

DDD Clinical, CDTL, and Division Summary Review

Date	31-OCTOBER-2022
From	Gary T Chiang, MD, MPH
Subject	Clinical, Cross-Discipline Team Leader, and Division Director Summary Review
BLA # and Supplement#	761118/S-0009
Applicant	Pfizer, Inc.
Date of Submission	18-FEB-2022
BSUFA Goal Date	18-DEC-2023
Proprietary Name	Abrilada (adalimumab-afzb)
Reference Product	US-Humira (adalimumab)
Proprietary Name	
Dosage Form(s)	No new proposed dosage forms
Applicant Proposed Indication(s)/Population(s)	Expansion of existing indications to include the following: <ul style="list-style-type: none">Treatment of moderate to severe hidradenitis suppurativa in adult patients
Applicant Proposed Dosing Regimen(s)	Proposed dosing regimen is consistent with the reference product dosing regimen: <ul style="list-style-type: none">Initial dose of 160 mg (given in one day or split over two consecutive days), followed by 80 mg two weeks later (Day 15). Begin 40 mg weekly or 80 mg every other week dosing two weeks later (Day 29).
Recommendation on Regulatory Action	Approval as a biosimilar
Recommended Indication(s)/Population(s)	For the treatment of moderate to severe hidradenitis suppurativa in adult patients
Recommended Dosing Regimen(s)	Same as reference product dosing regimen

1. Introduction

The Applicant, Pfizer, Inc., submitted a supplemental biologics license application for BLA 761118 (sBLA-009) to expand the indication for Abrilada (adalimumab-afzb) to include the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). This indication was not included in the initial approval of BLA 761118 because at the time of that approval, US-Humira (adalimumab) was eligible for orphan-drug exclusivity for “the treatment of moderate to severe hidradenitis suppurativa.” US-Humira’s orphan-drug exclusivity for this indication expired on September 9, 2022.

No new clinical information is included nor required for the Applicant’s submission. The Applicant has provided a scientific justification for extrapolation for the population currently being sought for licensure. The current submission provides for updated

labeling to include the new indication for adult patients only. A term of orphan-drug exclusivity for US-Humira for “the treatment of moderate to severe hidradenitis suppurativa (HS) in adolescent patients 12 years of age and older” expires on October 16, 2025.

2. Background

Abrilada (adalimumab-afzb) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor (TNF) alpha, produced by recombinant DNA technology in a mammalian cell expression system. Abrilada is supplied at 10 mg/0.2 mL (single-dose prefilled syringe), 20 mg/0.4 mL (single-dose prefilled syringe), and 40 mg/0.8 mL (single-dose prefilled syringe, single-dose prefilled pen, and single-dose glass vial for institutional use). Abrilada is administered by subcutaneous injection. Abrilada (adalimumab-afzb) was approved as a biosimilar to US-licensed Humira (US-Humira) on November 15, 2019 under section 351(k) of the Public Health Service Act (BLA 761118). Abrilada is currently approved for the treatment of:

1. Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
2. Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.
3. Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with PsA.
4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.
5. Crohn’s Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adults and pediatric patients 6 years of age and older 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 products.
6. Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine.

7. **Plaque Psoriasis (PsO):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

PF-06410293 (adalimumab-afzb) was approved as a biosimilar to U.S.-Humira on 15 November 2019 in patients with RA, JIA in patients 4 years of age and older, AS, adult CD, adult UC, PsA, PsO. The approval was based on the following:

- PF-06410293 is highly similar to U.S.-Humira, notwithstanding minor differences in clinically inactive components. The proposed strengths of PF-06410293 in prefilled syringes (40 mg/0.8 mL, 20 mg/0.4 mL, 10 mg/0.2 mL), in prefilled pen (40 mg/0.8 mL) and in a single-dose glass vial for institutional use only (40 mg/0.8 mL) are the same as those of U.S.-Humira. The dosage form and route of administration are also the same as those of U.S.-Humira.
- There are no clinically meaningful differences between PF-06410293 and U.S.-Humira based on PK, immunogenicity, safety and efficacy assessment from the PK similarity study (Study B5381007) in healthy subjects and the comparative clinical study in patients with moderately to severely active RA on stable background methotrexate (MTX) (Study B5381002).
- The PK portion of the scientific bridge was established based on results of a 3-way PK similarity study (Study B5381007) comparing PF-06410293 (40 mg/0.8 mL PFS), E.U.-Humira (40 mg/0.8mL), or U.S.-Humira (40 mg/0.8mL) to support the relevance of the data generated using E.U.-Humira as the comparator in the comparative clinical study (Study B5381002).
- An adequate scientific justification for extrapolation of data and information to support licensure as a biosimilar for each of the additional indications for which the Applicant was seeking licensure and for which U.S.-Humira has been previously approved.

In considering the totality of the evidence in the original BLA submission, review of the data submitted by the Applicant showed that Abrilada (adalimumab-afzb) is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-afzb and US-Humira in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of adalimumab-afzb for the non-studied indications sought for approval.

Review of the information submitted by the Applicant demonstrated that adalimumab-afzb is biosimilar to US-Humira for each of the following indications for which US-Humira has been previously approved and the Applicant was seeking licensure for adalimumab-afzb: RA, pJIA in patients 4 years of age and older, PsA, AS, adult PsO,

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CD in adults, and adult UC. See Biosimilar Multi-Disciplinary Evaluation and Review (BMER), dated November 15, 2019.

On 29 July 2022, under supplement 6, PF-06410293 the approved indications were expanded to include the following: treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 to less than 4 years of age and treatment of moderately to severely active Crohn's disease in pediatric patients ages 6 years to 17 years of age. Refer to Cross-Discipline Team Leader (CDTL) review dated July 21, 2022 for additional details.

Abrilada is approved in the following presentations:

- 40 mg/0.8 mL in a single-dose prefilled pen (Abrilada pen)
- 40 mg/0.8 mL in a single-dose prefilled glass syringe
- 20 mg/0.4 mL in a single-dose prefilled glass syringe
- 10 mg/0.2 mL in a single-dose prefilled glass syringe
- 40 mg/0.8 mL in a single-dose glass vial for institutional use only

3. CMC/Product Quality

For sBLA-009, no new product quality information was submitted nor required. There are no CMC or product quality issues that would preclude approval of the indication sought for licensure.

In accordance with 21 CFR Part 25, the Applicant claimed a categorical exclusion from the preparation of an environmental assessment (EA) for Abrilada for the additional indication being sought. In the sBLA submission, the Applicant provided information to support their claim.

In a review dated 15-October-2021, Dr. Ram Sihag and Susan Kirshner from the Office of Biotechnology Products/ Division of Biotechnology Review & Research II (OBP/DBRR II), provided the following comments from the CMC assessment team:

“An environmental analysis was submitted to support the new indication. The basis for the claim for categorical exclusion under 21 CFR 25.31(c) has not changed with the addition of the new indication and is considered appropriate and acceptable. Therefore, I recommend the approval of this labeling supplement.”

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA-009. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indication sought for licensure.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this sBLA. There are no clinical pharmacology issues that would preclude approval of the indication sought for licensure.

6. Clinical/Statistical-Efficacy

Adalimumab-afzb was previously evaluated in comparative clinical studies. The data were previously reviewed and summarized above and in the clinical and statistical reviews of the original BLA (refer to the BMER dated November 15, 2019) and sBLA S-006 by DPARP (refer to Dr. Juwaria Waheed Clinical review dated July 21, 2022). No new clinical/statistical efficacy information was submitted nor required for this sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

There are no clinical safety issues that would preclude approval of the indication sought for licensure.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

Abrilada (adalimumab-afzb) is an approved biosimilar for the treatment of RA, PsA, AS, CD in patients 6 years of age and older, UC, pJIA in patients 2 years of age and older, and PsO. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-afzb is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, as well as clinical data that demonstrated that there were no clinically meaningful differences between adalimumab-afzb and US-Humira in terms of safety, purity, and potency based on similar clinical PK in healthy subjects and similar efficacy, safety, and immunogenicity.

Justification for Extrapolation to Non-studied Indications in Original BLA

Additional points considered in the justification for extrapolation of data and information to support licensure of adalimumab-afzb as a biosimilar for each non-studied indication for which licensure was sought and for which US-Humira was previously approved included:

- PK similarity was demonstrated between adalimumab-afzb and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-afzb and US-Humira in the

indications sought for licensure. A similar PK profile would be expected between adalimumab-afzb and US-Humira in patients with JIA, PsA, AS, adult CD, UC and HS.

- In general, immunogenicity of US-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications, rather than by patient population, and the results were influenced by the type of assay used (per labeling for US-Humira). Similar immunogenicity was observed between adalimumab-afzb and US-Humira in patients with RA (See summary of evidence for switching study). Therefore, similar immunogenicity would be expected between adalimumab-afzb and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and HS.
- There were no clinically meaningful differences between adalimumab-afzb and US-Humira in patients with RA nor in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-afzb, US-Humira, and EU-Humira, a similar safety profile would be expected in patients with JIA, PsA, AS, adult CD, UC, and HS.
- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-afzb and US-Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Justification for Extrapolation to Moderate to Severe HS Indication

In this sBLA, the Applicant has cross-referenced the previously submitted justification for extrapolation of the data and information in support of licensure of adalimumab-afzb for this indication. The scientific justification for extrapolation to non-studied indications which was submitted with the original BLA is also applicable to HS and supports licensure of adalimumab-afzb for the treatment of adult patients with moderate to severe HS.

9. Pediatrics

The Applicant submitted an amended PSP which addressed the entire pediatric age range for HS in the submission. A term of orphan-drug exclusivity for US-Humira for “the treatment of moderate to severe hidradenitis suppurativa (HS) in adolescent patients 12 years of age and older” expires on October 16, 2025. The Applicant proposed to fulfill PREA requirements for adolescents ages 12 years to 17 years for this indication by satisfying the statutory requirements for showing biosimilarity and providing an

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adequate scientific justification for extrapolating the pediatric information from US-Humira to Abrilada; however, FDA cannot license Abrilada for this indication in this age group until US-Humira's orphan drug exclusivity for it expires on October 16, 2025. The labeling for US-Humira does not contain adequate pediatric information for HS patients younger than 12 years of age, and no pediatric assessment will be required of the Applicant under PREA for HS patients younger than 12 years of age. The Applicant refers to the following guidance for industry: "Questions and Answers on Biosimilar Development and the BPCI Act."

On 25-April-2023, the Pediatric Review Committee (PeRC) reviewed the PSP and agreed with the Applicant's proposal.

10. Other Relevant Regulatory Issues

This sBLA was held past its December 18, 2022, goal date because at that time the Agency was carefully considering the complex legal and regulatory implications of *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021), which caused uncertainty about the scope of orphan-drug exclusivity. A term of orphan-drug exclusivity for US-Humira (adalimumab), BLA 125057, for "the treatment of moderate to severe hidradenitis suppurative (HS) in adolescent patients 12 years of age and older" will expire on October 16, 2025.

On January 24, 2023, the Agency published a notice in the Federal Register announcing that, at this time, while complying with the court's order in *Catalyst*, the Agency intends to continue to apply its regulations to matters beyond the scope of that order. See Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. 4086 (Jan. 24, 2023). These regulations tie the scope of orphan-drug exclusivity to the uses or indications for which the drug is approved. Having made this announcement, the Agency may now take action on this sBLA.

Reference is made to the Applicant's response, dated February 2, 2023, to an Information Request, dated January 31, 2023, requesting that action for this sBLA is taken in the context of biosimilarity. Accordingly, this sBLA has been evaluated in the context of biosimilarity.

11. Labeling

Prescribing Information

Labeling for Abrilada was updated to include the indication of moderate to severe HS in adult patients.

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Labeling consultants, including Office of Therapeutic Biologics and Biosimilar (OTBB), Office of Biotechnology Products (OBP)-labeling, Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP) are reviewing the proposed labeling. The final label will be included in the approval letter.

12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of adalimumab-afzb.

14. Recommended Regulatory Action

Approval.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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