CDER Clinical, CDTL, and Division Summary Memo

<table>
<tr><td>Date</td><td>July 11, 2022</td></tr>
<tr><td>From</td><td>Susanne Anderson</td></tr>
<tr><td>Subject</td><td>Clinical, Cross-Discipline Team Leader and Division Summary Review</td></tr>
<tr><td>BLA # and Supplement#</td><td>761154/S-002</td></tr>
<tr><td>Applicant</td><td>Mylan Pharmaceuticals Inc.</td></tr>
<tr><td>Date of Submission</td><td>September 30, 2021</td></tr>
<tr><td>BSUFA Goal Date</td><td>July 29, 2022 (actual Saturday July 30, 2022)</td></tr>
<tr><td>Proprietary Name</td><td>Hulio (adalimumab-fkjp)</td></tr>
<tr><td>Reference Product Proprietary Name</td><td>Humira</td></tr>
<tr><td>Dosage Form(s)</td><td>No new proposed dosage forms</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>Expansion of existing indications to include the following:
Treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 years to less than 4 years of age (15 kg and greater)
Treatment of moderately to severely active Crohn’s disease in pediatric patients ages 6 years to 17 years of age</td></tr>
<tr><td>Applicant Proposed Dosing Regimen(s)</td><td>Proposed dosing regimen is consistent with the reference product dosing regimen.

Polyarticular Juvenile Idiopathic Arthritis (2 years of age and older):
<table>
<tr><th>Pediatric Weight
2 Years of Age and Older</th><th>Recommended Dosage</th></tr>
<tr><td>15 kg (33 lbs) to less than 30 kg (66 lbs)</td><td>20 mg every other week</td></tr>
<tr><td>30 kg (66 lbs) and greater</td><td>40 mg every other week</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>Pediatric Crohn's Disease (6 years of age and older)
<table>
<tr><th rowspan="2">Pediatric Weight</th><th colspan="2">Recommended Dosage</th></tr>
<tr><th>Days 1 and 15</th><th>Starting on Day 29</th></tr>
<tr><td>17 kg (37 lbs) to less than 40 kg (88 lbs)</td><td>Day 1: 80 mg
Day 15: 40 mg</td><td>20 mg every other week</td></tr>
<tr><td>40 kg (88 lbs) and greater</td><td>Day 1: 160 mg (single dose or split over two consecutive days)
Day 15: 80 mg</td><td>40 mg every other week</td></tr>
</table></td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s)</td><td>• Moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.
• Moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

(Expansion of existing indications to include pediatric patients with pJIA 2 years to less than 4 years of age and pediatric patients with CD 6 years to 17 years of age)</td></tr>
<tr><td>Recommended Dosing Regimen(s)</td><td>Same as reference product dosing regimen</td></tr>
</table>

1. Introduction

The Applicant submitted supplement 002 to Biologic License Application (BLA) 761154 to expand the indications of polyarticular Juvenile Idiopathic Arthritis (pJIA) to include pediatric patients 2 years to less than 4 years of age, and Crohn's Disease (CD) to include pediatric patients 6 years to 17 years of age, that were previously under orphan exclusivity, and to provide the pediatric assessment for Ulcerative Colitis (UC) in pediatric patients 5 years to 17 years of age, which remains under orphan exclusivity. Supplement 002 was submitted to fulfill the Pediatric Research Equity Act (PREA) Post-Marketing Requirements (PMRs) that were issued with the original approval of adalimumab-fkjp on July 6, 2020. No new clinical information is included nor required for this submission. The Applicant has provided a scientific justification for extrapolation for each of the populations currently being sought for licensure.

2. Background

Adalimumab-fkjp (Hulio) is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against tumor necrosis factor (TNF)-alpha. Adalimumab-fkjp was approved as a biosimilar to US-licensed Humira (US-Humira) on July 6, 2020 under section 351(k) of the Public Health Service Act (BLA 761154), 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 4 years of age and older.
3. Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with PsA.
4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.
5. Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active CD 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. The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers.
7. Plaque Psoriasis (Ps): 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.

The original application included the following:

- A comprehensive comparative analytical assessment of adalimumab-fkjp, US-Humira, and EU-approved Humira (EU-Humira). These included comparative characterization of physicochemical attributes and comparative functional assessments.
- A 4-week repeat-dose toxicology study in monkeys to compare the effects of adalimumab-fkjp to those of EU-Humira.
- A pharmacokinetic (PK) similarity study (FKB327-001) in healthy subjects following a single subcutaneous (SC) 40 mg dose of adalimumab-fkjp, EU-Humira, or US-Humira.

- A comparability study (FKB327-005) of adalimumab-fkjp in healthy subjects following a single SC dose of adalimumab-fkjp by vial, pre-filled syringe, or autoinjector.
- A comparative clinical study (FKB327-002) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-fkjp and US-Humira in combination with methotrexate in patients with moderately to severely active RA.
- An open-label extension study (FKB327-003) comparing efficacy and safety between adalimumab-fkjp and US-Humira in RA.
- A scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) for extrapolation of data and information submitted in the application to support licensure of adalimumab-fkjp for each of the additional indications for which Mylan was seeking licensure and for which US-Humira had been previously licensed.

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that adalimumab-fkjp is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-fkjp 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-fkjp for the non-studied indications sought for approval. Review of the information submitted by the Applicant demonstrated that adalimumab-fkjp is biosimilar to US-Humira for each of the following indications for which US-Humira was previously approved and the Applicant was seeking licensure for adalimumab-fkjp: RA, pJIA in patients 4 years of age and older, PsA, AS, Ps, adult CD, and adult UC. See Biosimilar Multi-Disciplinary Evaluation and Review (BMER), dated July 2, 2020.

Hulio is approved in the following presentations:

- 40 mg/0.8 mL single-dose prefilled pen
- 40 mg/0.8 mL single-dose prefilled syringe
- 20 mg/0.4 mL single-dose prefilled syringe

At the time of the BLA approval, the following PMRs were required:

- **3894-1** Assessment of Hulio (adalimumab-fkjp) for the treatment of polyarticular JIA in patients ages 2 to less than 4 years of age
    - Final Report Submission September 2021
- **3894-2** Assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric Crohn's disease in patients 6 years to 17 years of age
    - Final Report Submission September 2021
- **3894-3** assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric UC in patients 5 years to 17 years of age
    - Final Report Submission September 2021

- **3894-4** Develop a presentation that can be used to accurately administer Hulio to pediatric patients who weigh less than 15 kg
    - Final Report Submission December 2023

The Applicant submitted this supplemental BLA (sBLA) on September 20, 2021 to provide pediatric assessments to address PMR 3894-1, PMR 3894-2, and PMR 3894-3, and to update labeling based on these assessments to expand the indication for pJIA to include patients 2 years of age and older, and the indication for CD to include adults and pediatric patients 6 years of age and older. The inclusion of these indications was not sought in the original BLA due to orphan drug exclusivities that have since expired for pJIA and CD. This submission includes a scientific justification, updated to include additional information in pediatric inflammatory bowel disease, for extrapolation for the populations currently being sought for licensure and labeling updates to include the expanded indications and for alignment with the reference product. Hulio cannot be approved for the indication of UC in pediatric patients 5 years to 17 years of age due to existing exclusivity until February 24, 2028. No new nonclinical or clinical information was included nor required for this submission.

3. Product Quality

No new product quality information was submitted nor required for this sBLA. There are no CMC or product quality issues that would preclude approval of the indications sought for licensure.

4. Nonclinical Pharmacology/Toxicology

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

6. Clinical/Statistical-Efficacy

Adalimumab-fkjp was previously studied in patients with RA in the comparative clinical study (FKB327-002 and open-label extension FKB327-003). The data were previously reviewed and summarized in the BMER dated July 2, 2020 for the original application. 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 indications sought for licensure.

7. Safety

Adalimumab-fkjp was previously studied in patients with RA in the comparative clinical study (FKB327-002 and open-label extension FKB327-003) and in healthy subjects in the PK studies (FKB327-001 and FKB327-005). The data were previously reviewed and summarized in the BMER dated July 2, 2020 for the original application. No new safety data were submitted nor required for this sBLA. There are no clinical safety issues that would preclude approval of the indications sought for licensure.

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

The Guidance for Industry Questions and Answers on Biosimilar Development and the Biologics Price Competition and Innovation (BPCI) Act (September 2021) notes that in the context of the potential biosimilar product under the Act, the biosimilar applicant may fulfill the PREA requirements by satisfying the statutory requirements for demonstrating biosimilarity and providing an adequate scientific justification under the BPCI Act for extrapolating data and information to support a licensure for each condition of use for which licensure is sought.[1]

Adalimumab-fkjp is an approved biosimilar for the treatment of RA, PsA, AS, adult CD, adult UC, pJIA in patients 4 years of age and older, and Ps. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-fkjp 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-fkjp and US-Humira in terms of safety, purity, and potency based on similar clinical PK, and similar efficacy, safety, and immunogenicity in RA.

Additional points considered in the justification for extrapolation of data and information to support licensure of adalimumab-fkjp 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-fkjp and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-fkjp and US-Humira in the indications sought for licensure. A similar PK profile would be expected between adalimumab-fkjp and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and Ps.
- 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

[1] For more information on extrapolation in this context, see FDA's Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)

the type of assay used[2]. Similar immunogenicity was observed between adalimumab-fkjp and US-Humira in patients with RA, and in healthy subjects. Therefore, similar immunogenicity would be expected between adalimumab-fkjp and US-Humira in patients with JIA, PsA, AS, adult CD, UC, and Ps.

- There were no clinically meaningful differences between adalimumab-fkjp and US-Humira in patients with RA, nor in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-fkjp and US-Humira, a similar safety profile would be expected in patients with JIA, PsA, AS, adult CD, UC, and Ps.
- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-fkjp 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.

The scientific justification for extrapolation in pJIA submitted with the original BLA included the entire pJIA population for which US-Humira is approved. However, at that time, the Applicant sought licensure for pJIA 4 years of age and older as there was remaining orphan drug exclusivity for pJIA 2 years to less than 4 years of age.

In the current submission, the Applicant has provided a scientific justification, updated to include additional information in pediatric inflammatory bowel disease, for extrapolation of the data and information to support the licensure of adalimumab-fkjp for the treatment of polyarticular JIA in patients 2 years to less than 4 years of age, CD in pediatric patients 6 to 17 years of age (b) (4) The justification for extrapolation to support licensure in pJIA 2 to less than 4 years of age is described below. Refer to Section 16 Appendix: Division of Gastroenterology Memo for discussion of the justification for extrapolation to support licensure in CD 6 years of age and older (b) (4)

Scientific considerations outlined above for the extrapolation of biosimilarity to the populations of pJIA 4 years of age and older are also relevant for the population of pJIA 2 to less than 4 years of age.

- There is no data or scientific evidence that PK and immunogenicity differ in patients with pJIA 2 years to less than 4 years of age and patients with pJIA 4 years of age and older such that the same justification for extrapolation could not apply.
- In terms of safety and toxicity, the same safety data which supported approval of the non-studied indications in the original application, including pJIA in patients 4 years of age and older, are relevant to support safety in patients with pJIA 2 years to less than 4 years of age.
- Regarding the mechanism of action, the shared importance of TNF in the pathophysiology of disease and clinical response in RA and pJIA support extrapolation to the existing pJIA data for the reference product. There are no scientific data that suggest that the mechanism of action differs in patients with

[2] US-Humira prescribing information

pJIA in the 2 years to less than 4 years of age population such that the same justification for extrapolation could not apply to the younger subgroup of pJIA patients.

Therefore, given that there are no data or scientific evidence that the mechanism of action, exposure relationship, immunogenicity, safety, or toxicity of adalimumab-fkjp are expected to differ between pJIA in patients 2 years to less than 4 years of age and in patients 4 years of age and older, it is reasonable to extrapolate the data and information to support licensure of an expanded indication for adalimumab-fkjp to include the treatment of patients with pJIA 2 years to less than 4 years of age. As discussed in Section 16, the Division of Gastroenterology (DG) review team also determined that the Applicant has provided an adequate extrapolation justification for pediatric CD patients 6 years of age and older (b) (4)

In conclusion, the totality of evidence discussed above and in Section 16 is adequate to justify extrapolating the data and information submitted to the BLA to support a determination of biosimilarity for the indication of polyarticular JIA in patients 2 years of age and older and for the indication of Crohn's disease in adults and pediatric patients 6 years of age and older. (b) (4) FDA has determined that US-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5 to 17 years. FDA therefore cannot license adalimumab-fkjp for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

To address the PREA-PMR requirements for these indications and age-groups, the Applicant has satisfied the statutory requirements by demonstrating biosimilarity and also provided an adequate scientific justification under the BPCI Act for extrapolating the findings of biosimilarity to the non-studied conditions of use for which the Applicant is seeking licensure and for which US-Humira has been previously approved. The Division of Rheumatology and Transplant Medicine (DRTM) and the DG review teams, as well as the Pediatric Review Committee (PeRC), have determined that the information provided in S-002 fulfills the requirements of PMR 3894-1, PMR 3894-2, and PMR 3894-3 as issued at the time of the approval of original BLA.

9. Pediatrics

On July 6, 2020, adalimumab-fkjp was approved as a biosimilar to US-Humira. It was considered to have a new active ingredient and, therefore, PREA applied. At that time, the PREA-required pediatric assessments for pJIA in patients 2 years to less than 4 years of age, pediatric CD in pediatric patients 6 years to 17 years of age, pediatric UC in pediatric patients 5 years to 17 years of age, and development of a presentation to accurately administer adalimumab-fkjp to pediatric patients who weigh less than 15 kg were deferred.

At the time of the BLA approval, the following PMRs were issued with corresponding due dates as presented below:

PMR #	PMR Details	Final Report Due Date
3894-1	Assessment of Hulio (adalimumab-fkjp) for the treatment of polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 to less than 4 years of age	September 2021
3894-2	Assessment of Hulio (adalimumab-fkjp) for the treatment of Pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.	September 2021
3894-3	Assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age	September 2021
3894-4	Develop a presentation that can be used to accurately administer Hulio (adalimumab-fkjp) to pediatric patients who weigh less than 15 kg	December 2023

In the current submission, the Applicant provided final reports to fulfill PMRs 3894-1, 3894-2, and 3894-3. The current supplement provides scientific justification for extrapolation proposing to fulfill the PREA PMRs (3894-1, 3894-2, and 3894-3).

The DRTM and DG review teams have determined that the Applicant has provided adequate information to fulfill the requirements of PMRs 3894-1, 3894-2, and 3894-3 as issued with the original BLA approval. The submission was reviewed at the FDA PeRC on June 28, 2022. PeRC agreed with the Divisions' assessment and recommendation that the provided information fulfills the intent of PMR 3894-1, 3894-2, and 3894-3.

PMR 3894-4 for the development of a presentation that can be used to accurately administer Hulio (adalimumab-fkjp) to pediatric patients who weigh less than 15 kg remains deferred until December 2023. The 40 mg/0.8 mL PFS and 20 mg/0.4 mL PFS for adalimumab-fkjp do not allow for weight-based dosing for pediatric patients who weigh less than 15 kg. However, this does not preclude the use of adalimumab-fkjp in younger pediatric patients (i.e., 2 to less than 4 years of age who weigh 15 kg or more). According to the Centers for Disease Control and Prevention clinical growth charts[3], the median weights for female and male children 2 years of age is 12 and 12.7 kg, respectively, and 15.9 kg and 16.3 kg, respectively, for children 4 years of age, indicating that the 20 mg/0.4 mL pre-filled syringe could be used in up to half of the pJIA patients in this younger age group.

10. Other Relevant Regulatory Issues

Not applicable.

[3] https://www.cdc.gov/growthcharts/clinical_charts.htm

11. Labeling

Prescribing Information

Revisions in the proposed United States Prescribing Information (USPI) update the labeling to include the indications of Crohn's disease in pediatric patients 6 to 17 years of age and polyarticular JIA in patients 2 to less than 4 years of age, to include data from associated clinical studies PCD-I and JIA-II, respectively, and to incorporate relevant information, where appropriate, from the US-licensed Humira labeling approved on February 24, 2021 (BLA 125057/S-417). Updates to references to Hulio, adalimumab, and adalimumab products were made for consistency with labeling practice. Table 1 presents a high level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency. Revisions made by the Agency are presented in italics below.

Table 1: Summary of Significant Labeling Changes

Section	Labeling Changes and Discussion
Section 1 Indications and Usage	• Revision of existing pJIA indication from "patients 4 years of age and older" to "patients 2 years of age and older (15 kg and greater)" ○ *Consistent with labeling practice, the Agency recommended that text referring to weight restrictions on dosing be removed from the indication statement. Dosing and administration instructions for pJIA based on weight are included in Section 2.2.* • Update of existing adult CD indication as follows, "treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older." Additional revisions of indication statement to remove specific claims for alignment with the reference product. • Revision of indication statement for UC to remove specific claims for alignment with the reference product. • Addition of subheading 'Limitation of Use' above statement regarding effectiveness in patients who have lost response to or were intolerant to TNF blockers.

Section 2 Dosage and Administration	• RA: Addition of 80 mg every other week dose, for alignment with the reference product.
	• CD:
	  ○ Removal of statement that use of adalimumab products beyond one year has not been evaluated, for alignment with the reference product.
	  ○ Addition of dosing information for pediatric patients with CD
	  ○ *The Agency provided additional revisions to the description of the dosing on Day 1 of treatment for adult CD and adult UC, consistent with the reference product labeling.*
	• Addition of guidance on missed dose, for alignment with the reference product.

Section 6 Adverse Reactions	• Update to listing of clinically significant adverse reactions described elsewhere in labeling, for alignment with the reference product.
Section 6.1 Clinical Trials Experience	• Addition of liver enzyme elevation data from an open-label study of adalimumab in patients with pJIA ages 2 years to less than 4 years, for alignment with the reference product. • *The Agency recommended addition of liver enzyme elevation data from pediatric patients with CD, for alignment with the reference product labeling.* • Addition of safety data from the JIA-II study pertaining to the pediatric population with pJIA. • Addition of safety data from the PCD-I study pertaining to patients with pediatric CD.
Section 6.2 Immunogenicity	• Relocation and reformatting of immunogenicity data to Section 6.2 Immunogenicity for consistency with the reference product labeling.
Section 8.4 Pediatric Use	• Revisions to statements describing pediatric populations in which the safety and efficacy of Hulio have been established and those in which the safety and effectiveness have not been established. • Addition of description of safety in pJIA 2 to less than 4 years of age (Study JIA-II) and safety and effectiveness in pediatric Crohn's disease (Study PCD-1). • *Addition of the following statement: "A pediatric assessment of HULIO demonstrates that HULIO is safe and effective for pediatric patients in an indication for which Humira (adalimumab) is approved. However, HULIO is not approved for such indication due to marketing exclusivity for Humira (adalimumab)."*

Section 11 Description	• *The Agency advised the Applicant to include the specific cell line expression system (e.g., CHO cell line) used to produce Hulio.*
Section 12.3 Pharmacokinetic	• Addition of PK data relevant to the indication of JIA in patients 2 to 4 years of age and in patients with pediatric CD. • Updates to presentation of PK information for consistency with the reference product.
Section 14.2 Juvenile Idiopathic Arthritis	• Addition of description of Study JIA-II in pediatric patients with JIA 2 years of age and older.
Section 14.6 Pediatric Crohn's Disease	• Addition of subsection 14.6 Pediatric Crohn's disease including description of design and efficacy data from Study PCD-I.

Other Labeling

Updates to the Medication Guide were made for consistency with the reference product labeling. In addition, there were minor editorial revisions proposed for the final printed carton and container labels, instructions for use of the pen and syringe, and quick reference guide.

Labeling consultants, including the Division of Medication Error Prevention and Analysis (DMEPA), the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP), have reviewed the submitted labeling and found the proposed revisions acceptable. All labeling changes were agreed upon with the Applicant.

12. Postmarketing Recommendations

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

14. Recommended Regulatory Action

Approval.

15. DRTM Designated Signatory Comments

I concur with the team's assessment of the data and information submitted in this supplemental BLA.

The information submitted fulfills PREA-required assessments for JIA in patients 2 to less than 4 years of age, pediatric Crohn's disease, and pediatric ulcerative colitis (PMR 3894-1, PMR 3894-2, and PMR 3894-3, respectively, from the approval of original BLA 761154, July 6, 2020). The labeling has been updated to expand the indications for pJIA to patients 2 years of age and older, and for Crohn's disease to adults and pediatric patients 6 years of age and older. As US-Humira has existing orphan drug exclusivity for UC, in pediatric patients 5 years to 17 years, adalimumab-fkjp cannot be licensed for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028. PMR 3894-4 for the development of a presentation that can be used to accurately administer Hulio (adalimumab-fkjp) to pediatric patients who weigh less than 15 kg remains deferred until December 2023. No additional data, new PMRs, PMCs, or REMS are required for this supplement.

16. Appendix: Division of Gastroenterology Memo

Hulio (FKB327) is currently approved for the treatment of inflammatory bowel disease (IBD) indications of Crohn's disease (CD) and ulcerative colitis (UC) in adults, in addition to other indications.[4] While the IBD indications were not directly studied in the FKB327 clinical program, as noted in the DG extrapolation rationale of the original BLA[5] review dated 07/02/2020, consistent with the principles of the FDA Guidance For Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product[6], the Applicant had provided sufficient scientific justification based on the mechanism of action, PK, immunogenicity and toxicity profile, and sufficient information, including clinical data from the studied populations (healthy subjects and patients with rheumatoid arthritis, RA), to support licensure of FKB327 for UC and CD in adults. At the time of the original BLA application, the Applicant did not seek the licensure of the pediatric CD indication due to pending orphan drug exclusivity. In addition, US-Humira was not licensed for the pediatric UC indication at the time. Thus, the approval letter for BLA 761154, dated 07/06/2020 included the following PREA PMRs to address the pediatric IBD indications:

- 3894-2: Assessment of Hulio (adalimumab-fkjp) for the treatment of Pediatric Crohn's disease (CD) in pediatric patients 6 years to 17 years of age.
  Final Report Submission: September 2021
- 3894-3: Assessment of Hulio (adalimumab-fkjp) for the treatment of pediatric ulcerative colitis (UC) in pediatric patients 5 years to 17 years of age.
  Final Report Submission: September 2021

The orphan drug exclusivity of US-Humira for pediatric CD had since expired on September 23, 2021. Furthermore, on February 24, 2021, US-Humira was licensed for the treatment of moderately to severely active UC in pediatric patients 5 years and older, and eligible for an orphan drug exclusivity until February 24, 2028. With the submission of BLA 761154/S-002, the Applicant intends to address the pending PREA PMRs for pediatric CD (3894-2) and pediatric UC (3894-3) for Hulio and is seeking the licensure for the pediatric CD indication.

The Applicant has provided justification for extrapolating data and information submitted in the original application and supplement to support licensure of FKB327 as a biosimilar for each of the pediatric IBD indications for which licensure is sought and for which US-Humira has been previously approved. The Applicant's justification was evaluated and considered adequate, as summarized below:

- Mechanism of Action (MOA) - Similar to the studied indication (RA), TNF-α plays a central role in the pathogenesis of IBD, as evidenced by the efficacy of approved TNF-α inhibitors in the treatment of UC and/or CD. In addition to the binding and neutralization of sTNFα, the efficacy of adalimumab in the treatment of IBD is thought to also involve reverse signaling via binding to tmTNF-α, and other plausible

[4] Hulio USPI accessed on 02/25/2022:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761154s000lbl.pdf
[5] BLA 761154 Hulio - BMER Section 7.6.1., Division of Gastroenterology Extrapolation Review (07/02/2020)
[6] Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)

mechanisms of action involving the Fc region of the antibody.[7,8,9] The mechanisms by which adalimumab exerts its therapeutic effect are expected to be the same in adults vs. pediatric CD (b) (4) patients. Together with demonstrated structural and functional similarity between FKB327 and US-Humira, the mechanisms of action of FKB327 are not expected to be different from that of US-Humira in pediatric CD (b) (4) patients, to the extent that the mechanisms are known or can be reasonably determined.

- Pharmacokinetics (PK) - There are no significant differences in the PK characteristics of US-Humira in healthy subjects or across its various approved indications. Adalimumab concentrations are similar in adult vs. pediatric CD and UC patients (Humira USPI, 2021). Together with the data from the original BLA that demonstrated PK similarity between FKB327 vs. US-Humira in healthy volunteers (Study FKB327-001), and between FKB327 vs. US-Humira in patients with RA (FKB327-002 and FKB327-003), the PK following FKB327 are not expected to be different to that of US-Humira in pediatric CD (b) (4) patients.
- Immunogenicity - There is no scientific data or evidence to assume that the mechanisms involved in the development of ADAs would differ across indications to preclude extrapolation of immunogenicity data. Immunogenicity rates of US-Humira are comparable between adult vs. pediatric CD and UC patients (Humira USPI, 2021). Together with the comparable immunogenicity in healthy volunteers (FKB327 vs. US-Humira, in study FKB327-001) and in RA patients (FKB327 vs. US-Humira, in FKB327-002 and FKB327-003), the immunogenicity of FKB327 is not expected to be different from that of US-Humira in pediatric CD (b) (4) patients.
- Safety - The safety profile of US-Humira was comparable in adult vs. pediatric CD and pediatric UC patients (Humira USPI, 2021). Together with the data submitted to the original BLA that demonstrated comparable safety profile of FKB327 vs. US-Humira in adult RA patients, the safety of FKB327 is not expected to be different from that of US-Humira in pediatric CD (b) (4) patients.

(b) (4) FDA has determined that US-Humira is eligible for orphan drug exclusivity for pediatric UC, ages 5-17 years. FDA therefore cannot license FKB327 for this indication prior to the expiration of the orphan drug exclusivity on February 24, 2028.

[7] Oikonomopoulos A, et al., Current Drug Targets 2013; 14:1421-32.
[8] Tracey D, et al., Pharmacology & Therapeutics 2008; 117:244–79.
[9] Olesen, C.M, et.al., Pharmacology & Therapeutics 159 (2016), 110-119.

Regulatory Recommendations: The Division of Gastroenterology concludes that the totality of the evidence provided by the Applicant supports licensure of FKB327 for each of the following indication(s) for which the Applicant is seeking licensure of FKB327:

- the treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

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