Office of Therapeutic Biologics and Biosimilars
Clinical, Cross-Discipline Team Leader, and Division Memo

Date	See Electronic Stamp Date
From	Sabiha Khan, MD, Clinical Reviewer (OTBB) Thomas Herndon, MD, CDTL (OTBB) Raj Nair, MD, MD, Division Signatory (OII/DRTM)
Subject	Cross-Discipline Team Leader Review for 351(k) BLA CMC-Prior Approval Supplement (PAS) seeking: • Approval for Yuflyma 10 mg/0.1 mL in a pre-filled syringe (PFS) as an interchangeable biosimilar to US-licensed Humira 10 mg/0.1 mL in a PFS
Application Type	Prior Approval Supplement (PAS)-CMC
BLA # and Supplement#	761219/S-019
Applicant	Celltrion
Date of Submission	June 30, 2025
BsUFA Goal Date	October 30, 2025
Product Code Name	CT-P17
Nonproprietary Name	adalimumab-aaty
Proprietary Name	Yuflyma
Reference Product	Humira (adalimumab) (US-licensed Humira, US-Humira)
Approved Indication(s)	- Rheumatoid Arthritis (RA) - Juvenile Idiopathic Arthritis (JIA) (2 years of age and older) - Psoriatic Arthritis (PsA) - Ankylosing Spondylitis (AS) - Crohn's Disease (CD) in adults and pediatric patients 6 years of age and older - Ulcerative Colitis (UC) in adult patients. - Plaque Psoriasis (PsO) in adult patients - Hidradenitis Suppurativa (HS) in adult patients. - Uveitis (UV) in adult patients.
Purpose of the Submission	Seeking approval of Yuflyma (adalimumab-aaty) injection 10 mg/0.1 mL in a PFS for subcutaneous use as an interchangeable biosimilar to US-licensed Humira (adalimumab) (US-Humira) 10 mg/0.1 mL in a PFS
New Indication(s) and/or Population	None
New Dosing Regimen(s)	Juvenile Idiopathic Arthritis (2 years of age and older): 10 kg (22 lbs) to less than 15 kg (33 lbs): 10 mg every other week
Recommendation on Regulatory Action	Approval of: • Yuflyma (adalimumab-aaty) injection 10 mg/0.1 mL in a PFS for subcutaneous use as an interchangeable biosimilar to US-Humira (adalimumab) injection 10 mg/0.1 mL in a PFS for subcutaneous use.

1. Introduction

Celltrion, Inc. (hereafter referred to as “the Applicant”) has submitted a supplemental Biologics License Application (sBLA) under section 351(k) of the Public Health Service (PHS) Act, which seeks approval of Yuflyma 10 mg/0.1 mL in a pre-filled (PFS) for subcutaneous use as an interchangeable biosimilar to US-licensed Humira (adalimumab, US-Humira) 10 mg/0.1 mL in a PFS for subcutaneous use. This submission is to fulfill Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) 4433-1 to develop presentation(s) that can be used to accurately administer Yuflyma to pediatric patients weighing 10 kg to less than 40 kg.

CT-P17 is a tumor necrosis factor (TNF) blocker approved under the proprietary name of Yuflyma (proper name: adalimumab-aaty) as biosimilar to US-Humira on May 23, 2023.

According to its FDA-approved labeling, Yuflyma is supplied as:

- Single-dose prefilled auto-injector (AI): 80 mg/0.8 mL, 40 mg/0.4 mL
- Single-dose prefilled syringe with safety guard (PFS-S): 80 mg/0.8 mL, 40 mg/0.4 mL
- Single-dose PFS: 80 mg/0.8 mL, 40 mg/0.4 mL, 20 mg/0.2 mL

Yuflyma is administered by subcutaneous injection.

The following Yuflyma products are approved as interchangeable to US-Humira:

- Yuflyma 20 mg/0.2 mL in a PFS is interchangeable with US-Humira injection 20 mg/0.2 mL in a PFS
- Yuflyma 40 mg/0.4 mL in a PFS and in a PFS-S is interchangeable with US-Humira 40 mg/0.4 mL in a PFS
- Yuflyma 40 mg/0.4 mL in a prefilled autoinjector (AI) is interchangeable with US-Humira 40 mg/0.4 mL in a prefilled pen
- Yuflyma 80 mg/0.8 mL in a PFS and in a PFS-S is interchangeable with US-Humira injection 80 mg/0.8 mL in a PFS
- Yuflyma 80 mg/0.8 mL in a prefilled AI is interchangeable with US-Humira 80 mg/0.8 mL in a prefilled pen

The status of the currently approved strengths and indications for Yuflyma are summarized in Table 1.

Table 1. Current status of Yuflyma approvals (biosimilar vs interchangeable)

Strength	Presentation		
	PFS	PFS with Safety Guard	AI
20 mg/0.2 mL	IC	NA	NA
40 mg/0.4 mL	IC	IC	IC
80 mg/0.8 mL	IC	IC	IC

IC: Interchangeable; Bs: biosimilar; NA: not applicable (presentation not available for that strength)

To support the approval of Yuflyma 10 mg/0.1 mL in a PFS as an interchangeable biosimilar to US-Humira 10 mg/0.1 mL in a PFS, the Applicant provided adequate data and information in this supplement and original BLA, including comparative analytical data and comparative PK, efficacy, safety, and immunogenicity data, to support a demonstration that Yuflyma can be expected to produce the same clinical result as US-Humira in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

The approval of Yuflyma as interchangeable to US-Humira on April 7, 2025, was based on the following evidence for biosimilarity:

- Yuflyma is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components. The proposed strength of Yuflyma is (40 mg/0.4 mL) the same as that of US-Humira. The dosage form and route of administration is also the same as those of US-Humira.
- There are no clinically meaningful differences between Yuflyma and US-Humira based on PK, immunogenicity, safety and efficacy assessment from the PK similarity study (Study CT-P17 1.1) in healthy subjects and the switching study with PK endpoints in patients with plaque psoriasis (Study CT-P17 3.1).
- The PK portion of the scientific bridge was established based on results of a 3-way PK similarity study (Study CT-P17 1.1) comparing Yuflyma (40 mg/0.4 mL), EU-Humira (40 mg/0.4 mL), or US-Humira (40 mg/0.4 mL) to support the relevance of the data generated using EU-Humira as the comparator in the switching study with PK endpoints (Study CT-P17 3.3).
- 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 US-Humira has been previously approved.

The Applicant provided adequate data and information in Supplement 009, Supplement 017, and in the original BLA to support a demonstration that Yuflyma can be expected to produce the same clinical result as US-Humira in any given patient and that there were no significant differences in terms of PK, safety, or immunogenicity in patients who were switched between CT-P17 and EU-Humira.

For additional details, refer to the Biosimilar Multidisciplinary Evaluation and Review (BMER) of BLA 761219, Supplement 009, dated November 8, 2024, and Cross-Discipline Team Leader Review/Division Summary Review of BLA 761219, Supplement 017, dated April 7, 2025.

The submission for BLA 761219 Supplement 019 includes a series of comparative analyses conducted between CT-P17 and US-Humira. No new indications are proposed in this supplement. No new clinical information is included nor required for the Applicant’s submission.

2. Background

Yuflyma (adalimumab-aaty, CPT-17) is a recombinant human immunoglobulin G1 monoclonal antibody against tumor necrosis factor (TNF)-alpha. Adalimumab-aaty was approved as a biosimilar to US-licensed Humira (US-Humira) on May 23, 2023, under section 351(k) of the Public Health Service Act (BLA 761219).

Based on the most recent label, Yuflyma is currently approved for:

- 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 2 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.
- Crohn's Disease (CD): Treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.
- Ulcerative Colitis (UC): Treatment of moderately to severely active ulcerative colitis in adult patients.
- Plaque Psoriasis (Ps): 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.
- Hidradenitis Suppurativa (HS): Treatment of moderate to severe Hidradenitis suppurativa in adult patients.
- Uveitis (UV): treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

Refer to the Biosimilar Multidisciplinary Evaluation and Reviews (dated November 24, 2021, November 22, 2022, and May 22, 2023) from Division of Rheumatology and Transplant Medicine (DRTM), Division of Dermatology and Dentistry (DDD), and Division of Gastroenterology (DG) for additional details.

Table 2 summarizes the key regulatory interactions to support licensure of Yuflyma as interchangeable biosimilar to US-Humira for the following presentation:

- Yuflyma 10 mg/0.1 mL in a PFS as an interchangeable biosimilar to US-Humira 10 mg/0.1 mL in a PFS

Table 2. Key Regulatory Interactions

Meeting Type/Regulatory Action (Date[a])	Topics of Discussion and Major Agreements
BPD Type 2b Meeting (July 15, 2022)	• To discuss the study design of a proposed switching study to support a demonstration of interchangeability to US-Humira
Original BLA Approval (May 23, 2023)	• Yuflyma (adalimumab-aaty) was approved as a biosimilar to US-Humira (adalimumab). • The Approval Letter informed the Applicant of the following Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR): ○ 4433-1: Develop presentation(s) that can be used to accurately administer Yuflyma (adalimumab-aaty) to pediatric patients weighing 10 kg to less than 40 kg. Final Report Submission Date: 6/2025
BPD 2b Written Responses (October 20, 2023)	• To seek Agency advice on the proposal to extrapolate data generated from the proposed switching study (b) (4) and on the planned comparative risk assessment to support interchangeability of all devices and strengths of Yuflyma.

[a]Date of entry into Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)

3. Summary of Conclusions of Other Review Disciplines

3.1. Product Quality

The Office of Product Quality Assessment III (OPQAIII) completed assessment of this submission and determined that approval of Yuflyma (adalimumab-aaty) injection 10 mg/0.1 mL in a PFS is adequately supported by analytical comparability, process validation, available stability data, and extractable and leachable risk assessment. OPQAIII recommends approval of this supplement. See review dated October 21, 2025, for additional details.

The proposed labels and labeling were reviewed by OPQAIII Labeling for compliance with requirements in the Code of Federal Regulations and for consistency with recommended labeling practices, and were found to be acceptable. See review dated October 22, 2025, for additional details.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) reviewed the submitted information from a sterility assurance perspective and has recommended approval of the supplement. See review dated October 14, 2025, for additional details.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

Not applicable.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis 1 (DMEPA1) evaluated the proposed Yuflyma Prescribing Information, medication guide, instructions for use, container label, and carton labeling and did not identify areas of vulnerability that may lead to medication errors. See review dated September 11, 2025, for details.

3.3. Office of Study Integrity and Surveillance (OSIS)

Not applicable.

3.4. Office of Scientific Investigations (OSI)

Not applicable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this BLA supplement.

6. Clinical Evaluation and Recommendations

6.1. Efficacy

No new efficacy data was submitted nor required for this BLA supplement.

6.2. Safety

No new safety data was submitted nor required for this BLA supplement.

6.3. Interchangeability Assessment/Extrapolation

Yuflyma was approved as biosimilar to US-Humira on May 23, 2023. As part of the submission seeking interchangeability for Yuflyma (Provisional Determination action on November 8, 2024, and Approval action on April 7, 2025), the Applicant provided evidence addressing the following:

The any given patient standard:

- The Applicant provided adequate data and information in the supplement and in the original BLA, including the comparative analytical data and comparative PK, efficacy, safety and immunogenicity data, to support a demonstration that Yuflyma can be expected to produce the same clinical result as US-Humira in any given patient.

The switching standard:

- The switching study with PK endpoints, Study CT-P17 3.3, a randomized, active-controlled, double-blind, multicenter study to evaluate PK, efficacy, safety, and immunogenicity in patients with plaque psoriasis was used as a switching study. There were no significant differences in terms of PK, safety, or immunogenicity in patients who were switched between CT-P17 and EU-Humira. Therefore, the risk in terms of safety or diminished efficacy of alternating or switching between use of Yuflyma and US-Humira is not greater than the risk of using US-Humira without such alternation or switch

For additional details, refer to the BMER of BLA 761219, Supplement 009, dated November 8, 2024, and Cross-Discipline Team Leader Review/Division Summary Review of BLA 761219, Supplement 017, dated April 7, 2025.

- Given the above, the information submitted by the Applicant demonstrates that Yuflyma 10 mg/0.1 mL in a prefilled syringe is interchangeable with US-Humira 10 mg/0.1 mL in a prefilled syringe.

7. Labeling

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product. The final labeling will be attached to the approval letter.

8. Pediatrics

On May 23, 2023, Yuflyma (adalimumab-aaty) was approved as biosimilar to US-Humira. It was considered to have a new active ingredient and triggered PREA. At that time, the following PREA-PMRs were issued:

4433-1 Develop presentation(s) that can be used to accurately administer Yuflyma (adalimumab-aaty) to pediatric patients weighing 10 kg to less than 40 kg.

4433-2: Assessment of Yuflyma (adalimumab-aaty) for the treatment of pediatric hidradenitis suppurativa (HS) in patients 12 years to 17 years of age.

4433-3: 4433-3 Assessment of Yuflyma (adalimumab-aaty) for the treatment of pediatric ulcerative colitis (UC) in patients 5 years to 17 years of age.

The presentations (40 mg/0.4 mL AI, 40 mg/0.4 mL PFS-S, and 40 mg/0.4 mL PFS) approved under the Original BLA can be used to accurately administer Yuflyma (adalimumab-aaty) to pediatric patients weighing 30 kg and greater. On September 29, 2023, under BLA 761219 Supplement 001, Yuflyma 20 mg/0.2 mL PFS was approved as biosimilar to US-Humira. This presentation can be used to accurately administer Yuflyma (adalimumab-aaty) to pediatric patients weighing 15 kg to less than 30 kg. The current Supplement seeks the approval of Yuflyma 10 mg/0.1 mL PFS, which can be used to accurately administer Yuflyma (adalimumab-aaty) to pediatric patients weighing 10 kg to less than 15 kg.

The Applicant has provided adequate information to fulfill the requirements of PREA-PMR 4433-1 from the approval of Original BLA.

A Pediatric Review Committee (PeRC) meeting occurred on October 21, 2025. The PeRC recommends the following: PREA PMR 4433-1 is considered fulfilled.

9. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies (REMS)

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

11.2. Recommendations for Postmarket Requirements and Commitments (PMCs)

None

10. Other Relevant Regulatory Issues

None.

11. Recommended Regulatory Action

Approval.

12. Recommended Comments to the Applicant

None.

13. Division Director or Designated Signatory Comments

I concur with the review team’s assessment of the data and information submitted in this supplemental BLA and support the regulatory action.

14. Appendices

None.

14.1. References

None.

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/

SABIHA KHAN
10/30/2025 11:58:28 AM

THOMAS M HERNDON
10/30/2025 12:05:03 PM

RAJ NAIR
10/30/2025 12:05:36 PM