Lekarze Spolka Partnerska Ulica Studzienna 36-36/A	Site 48003 Study Protocol 20120262	May 30-June 3, 2016	NAI

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
82-300 Elblag Warminsko-Mazurskie, Poland	Subjects n=40 enrolled subjects		
Maria Greenwald, M.D., Ph.D. Desert Medical Advances 72855 Fred Waring Dr. A-6 Palm Desert, CA 92260	Site 66011 Study Protocol 20120262 Subjects n=17 enrolled subjects	May 19-20, 2016	Preliminary: NAI
Amgen, Inc. One Amgen Center Drive Mail Stop 28-2-D Thousand Oaks, CA 91320	Sponsor for: Study Protocol 20120262 Subjects N=526	April 11-13 , 2016	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. **Piotr Adrian Klimiuk, M.D., Ph.D./Study Protocol 20120262/Site 840025**
   Bialystok, Poland

The inspection was conducted from May 16 to 19, 2016. A total of 27 subjects were screened and 21 subjects enrolled. Twenty one subjects completed the study.

An audit of 16 enrolled subjects' records was conducted for eligibility criteria assessments at screening and at randomization. An audit of 21 subjects' records was conducted for primary efficacy raw data. No source record discrepancies were observed, in the patient data listings provided to ORA by CDER for the inspection.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess

the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Artur Racewicz, M.D., Ph.D. /Study Protocol 20120262/Site 48001
Bialystok, Poland

The inspection was conducted from May 9 to 12, 2016. A total of 38 subjects were screened and 30 subjects enrolled and randomized. Six patients discontinued from the study after enrollment (Note: three subjects eventually withdrew from further participation in the study and three additional subjects withdrew due to an adverse event). Twenty four subjects completed the study.

An audit of 30 enrolled and randomized subject's records for primary efficacy raw data. For adverse event including SAEs, a single source record discrepancy (Subject 007 reported a "common cold" episode at Week 18 , as per the patient data listing provided to ORA by CDER for inspection.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Jan Brzezicki, M.D., Ph.D. /Study Protocol 20120262/Site 48003
Warminsko-Mazurskie, Poland

The inspection was conducted from May 30 to June 3, 2016. A total of 42 subjects were screened and 40 subjects enrolled. Two subjects discontinued early due to lack of efficacy. Thirty eight subjects completed the study. An audit of 25 enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Maria Greenwald, M.D., Ph.D./Study Protocol 20120262/Site 66011
Palm Desert, CA 92260

The inspection was conducted from May 19 to 20, 2016. A total of 24 subjects were screened and 17 subjects were enrolled and completed the study. An audit of seventeen enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR-CRO

5. Amgen, Inc.
Thousand Oaks, CA 91320

The inspection was conducted from April 11 to 13, 2016. This sponsor inspection was performed to ensure that there were no monitoring violations for this biosimilar application. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors; review of controls and security of electronic systems; and data collection and handling procedures; adequacy of monitoring and corrective actions taken by the sponsor/monitor for the studies; clinical site study personnel training in Good Clinical Practices, and memorandum documents and reporting updates to clinical site investigators regarding serious unexpected adverse events.

In general, this site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued at the end of the sponsor inspection. No monitoring problems were found during the sponsor inspection. Data submitted by this sponsor appear acceptable in support of the requested indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
Review Division /Division Director/Badrul Chowdhury
Review Division/Associate Division Director/Sahra Yim
Review Division /Medical Team Leader/Nikolay Nikolov
Review Division/Medical Officer/Keith Hull
Review Division /Project Manager/Sadaf Nabavian
Review Division/Medical Officer/Anthony Orencia
OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Anthony Orencia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

ANTHONY J ORENCIA
07/13/2016

SUSAN D THOMPSON
07/15/2016

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

BIMO INSPECTION ASSIGNMENT - GENERAL INFORMATION

Memorandum of BLA - **Initiated in Vivo Bioequivalence Inspection Assignment**

Date: 6/6/2016

From: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: **ORANYKBIMO@fda.hhs.gov**
Subject: Premarket Original BIMO Inspection Assignment

Preannounce: No

Compliance Program: 7348.001 (BE)
Program Assignment Code: 48001S (BIOSIMILAR)
Priority: High
Operation Code: 12 (Domestic)

Application Number: BLA 761024
Product Name: ABP 501

Sponsor: **Amgen Inc., Thousand Oaks, CA**

Study/Protocol Number:

Application Number	Study/Protocol Number
BLA 761024	20110217 (b) (4)

Inspection Due Date: (b) (4)
EIR Due Date: **8/25/2016**

Center Participation: ☒Yes or ☐No.

Joint Regulatory Agency Participation: ☐Yes or ☒No.

Establishment(s) for inspection	FEI Number	FACTS Number
		(b) (4)

Note	
	Please contact the OSIS scientific point of contact (POC), Dr. Xiaohan Cai prior to the beginning of the inspection at Xiaohan.cai@fda.hhs.gov or 301-796-5182 to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection. Please follow the compliance program with emphasis on the specific instructions in the memorandum. If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact me immediately. **At the end of the inspection, send an e-mail to the OSIS scientific POC and cc CDER-OSIS-BEQ@fda.hhs.gov with any inspection findings.** **If a form FDA-483 is issued, send to CDER-OSIS-BEQ@fda.hhs.gov or fax it to the OSIS Project Specialist at (301) 847-8748.** **If EIR and exhibits are in OSAR (or in another electronic format), send the email notification regarding the availability of the documents in OSAR to CDER-OSIS-BEQ@fda.hhs.gov and cc Shila Nkah, OSIS Project Manager.** **If the EIR and exhibits are paper, send the documents to Angel Johnson, OSIS Project Specialist.** **Ms. Angel Johnson** **Project Specialist** **FDA/CDER/OTS/OSIS** **WO51 RM5331** **10903 New Hampshire Ave.** **Silver Spring, MD 20993-0002** **Important:** Forward any post-inspection correspondence from the establishment to CDER-OSIS-BEQ@fda.hhs.gov if electronic, or to the OSIS Project Specialist, if paper, as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct the inspection of the analytical portion of the following pharmacokinetic equivalence study. Background materials are available in ECMS under the ORA folder.

Do not reveal the study to be inspected, drug name, or the study investigator to the site prior to the start of the inspection. You should provide this information during the inspection opening meeting.

At the completion of the inspection, please send a scanned copy of completed sections A of this memo to the OSIS Scientific POC.

Application Number BLA 761024

Study #: 20110217 (b) (4)

Study Title: "A Randomized, Single-Blind, Single-Dose, 3-Arm, Parallel-Group Study to Determine the Pharmacokinetic Equivalence of ABP 501 and Adalimumab (Humira®) in Healthy Adult Subjects"

Investigator: (b) (4)

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The OSIS participants will select portions of one or more BE studies to support a surveillance assessment of activities since the (b) (4) inspection.

SECTION A – ANALYTICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist:

☐ Examine all pertinent items related to the analytical method used for the measurement of ABP 501, Adalimumab US, and Adalimumab EU concentrations in human serum.

☐ Compare the accuracy of the analytical data in the BLA 761024 submission against the original documents at the site.

☐ Determine if the site employed a validated analytical method to analyze the subject samples.

☐ Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.

☐ Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.

☐ Scrutinize the number of repeat assays of the subject serum samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.

☐ Examine correspondence files between the analytical site and the Applicant for their content.

☐ Examine calibration and maintenance records for the instruments used for sample analyses.

☐ Confirm that SOPs were followed during study conduct.

☐ Check the laboratory notebooks and source data in compliance with SOPs.

☐ Other comments:

_____
_____
_____

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS scientific POC prior to commencement of the inspection. Therefore, we request that the OSIS scientific POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to the OSIS scientific POC and CDER-OSIS-BEQ@fda.hhs.gov, as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

If the endorsed EIR and exhibits are in OSAR or submitted in another electronic format, send an email to CDER-OSIS-BEQ@fda.hhs.gov and cc the Shila Nkah OSIS Project Manager for the assignment.

If the endorsed EIR and exhibits are paper, send to the OSIS Project Specialist at the address below.

OSIS Project Specialist: Ms. Angel Johnson
Project Specialist
FDA/CDER/OTS/OSIS
WO51 RM5331
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Tel: 301-796-3374
Fax: 1-301-847-8748

OSIS Scientific POC: **Xiaohan Cai**
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)
Tel: 301-796-5182
Fax: 1-301-847-8748
E-mail:Xiaohan.cai@fda.hhs.gov

Email cc:
ORANYKBIMO@fda.hhs.gov
OSIS/Kassim/Taylor/Haidar/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OSIS/DGDBE/Cho/Skelly/Choi/Cai

Draft: XHC 5/24/16
Edit: MFS 6/01/16; JC 6/02/16
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL SITES/(b) (4)
/BLA 761024_ABP 501 (Biosimilar to Adalimumab)

OSIS file #: (b) (4)
FACTS: (b) (4)

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/s/

XIAOHAN CAI
06/07/2016

SEONGEUN CHO
06/07/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

BIMO Inspection Assignment - General Information Section

Memorandum of BLA - Initiated Bioequivalence Inspection Assignment

Date: March 4, 2016

From: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: ORAHQDFFIIOBBIMO@fda.hhs.gov

Subject: Premarket Original BIMO Inspection Assignment

Preannounce: No

Compliance Program: 7348.001
PAC Code: 48001S (BIOSIMILAR)
Priority: High
Operation Code: 11 (Foreign Inspection), 12 (Domestic Inspection), 31 (Sample Collection), 41 (Sample Analysis)
Application Number: BLA 761024
Product Name: ABP 501

Sponsor: Amgen, Inc. Thousand Oaks, CA

Study/Protocol Number: 20110217

Application Number	Study/Protocol Number
BLA 761024	20110217

Inspection Due Date**: 5/26/2016**
EIR Due Date**: 6/26/2016**
Center Participation**:** No
Joint Regulatory Agency Participation**:** No

Establishment(s) for inspection	FEI Number	FACTS Number
Clinical Site 1: ICON 8307 Gault Lane San Antonio, TX Tel: (210) 255-5437 **Clinical Site 2:** BioKinetic Europe Ltd. 14 Great Victoria Street Belfast, BT2 7BA, UK Tel: +44 28 9081 8381	Refer to ORA	**11620248**

Note	**Please contact Arindam Dasgupta prior to the beginning of the inspection at arindam.dasgupta@fda.hhs.gov or (301) 796-3326 to verify the focus and intent of the inspection.** We frequently receive real-time information from the review team that may change the focus of the inspection. Please follow the compliance program with emphasis on the specific instructions in the memorandum. If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact OSIS POC immediately. At the end of the inspection, send an e-mail to Arindam Dasgupta and CDER-OSIS-BEQ@fda.hhs.gov with any inspection findings. If a form FDA-483 is issued, send to CDER-OSIS-BEQ@fda.hhs.gov or fax it to the OSIS Project Specialist at (301) 847-8748. Forward the EIR and exhibits to CDER-OSIS-BEQ@fda.hhs.gov or Ms. Dinah Miller Project Specialist FDA/CDER/OTS/OSIS WO51 RM5333 10903 New Hampshire Ave. Silver Spring, MD 20993-0002 **Important:** Forward any post-inspection correspondence from the establishment to Arindam Dasgupta and CDER-OSIS-BEQ@fda.hhs.gov as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct inspections of the clinical portion of the following bioequivalence (BE) study. Background materials are available in ECMS under the ORA folder.

Please don't **reveal the study to be inspected, drug names, or the study investigators to the site when scheduling the inspection.** The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the OSIS POC.

Study to be audited

BLA 761204

Study #: 20110217
Study Title: "A randomized, single-blind, single-dose, 3-arm, parallel-group study to determine the pharmacokinetic equivalence of ABP 501 and adalimumab (Humira®) in healthy adult subjects."

Subject #: 203
Investigator: Alan S. Marion, MD, Ph.D.

Clinical Site 1: ICON
8307 Gault Lane
San Antonio, TX
Tel: (210) 255-5437

Clinical Site 2: BioKinetic Europe Ltd.
14 Great Victoria Street
Belfast, BT2 7BA, UK
Tel: +44 28 9081 8381

Investigator: Ronnie Beboso, MD

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should also include information on test and reference reserve samples retained at the site or at a third party for the

bioequivalence studies. Refer to Table 1 for an example. Please do spot checks to verify that the lot number(s) listed in the table match the reserve samples in the clinical site storage.

Table 1:

Study Number	Drug Name	Study Title	Sponsor	Submission Agency	Study Conduct Dates	Location of Reserve Samples	Quantity	Lot# for Test and Reference Samples
xxxx	Aspirin+Dipyridamole Capsules		xxxx	US-FDA	Dec 24-Dec 31, 2014	On site	300 for Test, 200 for Reference	xxxx and xxxx
xxxx	Montelukast Tablets		xxxx	Unknown	xx xx-xx, xxxx	Third Party		xxxx and xxxx
xxxx	xxxx		xxxx	Pilot	xx xx-xx, xxxx	Not Retained		xxxx and xxxx

SECTION A – RESERVE SAMPLES

Reserve samples must be collected for study 20110217. In addition, verify that the lot numbers on the reserve sample containers match those in the study report for the studies mentioned above.

Reserve samples establish the identity of the products tested in the actual study, allow for confirmation of the validity and reliability of the results of the study, and facilitate investigation of further follow-up questions that arise after the studies are completed. FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples for at least 5 years following a comparative clinical PK and/or PD study of the reference product and the proposed biosimilar product (or other clinical study in which PK or PD samples are collected with the primary objective of assessing PK similarity) that is intended to support a submission under section 351(k) of the PHS Act. For a 3-way PK similarity study, samples of both comparator products should be retained, in addition to samples of the proposed biosimilar product.

Please collect 10 dosage units each of the proposed biosimilar, reference product and, if applicable, comparator product, depending on the amount of product within each unit.

Please refer to CDER's "Draft Guidance for Industry, Biosimilars:

Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (May 2015), which clarifies the requirements for reserve samples under revised question: Q.I.10.

(http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf).

During the clinical site inspection, please:

☐ Verify if reserve samples were retained. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the OSIS POC immediately.

☐ If the reserve samples were stored at a third party site, (1) collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager; and (2) request the reserve samples to be shipped back to the site so that the samples can be collected during the inspection. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the OSIS POC immediately.

☐ Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance on the facility's letterhead, or Form FDA 463a Affidavit.

☐ Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Please identify and examine the following records, evaluate and comment on their completeness, and any unusual observations or concerns.

Data Audit Checklist:

☐ Confirm that informed consent was obtained prior to the study procedures for all subjects enrolled in the study 20110217.

☐ Randomly select and audit the study records for 70 subjects enrolled in the study 20110217.

☐ Compare the study reports submitted to FDA with the original documents at the site.

☐ Check for under-reporting of adverse events (AEs).

☐ Check for evidence of inaccuracy in the electronic data capture system.

☐ Check reports for the subjects audited.

- Number of subject records reviewed during the inspection:_____
- Number of subjects screened at the site:_____
- Number of subjects enrolled at the site:_____
- Number of subjects completing the study:_____

☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

☐ Confirm that site personnel followed SOPs during study conduct.

☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.

☐ Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).

☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

☐ Other comments:

_____
_____
_____

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to commencement of the inspection. Therefore, we request that the OSIS POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to the OSIS scientific POC and CDER-OSIS-BEQ@fda.hhs.gov as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

OSIS Scientific POC: Arindam Dasgupta, Ph.D.
Deputy Director

Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance
Tel: 1-301-796-3326
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OSI file #: 7103
FACTS: 11620248

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/s/

MOHSEN RAJABI ABHARI
03/04/2016

ARINDAM DASGUPTA
03/04/2016

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: BLA 761024

Application Type: New BLA

Drug Name(s)/Dosage Form(s): ABP 501 (a proposed biosimilar to US-Licensed Humira) Injection

Applicant: Amgen, Inc.

Receipt Date: November 25, 2015

Goal Date: September 25, 2016

1. Regulatory History and Applicant's Main Proposals

The applicant submitted a 351(k) BLA for their proposed biosimilar product to US-licensed Humira and seeking the same approved indications as the US-licensed Humir (b) (4) .

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. In the HL Section of the PI, the applicant added a box indicated to the reviewers, the box need to be removed.
2. At the bottom of the TOC, there's an extra statement that needs to be deleted.

---

4. Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Waiver Request has been submitted*

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

NO 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *Revision Date is ommitted*

Selected Requirements of Prescribing Information

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Selected Requirements of Prescribing Information

Revision Date in Highlights

NO 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *The applicanted stated the word Version (vs. "Revised")*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *Of note, the sponsor should delete the last sentence in the TOC "* [redacted] (b) (4) [redacted] ."

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *The applicant did not use the statement in the 5th bullett and instead stated "See FDA-approved patient labeling (Medication Guide and Instructions for Use)."*

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

SADAF NABAVIAN
02/05/2016

LADAN JAFARI
02/05/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 761024	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (b) (4) Established/Proper Name: ABP 501 Dosage Form: Injection (SQ) Strengths: Solution for injection: prefilled syringe: 20mg/0.4mL, 40mg/0.8mL; prefilled autoinjector: 40mg/0.8mL		
Applicant: Amgen, Inc. Agent for Applicant (if applicable):		
Date of Application: November 25, 2015 Date of Receipt: November 25, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: September 25, 2016	Action Goal Date (if different):	
Filing Date: January 22, 2016	Date of Filing Meeting: January 7, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Rheumatoid arthritis, adult Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis, Hidradentis Suppurativa (HS)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☒ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☒ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 111714	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☐		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☒	☐		For the indication of pJIA and pediatric CD
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☒	☐	☐	Humira has two unexpired orphan drug designations for the indication of pJIA and pediatric CD under the reference product, Humira, however the sponsor is not seeking for those 2 indications.
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☐	☐	

If yes, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	An Exclusivity Summary Memo to File is uploaded in DARRTS by MSchultz-DePalo dated 1/6/2016

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	☐	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	☒	☐		

If yes, ensure that the application is also coded with the supporting document category, "Form 3674." ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		a PeRC meeting will be requested
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	The team will proceed with filing without agreed iPSP
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	DPMH is aware of the submission and the fact that an agreed iPSP is not in place yet.
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☒ ☐	☐ ☒	☐ ☐	 Comments to be conveyed in the 74 Day Letter.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☒	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH, DPMH, OSE, Patient Labeling, OPDP Consults
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 10, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 7, 2016

BACKGROUND: Amgen Inc. submitted a new 351(K) BLA for a proposed biosimilar product ABP 501 to US-licensed Humira for the same indications as approved for Humira. (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sadaf Nabavian	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Nikolov Nikolay		Y
Division Director/Deputy	Badrul A. Chowdhury		Y
Office Director/Deputy			
Clinical	Reviewer:	Keith Hull (DPARP) Denis Cook (DDDP)	Y Y
	TL:	Nikolay Nikolov (DPARP) Gordana Diglisic (DDDP)	Y Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Jianmeng Chen	Y
	TL:	Ping Ji	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Yongman Kim (DPARP) Kathleen Fritsch (DDDP)	Y Y

	TL:	Gregory Levin (DPARP) Alosh Mohamed (DDDP)	Y Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carol Galvis	Y
	TL:	Marcie Wood	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Joel Welch	Y
	RBPM:	Keith Olin	N
• Drug Substance	Reviewer:	Bo Chi	N
• Drug Product	Reviewer:	Lakshmi Naraimhan	N
• Process	Reviewer:	Jun Park	Y
• Microbiology	Reviewer:	Colleen Thomas	N
• Facility	Reviewer:	Steve Fong	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	Jibril, Abdus-Samad	N
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Aman Sarai	N
	TL:	Marci Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Adewale Adeleye	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Anhtu Nguyen	
	TL:	Mishale Misty	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Nicole Verdun (TBBS)	Y
	TL:	Sue Lim/Christl Leah	Y
Other attendees	Daniel Orr (ORP)		Y
	Sonal Vaid (OCC)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: July 12, 2016 ☐ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**: Request confirmation from OPQ	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	NA
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SADAF NABAVIAN
02/05/2016

LADAN JAFARI
02/05/2016