Cross-Discipline Team Leader / Division Summary Memo

Date	See DARRTS stamped date.
From	Anil Rajpal, MD, MPH; Clinical Team Leader Ozlem Belen, MD, MPH; Deputy Division Director
Subject	Cross-Discipline Team Leader / Division Director Memo
NDA/BLA # and Supplement#	BLA 761219
Applicant	Celltrion, Inc.
Date of Submission	November 30, 2022
BsDUFA Goal Date	May 30, 2023
Proprietary Name	Yuflyma
Nonproprietary Name	adalimumab-aaty (CT-P17)
Applicant Proposed Indication(s)/Population(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) • Hiradenitis suppurativa (HS) in adult patients
Recommendation on Regulatory Action	Approval

Summary: The Applicant (Celltrion, Inc.) originally submitted BLA 761219 for Yuflyma (adalimumab-aaty; CT-P17), a proposed biosimilar to US-licensed Humira (adalimumab), on November 24, 2020. The BLA met conditions for approval except for facility inspection issues with the drug product manufacturing site (see the Biosimilar Multidisciplinary Evaluation and Review [BMER] dated November 24, 2021). The facilities reviewer concluded that sufficient facility and equipment controls were not in place to prevent contamination of and by the application product; the facilities reviewer noted that full-scale process performance qualification studies were attempted and failed before the pre-license inspection, which demonstrated that the process is not under control (see the BMER dated November 24, 2021, and the Office of Pharmaceutical Quality (OPQ) Executive Summary dated November 22, 2021). The OPQ team recommended a Complete Response (CR) action. The CR letter indicated that approval of the BLA will require resolving the issues identified at the drug product manufacturing site. Specifically, the CR letter stated the following:

> "During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

The Applicant resubmitted BLA 761219 on May 27, 2022. The facilities reviewer concluded that complete resolution of the objectionable observations identified during the original pre-license

inspection could not be verified during the BLA resubmission review clock (see the Cross-Discipline Team Leader [CDTL] / Division Summary Memo dated November 22, 2022, and the OPQ Executive Summary dated November 3, 2022). The OPQ team again recommended a CR action. The CR letter indicated that approval of the BLA will require resolving the issues identified at the drug product manufacturing site, and contained the same language as that shown above from the first review cycle.

The Applicant resubmitted BLA 761219 again on November 30, 2022. The facilities reviewer conducted a review of records requested under Section 704(a)(4) of the Food Drug and Cosmetic Act to assess corrective actions for multiple observations identified during the pre-license inspection and surveillance inspections, and concluded that the corrective actions to address product specific observations were adequate (see the OPQ Executive Summary dated May 1, 2023, and the Office of Pharmaceutical Manufacturing Assessment (OPMA) review dated May 17, 2023). The OPQ team recommends an Approval action (see the OPQ Executive Summary dated May 1, 2023, the Office of Biotechnology Products (OBP) review dated May 2, 2023, and the OPMA review dated May 17, 2023). The CDTL and Division Signatory concur with the assessment and recommendations.

Additionally, although not an approvability issue, since the current resubmission, the Agency has resolved the potential implications of *Catalyst Pharms., Inc. v. Becerra (Catalyst)* on the indication of treatment of moderate to severe hidradenitis suppurativa (HS) in adults noted in the second cycle CDTL / Division Summary Memo dated November 22, 2022. The Applicant thus submitted an amendment to seek licensure for the indications of treatment of moderate to severe HS in adults. In the last review cycle, the Division of Dermatology and Dentistry (DDD) concluded that the extrapolation justification supports licensure of CT-P17 as a biosimilar for the indication of treatment of moderate to severe HS in adults for which US-licensed Humira is adequate (see the Appendix).

Regulatory Action: The regulatory action is Approval.

Postmarketing Requirements: The postmarketing requirements below should be communicated in the Approval Letter.

4433-1 Assessment of Yuflyma (adalimumab-aaty) for the treatment of pediatric ulcerative colitis (UC) in patients 5 years to 17 years of age.
Final Report Submission: February 2028

4433-2 Assessment of Yuflyma (adalimumab-aaty) for the treatment of pediatric hidradenitis suppurativa (HS) in patients 12 years to 17 years of age.
Final Report Submission: October 2025

4433-3 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: June 2025

APPENDIX: Division of Dermatology and Dentistry Memo

This addendum serves to update the memorandum by the Division of Dermatology and Dentistry (DDD) describing the adequacy of the justification for extrapolation to moderate to severe hidradenitis suppurativa (HS) indication.

During the review of the original 351(k) BLA submission (received on November 24, 2020), the Applicant did not initially seek licensure for the indication of moderate to severe hidradenitis suppurativa (HS) in adult patients because of remaining Orphan Drug exclusivity (ODE) for US-Humira for the HS indication. While the data submitted by the Applicant showed that CT-P17 is biosimilar to US-Humira, the data were not sufficient to support a conclusion that the manufacture of CT-P17 was well-controlled and would lead to a product that is safe, pure and potent. Therefore, the FDA review teams recommended a Complete Response (CR) for the original application.

During the following review cycle, the Applicant submitted justification for extrapolation of the data and information to support of licensure of CT-P17 for HS in adult patients. The Division of Dermatology and Dentistry (DDD) determined that the Applicant's justification for extrapolation to moderate to severe HS indication was adequate, and data from the studied population is applicable to the non-studied HS indication. However, due to potential implications related to Catalyst Pharms., Inc. v. Becerra, the Applicant submitted amendments removing the indication of moderate to severe HS from the United States Package Insert (USPI) and pediatric study plan (PSP). Nonetheless, DDD's conclusion that the justification for extrapolation was adequate and data from the studied population is applicable to the HS indication in adult patients was documented as an appendix to the Cross-Discipline Team Leader/Division Summary Memo by Division of Rheumatology and Transplant Medicine (DRTM) dated November 22, 2022.
The original issues regarding facility inspection with the drug product manufacturing site had not been resolved, therefore in this second review cycle, the team again recommended a CR action.

On November 30, 2022, the Applicant resubmitted BLA 761219 for CT-P17. Since this resubmission, the Agency has resolved any potential Catalyst implications. The Applicant thus submitted an amendment to again seek licensure for the indication of treatment of moderate to severe HS in adults. DDD's conclusion during the prior review cycle stands--the extrapolation justification supports licensure of CT-P17 as a biosimilar for the indication of treatment of moderate to severe HS in adults for which US-licensed Humira is approved.

Additionally, the Applicant has requested deferral of their required pediatric assessments for the indication of treatment of HS in patients 12 years to 17 years of age. U.S.-licensed Humira (adalimumab) is eligible for orphan drug exclusivity (ODE) for HS in adolescent subjects ages 12 years to less than 18 years of age until ODE expiration of October 16, 2025. DDD and the Pediatric Review Committee (PeRC) agree with the deferral. A post-marketing requirement will be issued for the Applicant to satisfy requirements under the Pediatric Research Equity Act (PREA) for HS with the submission of an adequate scientific justification for extrapolation of pediatric data and information from US-Humira to CT-P17 to support licensure for the HS

indication in adolescent patients 12 years to 17 years of age, after expiration of the orphan drug exclusivity.

To address PREA for the entire pediatric age range for this indication, the Applicant referred to Q.A.I.16. in the Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2) for patients younger than 12 years of age in their initial pediatric study plan (iPSP). Because the labeling for US-Humira does not contain adequate pediatric information for patients younger than 12 years of age for the HS indication, and PREA requirements were waived for US-Humira for this age group and indication, DDD and PeRC agreed that the Applicant does not need to request a waiver of PREA requirements for this age group as documented in the iPSP.

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