CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761219Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Note an NDC change check PI vs C&C

Date of Assessment:	May 22, 2023
Assessor:	Scott Dallas, RPh Labeling Assessor* Office of Biotechnology Products (OBP)
Through:	Yun Wu, PhD Product Quality Assessor* OBP/Division of Biotechnology Review and Research 1 OBP TL Willie Wilson, OPMA micro DP & DS Lindsey Brown, TL Max Van Tassell CDRH Porsche Bennett OND RPM Sadaf Nabavian
Application:	BLA 761219
Applicant:	CELLTRION, Inc.
Submission Dates:	November 24, 2020 - first cycle initial submission May 27, 2022 – second cycle resubmission
Product:	Yuflyma (adalimumab-aaty) HUMIRA Biosimilar BLA 125057
Dosage form(s):	Injection
Strength and Container-Closure:	40 mg/0.4 mL in a single-dose prefilled syringe and a prefilled autoinjector
Purpose of assessment:	The applicant submitted a 351(k) biologics license application for a proposed biosimilar product to US-licensed Humira® (adalimumab).
Recommendations:	The prescribing information, medication guide, instructions for use, container labels, and carton labeling are **acceptable** from an OBP labeling perspective.

* James Barlow, RPh, was the Labeling Assessor and Cindy Osborn, PhD, was the Product Quality Assessor during the first review cycle.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information, medication guide, patient labeling, instructions for use submitted on May 19, 2023, and container labels submitted on April 17, 2023, and carton labeling submitted on April 27, 2023 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information, Medication Guide and Instructions for Use (submitted on May 27, 2022)
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- Container Labels for prefilled autoinjector (submitted on May 27, 2022)

- Container Labels for prefilled syringe without safety guard (submitted on May 27, 2022)

- Container Labels for prefilled syringe with safety guard (submitted on May 27, 2022)

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

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
DMEPA's Nonproprietary Name Suffix Advice letter dated March 2, 2023, found the nonproprietary name, adalimumab-aaty, conditionally acceptable for the proposed product.

Applicant's response: The Applicant revised the nonproprietary name to "adalimumab-aaty" throughout the labels and labeling.

OBP Labeling: The applicant's revision is acceptable.

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	☐ Yes ☐ No ☒ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(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), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

To applicant: Ensure the required manufacturer's name, "CELLTRION, Inc.", is displayed on the label. Consider deletion of the logo "(b) (4)" to ensure there is room for the manufacturer's name. Refer to 21 CFR 610.60 and 610.64. Please note that the entire address is not required on the container label because the label would be considered a partial label, refer to 21 CFR 610.60(c).

Applicant's response: The Applicant deleted the logo of "(b) (4)" and replaced it with the manufacturer's name, "CELLTRION, Inc." from container label.

OBP Labeling: The applicant's revision is acceptable.

The qualifying phrase "Manufactured by" and license number do not appear on the label due to lack of space, which is acceptable per 21 CFR 610.60(c).

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

Applicant's response: The Applicant intends to use the format for the expiration date in YYYY MM on the labeling.

OBP Labeling: The applicant's revision is acceptable.

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Considered partial label so statement not required on the container label.

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No

	☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

Applicant's response: The Applicant confirmed that container label is all transparent area except for the area where variable data is printed, so there is no problem with the liquid inside the device being visible.

OBP Labeling: The applicant's response is acceptable.

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A

Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Consider debolding the "Rx only" statement. Applicant's response: The Applicant debolded the "Rx only" statement OBP Labeling: The applicant's revision is acceptable.

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011	✓ Yes

Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic	☐ No ☐ N/A

Comment/Recommendation:

To applicant: Remove "barcode" placeholder and replace it with the actual barcode.

Applicant's response: The Applicant removed the barcode placeholder and replaced it with the actual barcode.

OBP Labeling: The applicant's revision is acceptable.

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Not required since this is considered a partial label.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Not required since this is considered a partial label.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Storage information will not be requested because of the size of the label.

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Include the finished dosage form on the principal display panel below the proper name as follows:

Yuflyma
(adalimumab-aaty)
Injection
40 mg/0.4 mL

Additionally, consider relocating the strength so it does not appear next to proprietary name.

Applicant's response: The Applicant revised the statements to appear as requested.

OBP Labeling: The applicant's revisions are acceptable.

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Revise the manufacturer statement to appear with the same information as in boxes 2-5 Form FDA 356h:

Manufactured by: CELLTRION, Inc.

Xxxxx

xxxxxx

US License No. 1996

Please ensure the name of the manufacturer appears exactly as represented on FDA Form 356h, box 2. Also refer to 21 CFR 600.3(t) and 610.61(b).

Applicant's response: The Applicant confirmed that the name and address of manufacturer in FDA Form 356h are correct information, and the Applicant revised the manufacturer statement to appear with the same information as Form FDA 356h.

OBP Labeling: The applicant's revision is acceptable.

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent

the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

Applicant's response: The Applicant intends to use the format for the expiration date in YYYY MM on the labeling.

OBP Labeling: The applicant's response is acceptable.

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The preservative text follows the reference product.

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise the number of containers/net quantity statement "(b) (4) " on the multiple counts of prefilled syringes or auto-injectors to display the number of units contained in a carton (i.e., 2, 4 or 6) (e.g., to read 6 Single-dose Prefilled Syringes)

Applicant's response: The Applicant revised the statement to display for the number of containers for multiple counts of each device as requested.

OBP Labeling: The applicant's revisions are acceptable.

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

USP General Chapters: <7> Labeling	

Comment/Recommendation:
Refer to the comments to the applicant under the "proper name (package labeling)" evaluation above.

Applicant's response: The Applicant revised the location of the product strength as requested.

OBP Labeling: The applicant's revision is acceptable.

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Recommend revising the storage statement to read:
Store in refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light until time of administration. If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for up to 30 days with protection from light.

In addition, in the space an individual is to record the date the syringe or pen is removed from refrigeration consider adding a statements similar to "Pen 1: ____/_____/_____", Pen 2: ____/_____/_____" etc… or "Syringe 1: ____/_____/_____" Syringe 2: ____/_____/_____" etc… based upon the number of syringes or pens that are supplied in a carton.

Applicant's response: The Applicant revised the storage statement to read as requested and implemented the space an individual is to record the date in relation to the storage statement as requested.

OBP Labeling: The applicant's revisions are acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Add the statement "Do not Shake." Directly following the statement "Do not Freeze". Consider using a combination of capital and lower-case lettering to improve the readability.

Applicant's response: The Applicant included a "Do not shake" statement as requested.

OBP Labeling: The applicant's revision is acceptable.

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
OBP quality confirmed that the container closure system is not made with dry natural rubber or natural rubber latex.

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: We note your formulation contains the (b) (4) sodium acetate (b) (4) The USP monograph for sodium acetate states sodium acetate amount is calculated on the anhydrous basis. Thus, the name and quantity of sodium acetate (b) (4) should be presented as sodium acetate (0.24 mg).

Recommend the inactive ingredients are listed in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients to read as follows:

Each 40 mg/0.4 mL single-dose (use the package type that applies, Prefilled Syringe or Auto-injector) contains:

Adalimumab-xxxx..... 40 mg
Acetic acid.....0.06 mg
Glycine.....7.51 mg
Polysorbate 80.....0.40 mg
Sodium acetate .....0.24 mg
and Water for Injection, USP

Applicant's response: The Applicant revised the ingredient information as requested.

OBP Labeling: The applicant's revision is acceptable.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment: Need to assess.

Comment/Recommendation:
Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for adalimumab products (i.e., there is no specific test method described in regulation for adalimumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for this product because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

To applicant: Remove the statement "No U.S. standard of potency" from the carton labeling. Although this statement appears on the carton labeling of the reference product, Humira, our current thinking is that 21 CFR 610.61(r) is not applicable, and thus no statement is required for your product's carton labeling.

Applicant's response: The Applicant removed the statement "No U.S. standard of potency" from the carton labeling.

OBP Labeling: The applicant's revision is acceptable.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	✓ Yes ☐ No ☐ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Remove "barcode" placeholder and replace it with the actual barcode. Applicant's response: The Applicant removed the barcode placeholder and replaced it with the actual barcode. OBP Labeling: The applicant's revision is acceptable.

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No

	☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise the statement of contents from "(b) (4)" to read similar to "Each carton contains xx single-dose (use the package type that applies, Prefilled Syringe(s)/Auto-injector(s)), x alcohol preps, 1 Medication Guide, 1 Prescribing Information, and 1 Instructions for Use"

Applicant's response: The Applicant revised the statement of contents as requested.

OBP Labeling: The applicant's revision is acceptable.
There are no misleading statements.

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise the number of containers/net quantity statement "(b) (4) r" on the multiple counts of prefilled syringes or auto-injectors to display the number of units contained in a carton (i.e., 2, 4 or 6) (e.g., 6 Single-dose Prefilled Syringes)

Applicant's response: The Applicant revised the net quantity statement as requested.

OBP Labeling: The applicant's revisions are acceptable.

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes

	☐ No ☐ N/A

Comment/Recommendation:

To applicant: For consistency, revise the [redacted](b) (4)" statement to "Recommended Dosage: See prescribing information."

Applicant's response: The Applicant revised the statement of dosage statement as requested.

OBP Labeling: The applicant's revision is acceptable.

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Per 21 CFR 208.24(d) and 21 CFR 610.60(a)(7) include the following statement of the principal display panel: "ATTENTION: Dispense the enclosed Medication Guide to each patient."

Applicant's response: The Applicant included a Medication Guide statement as requested.

OBP Labeling: The applicant's revision is acceptable.

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and	✓ Yes ☐ No ☐ N/A

Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revised to be in alignment with the most recently approved HUMIRA labeling.

Applicant's response: The Applicant revised as requested.

OBP Labeling: The applicant's revision is acceptable.

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A

Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
A "Do not shake" statement was inserted to subsection 2.8 General Considerations for Administration.
To applicant: A sentence to prevent shaking was inserted to align with the instruction for use messaging.

Applicant's response: The Applicant has inserted a "Do not shake" statement as requested.

OBP Labeling: The applicant's revision is acceptable.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The identifying characteristics of the drug product as a clear to opalescent, and colorless to pale brown solution were confirmed.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The quality information concerning the drug substance and the drug product was confirmed, except the applicant did not include the correct identifying characteristics of the drug product or include sodium acetate (b) (4) as an inactive ingredient. Comments concerning these two issues were sent to the applicant.

To Applicant: Updated to include the identifying characteristics of Yuflyma.

To Applicant: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, acetic acid, glycine, polysorbate 80, and sodium acetate.

We note your formulation contains (b) (4) sodium acetate (b) (4) The USP monograph for sodium acetate states sodium acetate amount is calculated on the anhydrous basis. Thus, the name and quantity of sodium acetate (b) (4) should be presented as sodium acetate (0.24 mg). (b) (4) was included in the Description section.

Provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to the Table that includes the calculation between mg of sodium acetate (b) (4) and mg of sodium acetate anhydrous (labeled as sodium acetate). The footnote should serve as a link between the name and quantity presented in section 3.2.P.1 (i.e., sodium acetate (b) (4)) to the name and quantity presented in the Prescribing Information and carton labeling (i.e., sodium acetate).

Lastly, inactive ingredients names have been revised to appear in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients

Applicant's response: The Applicant has updated to include the identifying characteristics of Yuflyma as requested.

The Applicant has revised the inactive ingredients list to include (b) (4) "sodium acetate (0.24 mg)" and updated Description and Composition Table in section 3.2.P.1 adding a footnote as requested.

OBP Labeling: The applicant's revision is acceptable.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*	☐ Yes ☐ No ☒ N/A

Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	☐ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	☐ Yes ☐ No ☐ N/A

Comment/Recommendation:
The storage and handling information were confirmed to be accurate by OBP quality and OPMA, except the applicant needed to include a "Do not shake" statement to prevent shaking of the drug product. A comment concerning the issue was sent to the applicant.

CDRH confirmed the exposure of the device to 30 days at room temperature was acceptable from a device/functionality perspective.

To Applicant: A sentence to prevent shaking was inserted to align with the instruction for use directions. (Do not shake)

Applicant's response: The Applicant has added "DO NOT FREEZE." Statement as requested.

OBP Labeling: The applicant's revision is acceptable.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Revised to include the qualifying phrase "Manufactured by;" and the corporate name presentation should be consistent with Form FDA 365h box 2. Thus a comma was inserted in the name "CELLTRION,Inc.".

Applicant's response: The Applicant has inserted a comma in the manufacturer name as requested.

OBP Labeling: The applicant's revision is acceptable.

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revised to include ingredient "sodium acetate" because it is in your formulation.

Applicant's response: The Applicant revised to include "sodium acetate" as requested.

OBP Labeling: The applicant's revision is acceptable.

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Note that the licensed manufacturer listed should be presented exactly as listed on the 356(h) form. Therefore, included a "comma" between "CELLTRION" and "Inc.".

Applicant's response: The Applicant has revised manufacturer information including a comma between "CELLTRION" and "Inc." as requested.

OBP Labeling: The applicant's revision is acceptable.

Patient Information Labeling Evaluation N/A

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
OBP Labeling: IFU title is acceptable as it's structured same as Humira IFU.

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**

Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *21 CFR 610.61 (add the US license number for consistency with the carton labeling),* *21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Please ensure the manufacturer information listed at the end of each piece of labeling.

Applicant's response: The Applicant has listed the manufacturer information at the end of each piece of labeling.

OBP Labeling: The applicant's revision is acceptable.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information, Medication Guide, and Instructions for Use (submitted on May 19, 2023)
  \\CDSESUB1\EVSPROD\bla761219\0071\m1\us\draft-labeling-text-clean.docx

- Container Labels for prefilled autoinjector (submitted on April 17, 2023)

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

Liming Lu

Digitally signed by Liming Lu
Date: 5/22/2023 08:17:26AM
GUID: 633d82d0001fb9cd8535e78c71271f3d

Yun Wu

Digitally signed by Yun Wu
Date: 5/22/2023 08:48:34AM
GUID: 5c7ebb5f0003cbdad081c0a0e3d728c4

BLA Executive Summary
Assessment Date: May 1, 2023

1. Application/Product Information

BLA number	761219
Submission Type	Resubmission (Third Round Review Cycle)
Regulatory Pathway	Biosimilar 351(k)
Associated IND/BLA	IND 135944
Review Designation	Standard Review
Applicant	CELLTRION, Inc.
Indication	Indications currently approved for US-licensed Humira (40 mg/0.4 mL strength): Rheumatoid Arthritis (RA), Juvenile Idopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), adult Crohn's Disease (CD), pediatric Crohn's Disease (pCD), Plaque Psoriasis (PsO), and Hidradenitis Suppurativa (HS)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Yuflyma
	Non-proprietary Name/Code Name: adalimumab-aaty
	OBP Naming: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [CTP17]
Drug Product Description	Sterile, preservative-free, clear to opalescent, colorless to pale brown solution supplied in a single-dose PFS, PFS-S or AI containing 100 mg/mL adalimumab-aaty, 10 mM sodium acetate, 250 mM glycine, 0.10% polysorbate 80, pH 5.2. Adalimumab-aaty is a therapeutic recombinant human monoclonal antibody.

Dosage Form	Liquid		
Strength	40 mg/0.4 mL (100 mg/mL)		
Route of Administration	Subcutaneous		
Primary Container Closure System	Pre-filled Syringe		
Device Information	Needle-safety guard and autoinjector		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance Drug product	Yun Wu/Cindy Osborn	Willie Wilson
	Comparative Analytical Assessment (CAA)	Cindy Osborn	Willie Wilson
	Immunogenicity Assay	Cindy Osborn	Willie Wilson
	Facility Microbiology	Lindsey Brown	Maxwell Van Tassell
	RBPM	Anh-Thy Ly	N/A
	ATL	Willie Wilson	
OPQ Issued Consults	CDRH/ODE and OC		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761219 for Yuflyma (adalimumab-aaty) manufactured by Celltrion, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Yuflyma (adalimumab-aaty) is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Yuflyma (adalimumab-aaty) is highly similar to US-licensed Humira (adalimumab), notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter
a. Manufacturing Location:
- **Drug Substance:** CELLTRION, Inc., Plant (b) (4) 20 Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, 22014, Republic of Korea; FEI: 3005241015
- **Drug Product:** (b) (4)

b. Fill size and dosage form:
Yuflyma is supplied as a 40 mg/0.4 mL (100 mg/mL) solution in a single dose prefilled syringe (PFS), PFS assembled with a needle safety guard (PFS-S) and autoinjector (AI).

c. Dating Period:
- **Drug Product:** 30 months at 5 ± 3°C, protected from light. This dating period may include storage at room temperature up to a maximum of 77°F (25°C) for a period up to 30 days, protected from light.
- **Drug Substance:** (b) (4)
- **For packaged products:** Not packaged
- **Stability Option:**
  - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:
- Yes
- Rationale, if exempted: Yuflyma is exempted from lot release per FR 95-29960.

4. Basis for Recommendation
a. Summary:
Yuflyma (adalimumab-aaty, CT-P17) is a recombinant human IgG1 monoclonal antibody developed as a biosimilar to US-licensed Humira

(adalimumab). Adalimumab-aaty binds to the cytokine, human tumor necrosis factor α (TNFα). The binding of adalimumab to TNFα prevents its interaction with cell surface TNF receptors (TNFR1 and TNFRII). The binding of adalimumab to soluble TNFα facilitates suppression of pro-inflammatory activities. The binding of adalimumab to transmembrane TNFα may facilitate reverse signaling, antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Adalimumab-aaty drug product is manufactured to have the same strength, dosage form and route of administration as the 40 mg/0.4 mL strength of US-licensed Humira in a single-dose prefilled syringe (PFS) and PFS assembled with an autoinjector (AI). Yuflyma is a sterile, preservative-free, clear and colorless to pale brown solution for subcutaneous injection supplied in single-dose PFS, PFS assembled with a needle-safety guard (PFS-S) and AI containing adalimumab-aaty at 40 mg/0.4 mL.

TNFα is a cytokine produced mainly by macrophages which has both immunostimulatory and immunosuppressive effects. Elevated levels of TNFα are associated with the pathologic inflammation and joint destruction in patients with rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis ankylosing spondylitis and psoriasis plaques. Adalimumab can suppress TNFα-induced pro-inflammatory activities by binding to soluble TNFα and blocking its interaction with cell surface TNF receptors (p55/TNFRI and p75/TNFRII). Adalimumab may also bind to transmembrane TNFα (tmTNFα) which can facilitate inhibition of tmTNFα-mediated effector function, induction of regulatory macrophages by FcγR crosslinking and destruction of TNFα-bearing cells by antibody-dependent cellular cytotoxicity (ADCC), reverse signaling and complement-dependent cytotoxicity.

Potency of CT-P17 is assessed using a quantitative cell-based hTNFα neutralization assay which utilizes hTNFα and the TNF-sensitive mouse sarcoma cell line, WEHI164. Serial dilutions of CT-P17 test articles and reference standard, in addition to hTNFα, are added to 96-well plates containing WEHI164 cells. Upon incubation, cellular metabolic activity is measured as an indicator of cell viability using a colorimetric method (absorbance at 450 nm and 650 nm). The 4-paramter logistic curves of the reference standard and test article are fitted with 10 concentration points and optical density values. The relative potency of test articles is measured by its ability to bind hTNFα and neutralize TNFα-mediated cytotoxicity relative to the CT-P17 reference standard.

Potency of CT-P17 is also assessed by a surface plasmon resonance (SPR) assay that utilizes FcγRIIIa ligand immobilized on a CM5 chip via amine coupling reaction. The method evaluates the relative binding affinity of the Fc region of CT-P17 test articles to the immobilized FcγRIIIa ligand in comparison with the reference standard. Binding affinity is measured in response units and the equilibrium association (dissociation/KD) constants are calculated based on a fitted model of the response curves.

The totality of the comparative analytical evidence supports that CT-P17 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. The three-way pairwise comparison of CT-P17, US-licensed Humira and EU-approved Humira support the establishment of the analytical component of the scientific bridge and to support the relevance of the data generated from clinical studies using EU-approved Humira as the comparator to the assessment of biosimilarity. The strength of 40 mg/0.4 mL CT-P17 in a single-dose PFS, PFS-S, and AI demonstrated the same strength as that as that of US-licensed Humira. Refer to Appendix for a detailed summary of the comparative analytical assessment.

CT-P17 DS is manufactured at Celltrion, Inc., Plant (b) (4), Incheon, Republic of Korea. (b) (4)

CT-P17 DP is manufactured, assembled, labeled, and packaged (b) (4)

Refer to the Complete Response Letters dated 11/24/2021 and 11/23/2022 for a description of the multiple objectionable observations identified during the pre-license inspection (PLI) and surveillance inspection of the drug product facility. During the current resubmission review cycle, a 704 (a) document review was conducted to assess corrective actions for multiple observations identified during the PLI and surveillance inspections. The corrective actions to address product specific observations were adequate.

The overall Yuflyma control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Yuflyma are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

Results from the ongoing leachables study for CT-P17 drug product pre-filled syringes stored under long-term (5 ± 3°C) and accelerated (25 ± 2°C, 60 ± 5% RH) conditions were available during the current review cycle through 24 months and 3 months, respectively, which indicate that the presence of leachates from the CT-P17 commercial container closure system does not pose a risk to safety or product quality. No significant increasing trends in leachates were observed during long-term storage through 24 months and the risk of any leachable exceeding a toxicological safety threshold at the 30-month shelf-life is low.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
CAA	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for Yuflyma (adalimumab-aaty) (i.e., there is no specific test method described in regulation for Yuflyma (adalimumab-aaty) that establishes an official standard of potency). We next considered whether potency is a factor for Yuflyma (adalimumab-aaty) within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Yuflyma (adalimumab-aaty) for purposes of § 610.61(r) because lot variability is not a concern for Yuflyma (adalimumab-aaty) as Yuflyma's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps:

None

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

- Stability (requalification) protocol for master cell bank and working cell bank
- Concurrent lifetime validation protocol for (b) (4)
- Concurrent lifetime validation protocol for (b) (4)

- Reprocessing validation protocol for (b) (4)
- Stability (requalification) protocol for current reference standards
- Post-approval annual stability protocol for drug substance with shelf-life extension

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

- Protocols approved:
  - Post-approval annual stability protocol for drug product with shelf-life extension
- Residual risk: None
- Future inspection points to consider:
  - Multiple deviations with regards to document handling, facility maintenance, and equipment maintenance should be evaluated during a future inspection.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

CELLTRION, Inc. (Celltrion) is seeking licensure for CT-P17 as a biosimilar to US-licensed Humira for the 40 mg/0.4 mL strength in a single-use pre-filled syringe (PFS), PFS + autoinjector (AI), and PFS assembled with a needle-safety guard (PFS-S). Celltrion performed a three-way pairwise comparative analytical assessment (CAA) to establish the analytical component of the scientific bridge among 10 lots of US-licensed Humira (40 mg/0.4 mL), 10 lots of EU-approved Humira (40 mg/0.4 mL) and 10 lots of CT-P17. The CT-P17 lots evaluated included four drug substance (DS) lots manufactured at Celltrion Plant (b) (4) using commercial Process D, three drug product (DP) lots manufactured at (b) (4) using clinical Process 3, and three process validation DP lots manufactured at the same DP site using commercial Process 4. All CT-P17 DP lots included in the CAA were independent of the DS lots evaluated. CT-P17 (Lot CTP17CLN001 and CTP17CLN003), US-licensed Humira (Lot 1104991), and EU-approved Humira (Lot 88407XH07, 91436XH11, 93460XH06 and 02005LX04) were administered during CT-P17 clinical development and were among the lots evaluated in the CAA. The CAA included the following analyses to support a demonstration that CT-P17 is highly similar to US-licensed Humira and to establish the analytical component of the scientific bridge:

Extensive comparative physicochemical and functional assessment of quality attributes. Additional comparative assessment to evaluate the correlation between glycosylation and biological activities, and to evaluate the mechanism of action in different cell types to support extrapolation to other indications (including Inflammatory Bowel Disease). Comparative assessments of the degradation profiles under forced degradation conditions.

Celltrion used a risk-based approach for the statistical evaluation of the analytical results: Very high risk-ranked quality attributes were tested using quantitative assays and were evaluated against the quality range (i.e., denoted QR2) determined by US-licensed Humira or EU-approved Humira mean ± a standard deviation multiplier of 2. Comparative analytical similarity was demonstrated if ≥ 90% of the CT-P17 lots were within the QR2. High and moderate risk-ranked quality attributes were tested using quantitative assays and were evaluated against the quality range (i.e., denoted QR3) determined by US-licensed Humira or EU-approved Humira mean ± a standard deviation multiplier of 3. Comparative analytical similarity was demonstrated if ≥ 90% of the CT-P17 lots were within the QR3. Low and very low risk-ranked quality attributes were tested using quantitative and qualitative assays and were evaluated by raw data visual comparison (i.e., denoted RD) without statistical analysis. All analytical methods used during the CAA were performed at CELLTRION Inc. R&D laboratories, (Incheon, South Korea). Results from method validation, qualification and verification studies were provided and adequately support the suitability of each method for its intended use during the CAA.

Based on our assessment of the CAA data, the results support a demonstration that CT-P17 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. Celltrion used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of CT-P17, and US-licensed Humira to

support a demonstration that CT-P17 is highly similar to US-licensed Humira. The number and type of lots tested and data analysis methods were appropriate to allow for a meaningful evaluation of the results of the CAA. While differences were observed in a limited number of attributes, these do not preclude a demonstration that CT-P17 and US-licensed Humira are highly similar. Refer to Section E – Same Strength(s) below for addition comments regarding the comparison of strength, dosage form and route of administration between CT-P17 and US-licensed Humira.

Celltrion also provided a comparison of stability studies under forced degradation conditions of thermal stress (50°C), oxidative stress (0.01% H_2O_2), photo stress (25 w/m2.hr; 25°C and 15 w/m2; 25°C) and high pH (pH 10). The comparative forced degradation studies support a demonstration of similar degradation profiles among the CT-P17, US-licensed Humira and EU-approved Humira lots.

In addition, the three-way pairwise comparisons of CT-P17, US-licensed Humira and EU-approved Humira were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU-approved Humira as the comparator to the assessment of biosimilarity. Celltrion supported the establishment of the analytical component of the scientific bridge using the same methods and statistical approaches used to support the demonstration that CT-P17 is highly similar to US-licensed Humira. Based on review of the data, we conclude that the analytical component of the scientific bridge was established.

B. Results of the Comparative Analytical Assessment

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure	Molecular mass (reduced/non-reduced)	Yes	Yes
	N-terminal sequence	Yes	Yes
	C-terminal sequence	Yes	Yes
	Amino acid sequence coverage	Yes	Yes
Post-translational	Oxidation	Yes	Yes

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Modifications	Deamidation	Yes	Yes
	Glycation	Yes	Yes
	N-terminal glutamine	Yes	Yes
	C-terminal variants	Yes	Yes
	Oligosaccharide profile	Yes	Yes
	N-linked glycan analysis	Yes	Yes
	Aglycosylated heavy chain	Yes	Yes
Higher Order Structure	Secondary structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Protein folding	Yes	Yes
	Thermal stability	Yes	Yes
	Disulfide bond	Yes	Yes
	Free thiols	Yes	Yes
Purity and Product-related Variants or Impurities	Charge heterogeneity	Yes	Yes
	Isoelectric point	Yes	Yes
	High molecular weight (HMW) species - Aggregation	Yes	Yes
	Low molecular weight (LMW) species - Fragmentation	Yes	Yes
Fab-mediated Bioactivity	Neutralization by soluble TNFa (sTNFα) binding	Yes	Yes
	sTNFα binding	Yes	Yes
	Transmembrane TNFa (mTNFα) binding	Yes	Yes

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	Apoptosis (reverse signaling)	Yes	Yes
Fc-mediated Bioactivity	ADCC	Yes	Yes
	CDC	Yes	Yes
	C1q binding	Yes	Yes
	FcγRIIIa binding	Yes	Yes
	FcγRIIIb binding	Yes	Yes
	FcγRIIa binding	Yes	Yes
	FcγRIIb binding	Yes	Yes
	FcγRI binding	Yes	Yes
	FcRn binding	Yes	Yes
Impact of Aglycosylation, Agalactosylation and Amannosylation on Bioactivity	FcγRIIIa binding	Yes	Yes
	FcRn binding	Yes	Yes
	CDC	Yes	Yes
	ADCC	Yes	Yes
	Neutralization by sTNFa binding	Yes	Yes
Additional Bioactivity Studies to Support Extrapolation to other Indications	Inhibition of TNFa-induced apoptosis (HCT116 cells)	Yes	Yes
	Inhibition of TNFa-induced IL-8 release (HCT116 cells)	Yes	Yes
	Inhibition of TNFa-induced VCAM-1 release (HUVEC cells)	Yes	Yes
	Regulatory macrophage induction	Yes	Yes
	$LT_{\alpha 3}$ binding	Yes	Yes
Drug Product Attributes	Protein concentration	Yes	Yes
	Extractable volume	Yes	Yes

Comparative assessment of the forced degradation stability studies was performed to evaluate potential differences in the degradation profiles across the CT-P17, US-licensed Humira, and EU-approved Humira lots when stored under thermal stress (50°C), oxidative stress (0.01% H_2O_2), photo stress (25 w/m^2.hr; 25°C and 15 w/m^2; 25°C) and high pH (pH 10). Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

C. Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

The clinical development of CT-P17 included three clinical studies:

- Study CT-P17 1.1 (PK similarity study): A randomized, multi-center, double-blind, three-arm, parallel group, single-dose, active comparator study designed to evaluate PK similarity between CT-P17, EU-Humira and US-Humira by PFS injection in healthy male and female subjects.
- Study CT-P17 1.2 (pilot study): A randomized, double-blind, two-arm, parallel-group, single-dose, active comparator study designed to evaluate the safety and PK of the CT-P17 and EU-Humira by PFS injection in 30 healthy male subjects.
- Study CT-P17 3.1 (comparative clinical study): A randomized, active-controlled, double-blind, multicenter study designed to evaluate efficacy, PK, PD, usability, overall safety and immunogenicity of multiple single-doses (40 mg) of either CT-P17 or EU-Humira administered by SC injection via PFS in combination with MTX in patients with moderate to severe active RA.

To support the relevance of the comparative clinical data (Study CT-P17 3.1) generated using EU-approved Humira as a comparator product to the assessment of biosimilarity, Celltrion performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way, pairwise PK similarity study (CT-P17 1.1). To support the establishment of the analytical component of the scientific bridge, Celltrion included comparison of CT-P17 to US-licensed Humira, CT-P17 to EU-approved Humira, and EU-approved Humira to US-licensed Humira. The same analytical methods used for supporting a demonstration that CT-P17 is highly similar to US-licensed Humira were used for the pairwise analytical comparisons with EU-approved Humira. The differences observed in the comparative analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See Section D below. The results support the establishment of the analytical component of the scientific bridge.

D. Assessment of Comparative Analytical Study Results

Quantitative Assessment of Analytical Study Results

All quality attributes evaluated against the QR2 and QR3 quality ranges met the comparative analytical acceptance criteria, except for the following:

1. Size Variants (Monomer, HMW and LMW): The US-licensed Humira QR3 for size variants measured by SEC-HPLC is 99.776-99.122% monomer, 0.148-0.746% HMW, and 0.064-0.146% LMW. This QR3 was slightly exceeded for monomer (98.99-99.03% in 2

out of 10 CT-P17 lots), HMW (0.80-0.87% in 3 out of 10 CT-P17 lots) and LMW (0.05-0.06% in 4 out of 10 CT-P17 lots). Three out of the 10 EU-approved Humira lots showed LMW results (0.15-0.18%) that slightly exceeded the US-licensed Humira QR3 (0.064-0.146%). The EU-approved Humira QR3 (i.e., 99.303-99.561% monomer, 0.352-0.506% HMW) was slightly exceeded for monomer (98.99-99.23% in 8 out of 10 CT-P17 lots) and HMW (0.59-0.87% in 9 out of 10 CT-P17 lots). The magnitude by which the US-licensed Humira and EU-approved Humira QR3 was exceeded (< 1%) is minor and is not anticipated to impact safety, efficacy or immunogenicity. Overall, the observed differences in SEC-HPLC results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

2. Size Variants (NGHC and H+L): Reduced CE-SDS analysis of all ten of the CT-P17 lots showed results for NGHC (0.59-0.72%) and H+L purity (99.17-99.32%) that slightly exceeded the US-licensed Humira QR3 (i.e., 0.893-1.143% NGHC; 98.683- 98.953% H+L). The NGHC and H+L results for each CT-P17 lot also exceeded the EU-approved Humira QR3 (i.e., 0.786-1.112% NGHC; 98.744-99.062% H+L). Two out of 10 (20%) EU-approved Humira lots showed 0.84-0.87% NGHC and 98.97-99.02% H+L results that slightly exceeded the US-licensed Humira QR3. The magnitude (<1.0%) by which the US-licensed Humira and EU-approved Humira QR3 was exceeded is minor and is not anticipated to impact safety, efficacy or immunogenicity. Differences in NGHC have the potential to impact N-linked glycan profile and subsequent Fc-mediated bioactivity. However, the observed differences in NGHC did not result in any differences in the downstream Fc-mediated bioactivity quality attributes described in Table A above. Overall, the observed differences in reduced CE-SDS results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

3. Charge Variants (Acidic Group, Main Peak and Basic Group 2): The US-licensed Humira QR3 for charge variants measured by IEC-HPLC is 11.936-16.464% acidic group, 60.447-69.423% main peak and 0.088-1.406% basic group 2. This QR3 was exceeded for acidic group (9.22-9.58% in 7 out of 10 CT-P17 lots), main peak (68.47-70.34% in 7 out of 10 CT-P17 lots) and basic group 2 (1.42-1.74% in 9 out of 10 CT-P17 lots). Seven out of the ten CT-P17 lots showed main peak results (69.67-70.70%) that exceeded the EU-approved Humira QR3 (58.565-69.051%). The acidic group (9.22-12.43%) and basic group 2 (1.32-1.74%) results for all ten CT-P17 lots exceeded the EU-approved Humira QR3 (13.007-16.496% acidic group; 0.752-1.184% basic group 2). The acidic group contains heavy chain deamidation at Asn329 (Fc region) and a heavy chain C-terminal variant at Lys451. Basic group 2 contains a cleaved N-terminal heavy chain variant at Gly08. IEC-HPLC characterization studies show that the enrichment of basic group 2 up to 33% is needed to show an impact on TNFα neutralization (84% relative potency), CDC (52% relative potency) and FcRn binding (no result due to abnormal sensorgram). Enrichment of the acidic group up to ~80% is needed to show a significant impact on biological activity (FcγRIIIa binding, FcRn binding, hTNFα neutralization and CDC). Therefore, the magnitude by which the IEC-HPLC results exceeded the US-licensed Humira and EU-approved Humira QR3 for acidic group (< 3.8%), main peak (< 1.65%) and basic group 2 (< 1%) is minor and did not result in

any difference in the Fab- and Fc-related biological activities described in Table A above. The magnitude by which the IEC-HPLC results exceeded the QR3 is also not anticipated to impact safety, PK or immunogenicity. Overall, the observed differences in IEC-HPLC results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

4. Oligosaccharide Profiling: The oligosaccharide profile analysis included the evaluation of potential differences in fucosylated (G0F+G1F+G2F), high mannose (Man5+Man6), afucosylated (G0-GN+G0) and total afucosylated (G0-GN+G0+Man5+Man6) glycan groups. The US-licensed Humira QR3 for oligosaccharide profile is 84.237-87.869% fucosylated glycans, 4.972-7.296% high mannose and 5.966-8.462% total afucosylated glycans. Five out of 10 CT-P17 lots showed 88.05-89.56% fucosylated glycans which slightly exceeded the US-licensed Humira QR3. All CT-P17 lots showed high mannose (2.83-4.72%) and afucosylated (2.98-3.47%) glycan results that exceeded the US-licensed Humira QR3. The EU-approved Humira lots that exceeded the US-licensed Humira QR3 showed results for fucosylated gylcans (83.19-84.18% in 6 out of 10 lots), high mannose (7.33-7.54% in 3 out of 10 lots) and total fucosylated glycans (8.51-8.73% in 3 out of 10 lots). Six out of the 10 CT-P17 lots showed 87.83-89.56% fucosylated glycans which exceeded the EU-approved Humira QR3 (80.871-87.829% fucosylated glycans). All CT-P17 lots also showed high mannose (2.83-4.72%) and afucosylated glycans (2.98-3.47%) which exceeded the EU-approved Humira QR3 (5.047-8.783% high mannose; 1.005-1.331% afucosylated). Overall, the US-licensed Humira and EU-approved Humira QR3 was exceeded by the CT-P17 lots by a maximum of 1.69% (fucosylated glycans), 2.21% (high mannose), 2.26% (afucosylated glycans) and 0.27% (total afucosylated glycans).

   Changes to the levels of high mannose glycans can influence the serum half-life in-vivo. High levels of afucosylated glycans (including high mannose) have also been reported to impact Fc-effector function (e.g., ADCC). The observed differences in high mannose, afucosylated and fucosylated glycans during the CAA did not result in differences in the Fc-mediate bioactivity quality attributes described in Table A. Overall, the magnitude by which the US-licensed Humira and EU-approved adalimumab QR3 for the oligosaccharide profile was exceeded is minor and is not anticipated to impact safety, PK, efficacy or immunogenicity. The observed differences in oligosaccharide profiling results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge. Additionally, we conferred with the clinical pharmacology reviewers, and the PK data are consistent with these conclusions.

E. Same Strength(s)

CT-P17 has the same dosage form and route of administration as US-licensed Humira. Celltrion is seeking licensure of 40 mg/0.4 mL CT-P17 in a single-use PFS, AI and PFS-S. US-licensed Humira is available at this strength (40 mg/0.4 mL) in a single-use PFS and AI. Celltrion is seeking approval of CT-P17 for the same strength as U.S.-licensed Humira. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed (b) (4)

(b) (4) The proposed presentations of CT-P17 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Humira (40 mg/0.4 mL). The strength of CT-P17 PFS, AI and PFS-S is the same as that of US-licensed Humira.

APPEARS THIS WAY ON ORIGINAL

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/s/

WILLIE N WILSON
05/01/2023 03:57:19 PM

Biosimilar to US-licensed Humira

Recommendation: Complete Response

EXECUTIVE SUMMARY

BLA 761219
Review Number: Second Round
Review Date: November 3, 2022

Drug Name/Dosage Form	Yuflyma (adalimumab-aaty) injection, for subcutaneous use
Strength/Potency	40 mg/0.4 mL (100 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Indications currently approved for US-licensed Humira (40 mg/0.4 mL strength): Rheumatoid Arthritis (RA), Juvenile Idopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), adult Crohn's Disease (CD), pediatric Crohn's Disease (pCD), and Plaque Psoriasis (PsO)
Applicant/Sponsor	CELLTRION, Inc.

Product Overview

Yuflyma (adalimumab-aaty, CT-P17) is a recombinant human IgG1 monoclonal antibody developed as a biosimilar to US-licensed Humira (adalimumab). Adalimumab-aaty binds to the cytokine, human tumor necrosis factor α (TNFα). The binding of adalimumab to TNFα prevents its interaction with cell surface TNF receptors (TNFR1 and TNFRII). The binding of adalimumab to soluble TNFα facilitates suppression of pro-inflammatory activities. The binding of adalimumab to transmembrane TNFα may facilitate reverse signaling, antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Adalimumab-aaty drug product is manufactured to have the same strength, dosage form and route of administration as the 40 mg/0.4 mL strength of US-licensed Humira in a single-dose prefilled syringe (PFS) and PFS assembled with an autoinjector (AI). Yuflyma is a sterile, preservative-free, clear and colorless to pale brown solution for subcutaneous injection supplied in single-dose PFS, PFS assembled with a needle-safety guard (PFS-S) and AI containing adalimumab-aaty at 40 mg/0.4 mL.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance/Drug Product/Immunogenicity	Yun Wu	OBP/DBRR1
Comparative Analytical Assessment	Yun Wu	OBP/DBRR1
OBP Labeling	Scott Dallas	OBP/IO
Drug Product Microbiology/Facilities	Lindsey Brown	OPMA/DBM
Facilities Assessment Lead	Zhong Li	OPMA/DBM
Microbiology Quality Assessment Lead	Maxwell Van Tassell	OPMA/DBM

CMC RBPM	Anh-Thy Ly	OPRO/DRBPM1
Application Technical Lead	Willie Wilson	OBP/DBRR1
OBP Review Chief	Qing Zhou	OBP/DBRR1
OBP Biosimilar Program and Policy	Marlene Schultz-DePalo	OBP/IO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Sadaf Nabavian	ORO/DROII
Signatory Authority	Nikolay Nikolov	OII/DRTM
Cross-disciplinary Team Lead	Anil Rajpal	OII/DRTM
Clinical Reviewer	Keith Hull	OII/DRTM
Nonclinical	Anup Srivastava/Carol Galvis	OII/DPTII
Clinical Pharmacology	Tao Liu/Ping Ji	OCP/DIIP
Biostatistics	Dong-Hyun Ahn/Yongman Kim	OB/DBIII
OSE/DMEPA	Davis Mathew/Nichelle Rashid	OSE/PMS
CDRH Consult	Suzanne Hudak	OHTIII/DHTIIIC

1. Names:
    a. Proprietary name: Yuflyma
    b. Trade name: Yuflyma
    c. Non-proprietary name: adalimumab-aaty
    d. CAS registry number: 331731-18-1
    e. Common name: CT-P17
    f. INN Name: adalimumab
    g. USAN Name: adalimumab
    h. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [CTP17]

2. Pharmacologic category: Therapeutic recombinant human monoclonal antibody biosimilar.

Submissions Reviewed:

Communication	Date
761219/42 (Resubmission)	5/27/2022
761219/45 Response to OPMA Information Request #1 (Manufacturing Schedule)	6/9/2022
761219/46 Partial Response to OBP Information Request #2	6/17/2022
761219/47 Partial Response to OBP Information Request #2	7/5/2022
761219/48 Response to OPMA Information Request #3	7/14/2022
761219/49 Response to OPMA Information Request #4 (Manufacturing Schedule)	7/15/2022
761219/52 Response to OBP Information Request #5	8/10/2022
761219/53 Response to CDRH Information Request #6	9/2/2022
761219/54 Response to CRL Additional Comment #3 (CDRH)	9/27/2022
761219/55 Response to OBP Information Request #7	10/7/2022

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

   A. DMFs: Refer to the First Round OPQ Executive Summary memo dated 11/22/2021

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.
   None

3. Consults:

Discipline/Topic	Date Requested	Recommendation	Assessor
CDRH/ODE & OC	6/1/2022	Complete Response	Porsche Bennett

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761219 for Yuflyma (adalimumab-aaty) manufactured by Celltrion, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Yuflyma is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

The Division of Biotechnology Manufacturing (DBM), Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ is recommending that a Complete Response letter be issued to Celltrion Inc., to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

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.

Additional CDRH Comment:

1. FDA conducted an inspection of your contract manufacturing organization (CMO), (b) (4) During the inspection, the inspector noted the following observations:

(b) (4)

At the time of your response to this CR letter, we would like an update on the corrections and corrective actions the CMO has taken to address all observations.

C. Approval Action Letter Language:
N/A

D. Benefit/Risk Considerations:
Yuflyma (adalimumab-aaty, CT-P17) is a proposed biosimilar to US-licensed Humira for the same indications as for the 40 mg/0.4 mL strength of US-licensed Humira (i.e., Rheumatoid Arthritis, Juvenile Idopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, adult Crohn's Disease, pediatric Crohn's Disease, and Plaque Psoriasis). CELLTRION performed a three-way pairwise comparative analytical assessment to establish the analytical component of the scientific bridge among US-licensed Humira (40 mg/0.4 mL), EU-approved Humira (40 mg/0.4 mL) and CT-P17. As part of the comparative analytical assessment, the molecular attributes of adalimumab were collectively assigned to appropriate assessment categories and a sufficient number of lots of each product were evaluated. A comprehensive array of analytical methods

was used. Each method was demonstrated to be suitable to detect and/or quantitate potential differences in critical quality attributes among CT-P17, US-licensed Humira and EU-approved Humira. The comparative analytical assessment data provided support the conclusion that Yuflyma is highly similar to US-licensed Humira and the analytical component of the scientific bridge.

The overall control strategy for Yuflyma manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency, and drug substance and drug product that have appropriate quality and are free of adventitious agents. The drug substance facility operates in compliance with cGMP and are acceptable for manufacturing. Multiple objectionable observations were identified during the pre-license inspection (PLI) of the drug product facility that could not be resolved during original BLA review clock (see Complete Response letter dated 11/24/2021). The complete resolution of the objectionable observations identified during the original PLI could not be verified during the BLA resubmission review clock (see Section G). Therefore, a Complete Response letter was issued to Celltrion to outline the deficiencies described in Section B.

E. Environmental Assessment or Claim of Categorical Exclusion:
A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.31(a) was provided and is acceptable.

F. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

N/A

II. Evaluation of the Comparative Analytical Assessment

Refer to the First Round OPQ Executive Summary memo dated 11/22/2021

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management
Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other notes

TNFα Binding Affinity (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.	(b) (4)	N/A
FcγRIIIa (V type) Binding Affinity (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.		CQAs known to impact FcγRIIIa binding affinity (e.g., glycosylation profile) are not likely to be affected by the DP manufacturing process or long-term storage. Therefore, FcγRIIIa binding is not controlled during DP release and stability testing.
Oligosaccharide Profile	Efficacy and Safety/ Immunogenicity	Cell culture manufacturing process. Change is not expected under recommended storage conditions through expiry.		N/A
Identity	Safety and Efficacy	Intrinsic to the molecule.		N/A
High Molecular Weight (HMW) species/ Aggregates (product-related impurities)	Efficacy and Safety/ Immunogenicity	Manufacturing process and exposure to heat and light stress Minimal change is expected during storage under recommended conditions through expiry.		N/A

			(b) (4)	
Low Molecular Weight Species (Fragments) (product-related impurities)	Efficacy	Manufacturing process and exposure to heat and light stress. Minimal increase in fragments is expected during storage under recommended conditions.		N/A
Oxidation of Heavy Chain Fc Region (Met256 and Met432)	Efficacy	Exposure to light and oxidative stress		Met256 and Met432 oxidation is not impacted under process-relevant stress conditions.
N-terminal Heavy Chain Cleavage at Gly8 (product-related impurity)	Efficacy	Exposure to light stress		
Protein Content (mg/mL)	Efficacy	Manufacturing process		N/A

Osmolality	Efficacy	Formulation process	(b) (4)	N/A
Appearance (color and clarity)	Efficacy and Safety	Formulation, contamination, or degradation		N/A
pH	Efficacy and Safety	Formulation process		N/A
(b) (4)	Efficacy and Safety	Intrinsic to (b) (4) DP formulation		N/A

B. Drug Substance [adalimumab-aaty] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

Category (type)	Risk	Origin	Control Strategy	Other notes
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line	(b) (4)	N/A
Host Cell DNA (process-related impurity)	Safety	Production cell line		N/A
(b) (4)	Safety and	Process-related		N/A

Leachate (process-related impurity)	Immunogenicity	impurity leached (b) (4)	(b) (4)	
Residual (b) (4) (process-related impurity)	Safety	Cell culture medium		N/A
Residual (b) (4) (process-related impurity)	Safety, immunogenicity	Cell bank cryopreservation medium or culture medium		(b) (4)
Leachables (process-related impurity)	Safety	Manufacturing components and the DS container closure system		N/A

Microbial Enumeration (Bioburden)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process	(b) (4)	N/A
Bacterial Endotoxins	Safety	Raw materials, manufacturing process		N/A

- Description (adalimumab-aaty):

  Adalimumab-aaty (CT-P17) is a recombinant human IgG1 monoclonal antibody manufactured in CHO cells. CT-P17 is composed of two light chains (214 amino acid residues each) linked by C-terminal disulfide bonds to two heavy chain (451 amino acid residue each). The total molecular weight of CT-P17 is 148 kilodaltons. The amino acid sequence of CT-P17 is identical to US-licensed Humira. The complementarity-determining region of CT-P17 facilitates binding to human tumor necrosis factor α (hTNFα). CT-P17 harbors one N-linked glycosylation site (Asn301) in the CH2 domain of the heavy chain which can facilitates Fc-effector function.

- Mechanism of Action (MoA):

  TNFα is a cytokine produced mainly by macrophages which has both immunostimulatory and immunosuppressive effects. Elevated levels of TNFα are associated with the pathologic inflammation and joint destruction in patients with rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis ankylosing spondylitis and psoriasis plaques. Adalimumab can suppress TNFα-induced pro-inflammatory activities by binding to soluble TNFα and blocking its interaction with cell surface TNF receptors (p55/TNFRI and p75/TNFRII). Adalimumab may also bind to transmembrane TNFα (tmTNFα) which can facilitate inhibition of tmTNFα-mediated effector function, induction of regulatory macrophages by FcγR crosslinking and destruction of TNFα-bearing cells by antibody-dependent cellular cytotoxicity (ADCC), reverse signaling and complement-dependent cytotoxicity.

- Potency Assay:

  In vitro hTNFα Neutralization Assay

  Potency of CT-P17 is assessed using a quantitative cell-based hTNFα neutralization assay which utilizes hTNFα and the TNF-sensitive mouse sarcoma cell line, WEHI164. Serial dilutions of CT-P17 test articles and reference standard, in addition to hTNFα, are added to 96-well plates containing WEHI164 cells. Upon incubation, cellular metabolic activity is

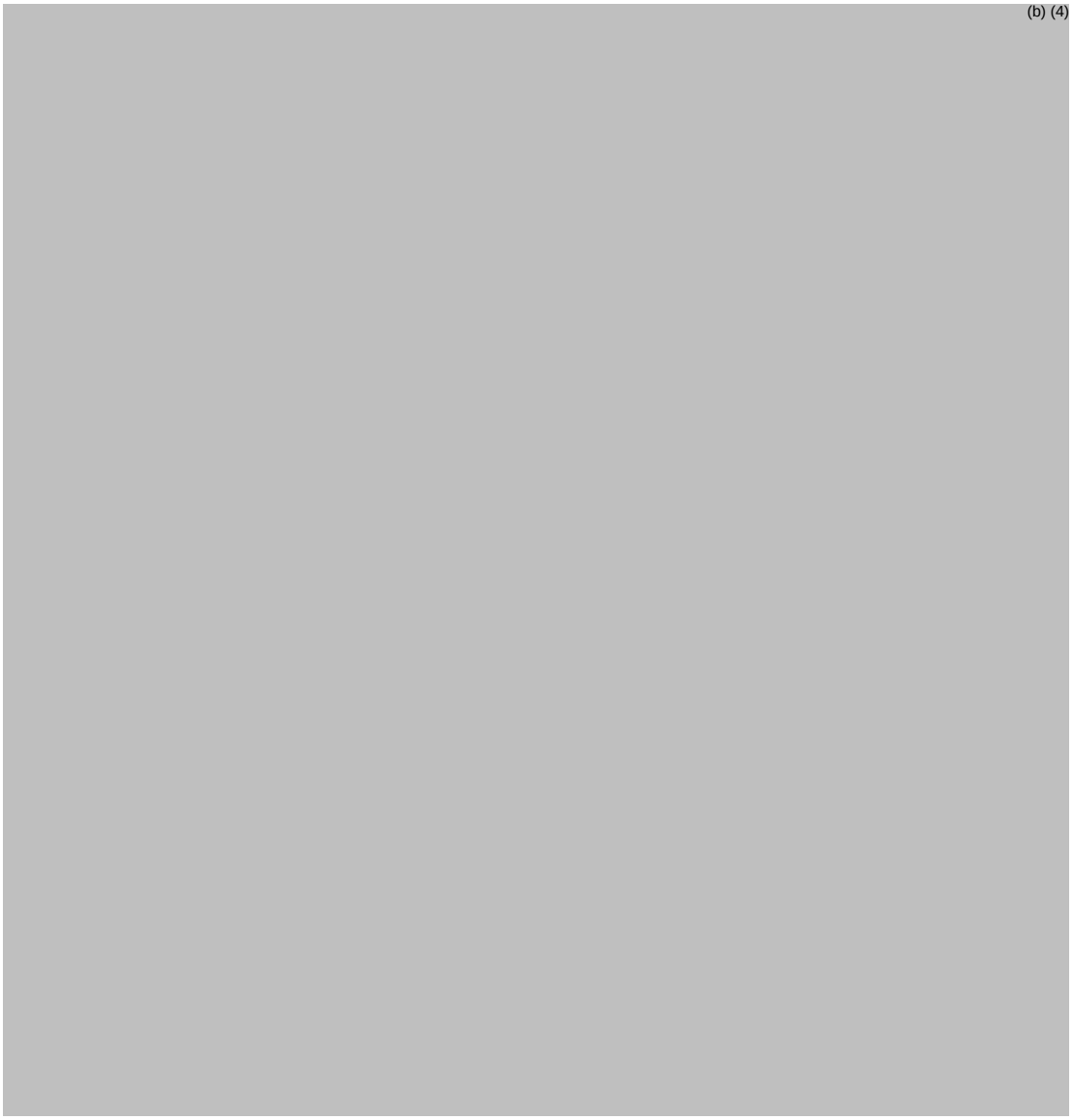
measured as an indicator of cell viability using a colorimetric method (absorbance at 450 nm and 650 nm). The 4-paramter logistic curves of the reference standard and test article are fitted with 10 concentration points and optical density values. The relative potency of test articles is measured by its ability to bind hTNFα and neutralize TNFα-mediated cytotoxicity relative to the CT-P17 reference standard.

FcγRIIIa (V type) Binding Affinity Assay

Potency of CT-P17 is assessed by a surface plasmon resonance (SPR) assay that utilizes FcγRIIIa ligand immobilized on a CM5 chip via amine coupling reaction. The method evaluates the relative binding affinity of the Fc region of CT-P17 test articles to the immobilized FcγRIIIa ligand in comparison with the reference standard. Binding affinity is measured in response units and the equilibrium association (dissociation/KD) constants are calculated based on a fitted model of the response curves.

- Reference Materials:

(b) (4)



(b) (4)

- **Critical starting materials or intermediates:**

(b) (4)

- **Manufacturing process summary:**

CT-P17 DS is manufactured at Celltrion, Inc., Plant (b) (4) Incheon, Republic of Korea. (b) (4)

(b) (4)

- **Container closure:**

  The DS container closure system is comprised of (b) (4) .

- **Dating period and storage conditions**:

  The dating period for CT-P17 DS is (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Yuflyma] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

The following table provides a summary of the identification, risk, and lifecycle knowledge management for the drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

CQA (type)	Risk	Origin	Control Strategy	Other
Particulate matter (visible and subvisible) (Product or process related impurities)	Safety/immunogenicity	Manufacturing process and container closure system	(b) (4)	N/A
Extractable Volume/ Dose Accuracy (general)	Efficacy/dosing	Manufacturing process		(b) (4)

Device Functionality (general)	Efficacy/dosing	Manufacturing Process	(b) (4)	Review of the device functionality control strategy is deferred to the CDRH assessor.
Leachables (process related impurities)	Safety	Manufacturing equipment and container closure		Long-term leachable study results for the DP container closure system were only available during the review cycle through 12 months at 5 ± 3ºC. A post-market commitment will be issued upon the BLA resubmission for providing updated study results annually in the BLA Annual Report and to submit the final study report, including the toxicological risk evaluation, to the BLA.
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process		N/A
Endotoxin (Contaminant)	Safety, Purity, Raw materials, manufacturing process	Controlled by the bioburden control and sterility-assurance strategies.		N/A
Container closure integrity	Safety (sterility assurance)	Container closure breaches during storage. May be impacted by storage conditions.		N/A

- Potency and Strength:
  Yuflyma is supplied at a strength of 40 mg/0.4 mL (100 mg/mL). Potency is defined as the percent hTNFα neutralization activity relative to the current

adalimumab-aaty WRS. The potency assay is the same as described for DS.

- **Summary of Product Design:**
  Yuflyma is a sterile, preservative-free, clear to opalescent, colorless to pale brown solution supplied in a single-dose PFS, PFS-S or AI. Yuflyma is intended for administration by subcutaneous injection. The single-dose PFS, PFS-S and AI contains 0.4 mL extractable volume (40 mg dose) of 100 mg/mL adalimumab-aaty, 10 mM sodium acetate, 250 mM glycine, 0.10% polysorbate 80, pH 5.2.

- **List of Excipients:**
  Sodium acetate, glycine and polysorbate 80 are all compendial excipients.

- **Reference Materials:**
  The same reference material is used for DS and DP.

- **Manufacturing process summary:**
  (b) (4)
  

- **Container closure:**
  The DP primary container closure system is comprised of a 1-mL (b) (4) glass syringe with a ½ -inch (29G thin wall) stacked stainless steel needle (b) (4) The syringe is closed with a (b) (4) elastomeric plunger stopper (b) (4) with a (b) (4) elastomeric rigid needle shield.

- **Dating period and storage conditions:**
  The dating period for assembled Yuflyma PFS, PFS-S and AI is 30 months from the date of the filling when stored at 5 ± 3ºC, protected from light. The assembled Yuflyma PFS, PFS-S and AI may be stored up to 30 days at 25±2ºC/ 60±5% RH, protected from light.

- **List of co-packaged components, if applicable: N/A**

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall recommendation: *Withhold*

DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, DS in-process testing, unprocessed bulk testing, DS release/stability testing, MCB/WCB testing/storage, DS release	CELLTRION, Inc., Plant (b) (4) Yeonsu-gu, Incheon, 22014, Republic of Korea	3005241015/ 688836030	704(a) document review.	None	Approve
MCB/WCB production, storage and testing	(b) (4)		No Evaluation Necessary	N/A	No Evaluation Necessary
MCB testing			No Evaluation Necessary	N/A	No Evaluation Necessary
MCB testing			No Evaluation Necessary	N/A	No Evaluation Necessary

MCB testing	(b) (4)		No Evaluation Necessary	N/A	No Evaluation Necessary
Unprocessed bulk testing			Approved based on profile	N/A	Approve
Unprocessed bulk testing			Approved based on profile	N/A	Approve
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
uDP manufacture, labeling/assembly/ packaging (PFS, PFS-S, AI), in-process testing, release testing, DP holding/storage, incoming device component controls	(b) (4)		For Cause Inspection	OAI	Withhold
Incoming device components controls, design controls, release/stability testing, in-process testing, DP release	CELLTRION, Inc., Plant (b) (4) Yeonsu-gu, Incheon, 22014, Republic of Korea	3005241015/ 688836030	Acceptable based on Profile	N/A	Approve
Release testing	(b) (4)		Acceptable based on Profile	N/A	Approve

G. Facilities:

Refer to the First Round OPQ Executive Summary memo dated 11/22/2021 for details regarding the evaluation of the drug substance (DS) manufacturing facility at Celltrion, Inc. (FEI 3005241015).

A withhold is recommended for this application based on the outcome of the for-cause inspection of the DP manufacturer, (b) (4) . A for-cause inspection by FDA from (b) (4) that resulted in an initial field recommendation of withhold the application. The objectionable conditions included: inadequate media fill program, inadequate investigations for deviations, insufficient airflow velocity (b) (4), inadequate qualification of production equipment, inadequate equipment clean hold time studies, and lack of control over QC instruments in the laboratory and production area, not performing electronic data review and audit trail reviews, backup data from electronic data generated by stand-alone instruments, are not verified for completeness and restoration, not maintaining device history file, Inadequate purchasing procedure and process, and not performing internal quality audit on medical devices. A review is being conducted by OMQ. The firm's responses and corrective actions to the FDA Form 483 observations will be completed after the action date for this application. Consequently, DBM concurs with the field recommendation to withhold the application based on the firm's readiness for commercial manufacturing.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
N/A

ii. Outstanding review issues/residual risk:
N/A

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
N/A

ii. Outstanding review issues/residual risk:
N/A

iii. Future inspection points to consider: 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/

WILLIE N WILSON
11/03/2022 09:07:21 PM

Biosimilar to US-licensed Humira

Recommendation: Complete Response

EXECUTIVE SUMMARY

BLA 761219
Review Number: First round
Review Date: November 22, 2021

Drug Name/Dosage Form	Yuflyma (adalimumab-aaty) injection, for subcutaneous use
Strength/Potency	40 mg/0.4 mL (100 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Indications currently approved for US-licensed Humira (40 mg/0.4 mL strength): Rheumatoid Arthritis (RA), Juvenile Idopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), adult Crohn's Disease (CD), pediatric Crohn's Disease (pCD), and Plaque Psoriasis (PsO)
Applicant/Sponsor	CELLTRION, Inc.

Product Overview

Yuflyma (adalimumab-aaty, CT-P17) is a recombinant human IgG1 monoclonal antibody developed as a biosimilar to US-licensed Humira (adalimumab). Adalimumab-aaty binds to the cytokine, human tumor necrosis factor α (TNFα). The binding of adalimumab to TNFα prevents its interaction with cell surface TNF receptors (TNFR1 and TNFRII). The binding of adalimumab to soluble TNFα facilitates suppression of pro-inflammatory activities. The binding of adalimumab to transmembrane TNFα may facilitate reverse signaling, antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. Adalimumab-aaty drug product is manufactured to have the same strength, dosage form and route of administration as the 40 mg/0.4 mL strength of US-licensed Humira in a single-dose prefilled syringe (PFS) and PFS assembled with an autoinjector (AI). Yuflyma is a sterile, preservative-free, clear and colorless to pale brown solution for subcutaneous injection supplied in single-dose PFS, PFS assembled with a needle-safety guard (PFS-S) and AI containing adalimumab-aaty at 40 mg/0.4 mL.

Quality Review Team

Discipline	Reviewer	Office/Division
Drug Substance/Drug Product/Immunogenicity	Cindy Osborn	OBP/DBRR1
Comparative Analytical Assessment	Cindy Osborn	OBP/DBRR1
OBP Labeling	James Barlow	OBP/IO
Drug Substance Microbiology/Facilities	Richard Ledwidge	OPMA/DBM
Drug Product Microbiology/Facilities	Lindsey Brown	OPMA/DBM

Facilities Assessment Lead	Zhong Li	OPMA/DBM
Microbiology Quality Assessment Lead	Maxwell Van Tassell	OPMA/DBM
CMC RBPM	Anh-Thy Ly	OPRO/DRBPM1
Application Technical Lead	Willie Wilson	OBP/DBRR1
OBP Review Chief	Qing Zhou	OBP/DBRR1
OBP Biosimilar Program and Policy	Marlene Schultz-DePalo	OBP/IO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Sadaf Nabavian	ORO/DROII
Signatory Authority	Nikolay Nikolov	OII/DRTM
Cross-disciplinary Team Lead	Anil Rajpal	OII/DRTM
Clinical Reviewer	Keith Hull	OII/DRTM
Nonclinical	Anup Srivastava/Carol Galvis	OII/DPTII
Clinical Pharmacology	Tao Liu/Ping Ji	OCP/DIIP
Biostatistics	Dong-Hyun Ahn/Yongman Kim	OB/DBIII
OSE/DMEPA	Davis Mathew/Nichelle Rashid	OSE/PMS
CDRH Consult	Suzanne Hudak	OHTIII/DHTIIIC

1. Names:
    a. Proprietary name: Yuflyma
    b. Trade name: Yuflyma
    c. Non-proprietary name: adalimumab-aaty
    d. CAS registry number: 331731-18-1
    e. Common name: CT-P17
    f. INN Name: adalimumab
    g. USAN Name: adalimumab
    h. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [CTP17]

2. Pharmacologic category: Therapeutic recombinant human monoclonal antibody biosimilar.

Submissions Reviewed:

Communication	Date
761219/1 (Original Submission)	11/24/2020
761219/3 Response to OPMA Information Request #1	1/5/2021
761219/7 Response to OBP Information Request #3	4/20/2021
761219/10 Response to OPMA Information Request #4	5/11/2021
761219/11 Partial Response to OBP Information Request #5	5/18/2021
761219/15 Response to OPMA Information Request #7	6/17/2021
761219/13 Partial Response to OBP Information Request #5	6/15/2021
761219/16 Response to OPMA Information Request #8	6/17/2021
761219/21 Partial Response to OPMA Information Request #9	7/2/2021
761219/23 Response to OPMA Information Request #11	7/21/2021
761219/25 Response to OBP Information Request #13	8/2/2021
761219/26 Response to OPMA Information Request #14	8/13/2021
761219/27 Partial Response to OPMA Information Request #9	8/17/2021
761219/28 Response to OBP Information Request #12	8/20/2021

761219/29 Response to OBP Information Request #15	8/27/2021
761219/30 Partial Response to OPMA Information Request #9	8/31/2021
761219/31 Partial Response to OPMA Information Request #9	9/30/2021
761219/33 Response to OBP Information Request #16	10/12/2021
761219/32 Response to OBP Information Request #17	10/8/2021
761219/35 Response to OPMA Information Request #18	10/21/2021
761219/35 Response to OPMA Information Request #18	10/22/2021
761219/37 Response to OBP Information Request #19	10/27/2021
761219/39 Response to OPMA Information Request #22	11/1/2021

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF#	DMF type	DMF Holder	Item Referenced	Code[1]	Status[2]	Date review completed	Comments (status)
(b) (4)	III		(b) (4)	3	Adequate	11/12/2021	None
	III			3	N/A	N/A	None

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There are enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

None

3. Consults:

Discipline/Topic	Date Requested	Recommendation	Assessor
CDRH/ODE & OC	12/21/2020	Approval	Suzanne Hudak Rumi Young (TL)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Recommendation: **Complete Response**

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761219 for Yuflyma (adalimumab-aaty) manufactured by Celltrion, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Yuflyma is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

The Division of Biotechnology Manufacturing (DBM), Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ is recommending that a Complete Response letter be issued to Celltrion Inc., to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

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.

Additional Comments:

1. Implement (b) (4) limits validated by bacterial retention study.
2. The endotoxin limit for the (b) (4) samples exceeds the endotoxin limit for release. This may allow for the production of a batch that may meet (b) (4) limits but exceeds the specification for release. Update the endotoxin (b) (4) limit and/or the release specification.

C. Approval Action Letter Language:
N/A

D. Benefit/Risk Considerations:
Yuflyma (adalimumab-aaty, CT-P17) is a proposed biosimilar to US-licensed Humira for the same indications as for the 40 mg/0.4 mL strength of US-licensed Humira (i.e., Rheumatoid Arthritis, Juvenile Idopathic Arthritis, Psoriatic Arthritis, Ankylosing

Spondylitis, adult Crohn's Disease, pediatric Crohn's Disease, and Plaque Psoriasis). CELLTRION performed a three-way pairwise comparative analytical assessment to establish the analytical component of the scientific bridge among US-licensed Humira (40 mg/0.4 mL), EU-approved Humira (40 mg/0.4 mL) and CT-P17. As part of the comparative analytical assessment, the molecular attributes of adalimumab were collectively assigned to appropriate assessment categories and a sufficient number of lots of each product were evaluated. A comprehensive array of analytical methods was used. Each method was demonstrated to be suitable to detect and/or quantitate potential differences in critical quality attributes among CT-P17, US-licensed Humira and EU-approved Humira. The comparative analytical assessment data provided support the conclusion that Yuflyma is highly similar to US-licensed Humira and the analytical component of the scientific bridge.

The overall control strategy for Yuflyma manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency, and drug substance and drug product that have appropriate quality and are free of adventitious agents. The drug substance facility operates in compliance with cGMP and are acceptable for manufacturing. Multiple objectionable observations were identified during the pre-license inspection (PLI) of the drug product facility that could not be resolved during the BLA review clock (see Section G). A Complete Response letter will be issued to Celltrion to outline the deficiencies and information and data required to support an approval.

E. Environmental Assessment or Claim of Categorical Exclusion:

A claim of categorical exclusion from environmental assessment (EA) according to 21 CFR 25.31(a) was provided and is acceptable.

F. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

N/A

II. Evaluation of the Comparative Analytical Assessment

I. Overview and Conclusions

CELLTRION, Inc. (Celltrion) is seeking licensure for CT-P17 as a biosimilar to US-licensed Humira for the 40 mg/0.4 mL strength in a single-use pre-filled syringe (PFS), PFS + autoinjector (AI), and PFS assembled with a needle-safety guard (PFS-S). Celltrion performed a three-way pairwise comparative analytical assessment (CAA) to establish the analytical component of the scientific bridge among 10 lots of US-licensed Humira (40 mg/0.4 mL), 10 lots of EU-approved Humira (40 mg/0.4 mL) and 10 lots of CT-P17. The CT-P17 lots evaluated included four drug substance (DS) lots manufactured at Celltrion Plant (b) (4) using commercial Process D, three drug product (DP) lots manufactured at (b) (4) using clinical Process 3, and three process validation DP lots manufactured at the

same DP site using commercial Process 4. All CT-P17 DP lots included in the CAA were independent of the DS lots evaluated. CT-P17 (Lot CTP17CLN001 and CTP17CLN003), US-licensed Humira (Lot 1104991), and EU-approved Humira (Lot 88407XH07, 91436XH11, 93460XH06 and 02005LX04) were administered during CT-P17 clinical development and were among the lots evaluated in the CAA. The CAA included the following analyses to support a demonstration that CT-P17 is highly similar to US-licensed Humira and to establish the analytical component of the scientific bridge:

Extensive comparative physicochemical and functional assessment of quality attributes.
Additional comparative assessment to evaluate the correlation between glycosylation and biological activities, and to evaluate the mechanism of action in different cell types to support extrapolation to other indications (including Inflammatory Bowel Disease).
Comparative assessments of the degradation profiles under forced degradation conditions.

Celltrion used a risk-based approach for the statistical evaluation of the analytical results:
Very high risk-ranked quality attributes were tested using quantitative assays and were evaluated against the quality range (i.e., denoted QR2) determined by US-licensed Humira or EU-approved Humira mean ± a standard deviation multiplier of 2. Comparative analytical similarity was demonstrated if ≥ 90% of the CT-P17 lots were within the QR2.
High and moderate risk-ranked quality attributes were tested using quantitative assays and were evaluated against the quality range (i.e., denoted QR3) determined by US-licensed Humira or EU-approved Humira mean ± a standard deviation multiplier of 3. Comparative analytical similarity was demonstrated if ≥ 90% of the CT-P17 lots were within the QR3.
Low and very low risk-ranked quality attributes were tested using quantitative and qualitative assays and were evaluated by raw data visual comparison (i.e., denoted RD) without statistical analysis.

All analytical methods used during the CAA were performed at CELLTRION Inc. R&D laboratories, (Incheon, South Korea). Results from method validation, qualification and verification studies were provided and adequately support the suitability of each method for its intended use during the CAA.

Based on our assessment of the CAA data, the results support a demonstration that CT-P17 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. Celltrion used a comprehensive array of analytical methods that were suitable to evaluate the critical quality attributes of CT-P17, and US-licensed Humira to support a demonstration that CT-P17 is highly similar to US-licensed Humira. The number and type of lots tested and data analysis methods were appropriate to allow for a meaningful evaluation of the results of the CAA. While differences were observed in a limited number of attributes, these do not preclude a demonstration that CT-P17 and US-licensed Humira are highly similar. Refer to Section V – Same Strength(s) below for addition comments regarding the comparison of strength, dosage form and route of administration between CT-P17 and US-licensed Humira.

Celltrion also provided a comparison of stability studies under forced degradation conditions of thermal stress (50°C), oxidative stress (0.01% H_2O_2), photo stress (25 w/m2.hr; 25°C and 15 w/m2; 25°C) and high pH (pH 10). The comparative forced degradation studies support a demonstration of similar degradation profiles among the CT-P17, US-licensed Humira and

EU-approved Humira lots.

In addition, the three-way pairwise comparisons of CT-P17, US-licensed Humira and EU-approved Humira were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU-approved Humira as the comparator to the assessment of biosimilarity. Celltrion supported the establishment of the analytical component of the scientific bridge using the same methods and statistical approaches used to support the demonstration that CT-P17 is highly similar to US-licensed Humira. Based on review of the data, we conclude that the analytical component of the scientific bridge was established.

II. Comparative Analytical Assessment Results

Table A. Quality Attributes Analyzed in the Comparative Analytical Assessment

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure	Molecular mass (reduced/non-reduced)	Yes	Yes
	N-terminal sequence	Yes	Yes
	C-terminal sequence	Yes	Yes
	Amino acid sequence coverage	Yes	Yes
Post-translational Modifications	Oxidation	Yes	Yes
	Deamidation	Yes	Yes
	Glycation	Yes	Yes
	N-terminal glutamine	Yes	Yes
	C-terminal variants	Yes	Yes
	Oligosaccharide profile	Yes	Yes
	N-linked glycan analysis	Yes	Yes
	Aglycosylated heavy chain	Yes	Yes
Higher Order Structure	Secondary structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Protein folding	Yes	Yes
	Thermal stability	Yes	Yes
	Disulfide bond	Yes	Yes
	Free thiols	Yes	Yes
Purity and Product-related Variants or Impurities	Charge heterogeneity	Yes	Yes
	Isoelectric point	Yes	Yes
	High molecular weight (HMW) species - Aggregation	Yes	Yes
	Low molecular weight (LMW) species - Fragmentation	Yes	Yes
Fab-mediated Bioactivity	Neutralization by soluble TNFa (sTNFα) binding	Yes	Yes

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	sTNFα binding	Yes	Yes
	Transmembrane TNFa (mTNFα) binding	Yes	Yes
	Apoptosis (reverse signaling)	Yes	Yes
Fc-mediated Bioactivity	ADCC	Yes	Yes
	CDC	Yes	Yes
	C1q binding	Yes	Yes
	FcγRIIIa binding	Yes	Yes
	FcγRIIIb binding	Yes	Yes
	FcγRIIa binding	Yes	Yes
	FcγRIIb binding	Yes	Yes
	FcγRI binding	Yes	Yes
	FcRn binding	Yes	Yes
Impact of Aglycosylation, Agalactosylation and Amannosylation on Bioactivity	FcγRIIIa binding	Yes	Yes
	FcRn binding	Yes	Yes
	CDC	Yes	Yes
	ADCC	Yes	Yes
	Neutralization by sTNFa binding	Yes	Yes
Additional Bioactivity Studies to Support Extrapolation to other Indications	Inhibition of TNFa-induced apoptosis (HCT116 cells)	Yes	Yes
	Inhibition of TNFa-induced IL-8 release (HCT116 cells)	Yes	Yes
	Inhibition of TNFa-induced VCAM-1 release (HUVEC cells)	Yes	Yes
	Regulatory macrophage induction	Yes	Yes
	$LT_{\alpha 3}$ binding	Yes	Yes
Drug Product Attributes	Protein concentration	Yes	Yes
	Extractable volume	Yes	Yes

Comparative assessment of the forced degradation stability studies was performed to evaluate potential differences in the degradation profiles across the CT-P17, US-licensed Humira, and EU-approved Humira lots when stored under thermal stress (50°C), oxidative stress (0.01% H_2O_2), photo stress (25 w/m^2.hr; 25°C and 15 w/m^2; 25°C) and high pH (pH 10). Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

III. Analytical Studies to Support the Use of a Non-US-Licensed Comparator Product

The clinical development of CT-P17 included three clinical studies:

- Study CT-P17 1.1 (PK similarity study): A randomized, multi-center, double-blind, three-arm, parallel group, single-dose, active comparator study designed to evaluate PK similarity between CT-P17, EU-Humira and US-Humira by PFS injection in healthy male and female subjects.
- Study CT-P17 1.2 (pilot study): A randomized, double-blind, two-arm, parallel-group, single-dose, active comparator study designed to evaluate the safety and PK of the CT-P17 and EU-Humira by PFS injection in 30 healthy male subjects.
- Study CT-P17 3.1 (comparative clinical study): A randomized, active-controlled, double-blind, multicenter study designed to evaluate efficacy, PK, PD, usability, overall safety and immunogenicity of multiple single-doses (40 mg) of either CT-P17 or EU-Humira administered by SC injection via PFS in combination with MTX in patients with moderate to severe active RA.

To support the relevance of the comparative clinical data (Study CT-P17 3.1) generated using EU-approved Humira as a comparator product to the assessment of biosimilarity, Celltrion performed three-way, pairwise comparative analytical assessments using a comprehensive array of analytical methods and a three-way, pairwise PK similarity study (CT-P17 1.1). To support the establishment of the analytical component of the scientific bridge, Celltrion included comparison of CT-P17 to US-licensed Humira, CT-P17 to EU-approved Humira, and EU-approved Humira to US-licensed Humira. The same analytical methods used for supporting a demonstration that CT-P17 is highly similar to US-licensed Humira were used for the pairwise analytical comparisons with EU-approved Humira. The differences observed in the comparative analytical studies do not preclude the establishment of the analytical component of the scientific bridge. See Section IV below. The results support the establishment of the analytical component of the scientific bridge.

IV. Assessment of Comparative Analytical Study Results

Quantitative Assessment of Analytical Study Results

All quality attributes evaluated against the QR2 and QR3 quality ranges met the comparative analytical acceptance criteria, except for the following:

1. Size Variants (Monomer, HMW and LMW): The US-licensed Humira QR3 for size variants measured by SEC-HPLC is 99.776-99.122% monomer, 0.148-0.746% HMW, and 0.064-0.146% LMW. This QR3 was slightly exceeded for monomer (98.99-99.03% in 2 out of 10 CT-P17 lots), HMW (0.80-0.87% in 3 out of 10 CT-P17 lots) and LMW (0.05-0.06% in 4 out of 10 CT-P17 lots). Three out of the 10 EU-approved Humira lots showed LMW results (0.15-0.18%) that slightly exceeded the US-licensed Humira QR3 (0.064-0.146%). The EU-approved Humira QR3 (i.e., 99.303-99.561% monomer, 0.352-0.506% HMW) was slightly exceeded for monomer (98.99-99.23% in 8 out of 10 CT-P17 lots) and HMW (0.59-0.87% in 9 out of 10 CT-P17 lots). The magnitude by which the US-licensed Humira and EU-approved Humira QR3 was exceeded (< 1%) is minor and is not anticipated to impact safety, efficacy or immunogenicity. Overall, the observed differences in SEC-HPLC results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the

scientific bridge.

2. Size Variants (NGHC and H+L): Reduced CE-SDS analysis of all ten of the CT-P17 lots showed results for NGHC (0.59-0.72%) and H+L purity (99.17-99.32%) that slightly exceeded the US-licensed Humira QR3 (i.e., 0.893-1.143% NGHC; 98.683- 98.953% H+L). The NGHC and H+L results for each CT-P17 lot also exceeded the EU-approved Humira QR3 (i.e., 0.786-1.112% NGHC; 98.744-99.062% H+L). Two out of 10 (20%) EU-approved Humira lots showed 0.84-0.87% NGHC and 98.97-99.02% H+L results that slightly exceeded the US-licensed Humira QR3. The magnitude (<1.0%) by which the US-licensed Humira and EU-approved Humira QR3 was exceeded is minor and is not anticipated to impact safety, efficacy or immunogenicity. Differences in NGHC have the potential to impact N-linked glycan profile and subsequent Fc-mediated bioactivity. However, the observed differences in NGHC did not result in any differences in the downstream Fc-mediated bioactivity quality attributes described in Table A above. Overall, the observed differences in reduced CE-SDS results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

3. Charge Variants (Acidic Group, Main Peak and Basic Group 2): The US-licensed Humira QR3 for charge variants measured by IEC-HPLC is 11.936-16.464% acidic group, 60.447-69.423% main peak and 0.088-1.406% basic group 2. This QR3 was exceeded for acidic group (9.22-9.58% in 7 out of 10 CT-P17 lots), main peak (68.47-70.34% in 7 out of 10 CT-P17 lots) and basic group 2 (1.42-1.74% in 9 out of 10 CT-P17 lots). Seven out of the ten CT-P17 lots showed main peak results (69.67-70.70%) that exceeded the EU-approved Humira QR3 (58.565-69.051%). The acidic group (9.22-12.43%) and basic group 2 (1.32-1.74%) results for all ten CT-P17 lots exceeded the EU-approved Humira QR3 (13.007-16.496% acidic group; 0.752-1.184% basic group 2). The acidic group contains heavy chain deamidation at Asn329 (Fc region) and a heavy chain C-terminal variant at Lys451. Basic group 2 contains a cleaved N-terminal heavy chain variant at Gly08. IEC-HPLC characterization studies show that the enrichment of basic group 2 up to 33% is needed to show an impact on TNFα neutralization (84% relative potency), CDC (52% relative potency) and FcRn binding (no result due to abnormal sensorgram). Enrichment of the acidic group up to ~80% is needed to show a significant impact on biological activity (FcγRIIIa binding, FcRn binding, hTNFα neutralization and CDC). Therefore, the magnitude by which the IEC-HPLC results exceeded the US-licensed Humira and EU-approved Humira QR3 for acidic group (< 3.8%), main peak (< 1.65%) and basic group 2 (< 1%) is minor and did not result in any difference in the Fab- and Fc-related biological activities described in Table A above. The magnitude by which the IEC-HPLC results exceeded the QR3 is also not anticipated to impact safety, PK or immunogenicity. Overall, the observed differences in IEC-HPLC results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge.

4. Oligosaccharide Profiling: The oligosaccharide profile analysis included the evaluation of potential differences in fucosylated (G0F+G1F+G2F), high mannose (Man5+Man6), afucosylated (G0-GN+G0) and total afucosylated (G0-GN+G0+Man5+Man6) glycan groups. The US-licensed Humira QR3 for oligosaccharide profile is 84.237-87.869% fucosylated glycans, 4.972-7.296% high mannose and 5.966-

8.462% total afucosylated glycans. Five out of 10 CT-P17 lots showed 88.05-89.56% fucosylated glycans which slightly exceeded the US-licensed Humira QR3. All CT-P17 lots showed high mannose (2.83-4.72%) and afucosylated (2.98-3.47%) glycan results that exceeded the US-licensed Humira QR3. The EU-approved Humira lots that exceeded the US-licensed Humira QR3 showed results for fucosylated gylcans (83.19-84.18% in 6 out of 10 lots), high mannose (7.33-7.54% in 3 out of 10 lots) and total fucosylated glycans (8.51-8.73% in 3 out of 10 lots). Six out of the 10 CT-P17 lots showed 87.83-89.56% fucosylated glycans which exceeded the EU-approved Humira QR3 (80.871-87.829% fucosylated glycans). All CT-P17 lots also showed high mannose (2.83-4.72%) and afucosylated glycans (2.98-3.47%) which exceeded the EU-approved Humira QR3 (5.047-8.783% high mannose; 1.005-1.331% afucosylated). Overall, the US-licensed Humira and EU-approved Humira QR3 was exceeded by the CT-P17 lots by a maximum of 1.69% (fucosylated glycans), 2.21% (high mannose), 2.26% (afucosylated glycans) and 0.27% (total afucosylated glycans).

Changes to the levels of high mannose glycans can influence the serum half-life in-vivo. High levels of afucosylated glycans (including high mannose) have also been reported to impact Fc-effector function (e.g., ADCC). The observed differences in high mannose, afucosylated and fucosylated glycans during the CAA did not result in differences in the Fc-mediate bioactivity quality attributes described in Table A. Overall, the magnitude by which the US-licensed Humira and EU-approved adalimumab QR3 for the oligosaccharide profile was exceeded is minor and is not anticipated to impact safety, PK, efficacy or immunogenicity. The observed differences in oligosaccharide profiling results do not preclude the demonstration that CT-P17 is highly similar to US-licensed Humira or the establishment of the analytical component of the scientific bridge. Additionally, we conferred with the clinical pharmacology reviewers, and the PK data are consistent with these conclusions.

V. Same Strength(s)

CT-P17 has the same dosage form and route of administration as US-licensed Humira. Celltrion is seeking licensure of 40 mg/0.4 mL CT-P17 in a single-use PFS, AI and PFS-S. US-licensed Humira is available at this strength (40 mg/0.4 mL) in a single-use PFS and AI. Celltrion is seeking approval of CT-P17 for the same strength as U.S.-licensed Humira. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed as part of manufacturing process controls. The proposed presentations of CT-P17 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Humira (40 mg/0.4 mL). The strength of CT-P17 PFS, AI and PFS-S is the same as that of US-licensed Humira.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other notes
TNFα Binding Affinity (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.	(b) (4)	N/A
FcγRIIIa (V type) Binding Affinity (potency)	Efficacy	Intrinsic to the molecule. Minimal change is expected under recommended storage conditions through expiry.		CQAs known to impact FcγRIIIa binding affinity (e.g., glycosylation profile) are not likely to be affected by the DP manufacturing process or long-term storage. Therefore, FcγRIIIa binding is not controlled during DP release and stability testing.
Oligosaccharide Profile	Efficacy and Safety/ Immunogenicity	Cell culture manufacturing process. Change is not expected under recommended storage conditions through expiry.		N/A
Identity	Safety and Efficacy	Intrinsic to the molecule.		N/A
High Molecular Weight (HMW) species/ Aggregates (product-related impurities)	Efficacy and Safety/ Immunogenicity	Manufacturing process and exposure to heat and light stress Minimal change is expected during storage under recommended		N/A

(b) (4)

		conditions through expiry.	
Low Molecular Weight Species (Fragments) (product-related impurities)	Efficacy	Manufacturing process and exposure to heat and light stress. Minimal increase in fragments is expected during storage under recommended conditions.	N/A
Oxidation of Heavy Chain Fc Region (Met256 and Met432)	Efficacy	Exposure to light and oxidative stress	Met256 and Met432 oxidation is not impacted under process-relevant stress conditions.
N-terminal Heavy Chain Cleavage at Gly8 (product-related impurity)	Efficacy	Exposure to light stress	
Protein Content (mg/mL)	Efficacy	Manufacturing process	N/A

			(b) (4)	
Osmolality	Efficacy	Formulation process		N/A
Appearance (color and clarity)	Efficacy and Safety	Formulation, contamination, or degradation		N/A
pH	Efficacy and Safety	Formulation process		N/A
(b) (4)	Efficacy and Safety	Intrinsic to (b) (4) DP formulation		N/A

B. Drug Substance [adalimumab-aaty] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

Category (type)	Risk	Origin	Control Strategy	Other notes
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line	(b) (4)	N/A
Host Cell DNA (process-related impurity)	Safety	Production cell line		N/A

			(b) (4)	
(b) (4) Leachate (process-related impurity)	Safety and Immunogenicity	Process-related (b) (4)		N/A
Residual (b) (4) (process-related impurity)	Safety	Cell culture medium		N/A
Residual (b) (4) (process-related impurity)	Safety, immunogenicity	Cell bank cryopreservation medium or culture medium		(b) (4)

Leachables (process-related impurity)	Safety	Manufacturing components and the DS container closure system	(b) (4)	N/A
Microbial Enumeration (Bioburden)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process		N/A
Bacterial Endotoxins	Safety	Raw materials, manufacturing process		N/A

- Description (adalimumab-aaty):

  Adalimumab-aaty (CT-P17) is a recombinant human IgG1 monoclonal antibody manufactured in CHO cells. CT-P17 is composed of two light chains (214 amino acid residues each) linked by C-terminal disulfide bonds to two heavy chain (451 amino acid residue each). The total molecular weight of CT-P17 is 148 kilodaltons. The amino acid sequence of CT-P17 is identical to US-licensed Humira. The complementarity-determining region of CT-P17 facilitates binding to human tumor necrosis factor α (hTNFα). CT-P17 harbors one N-linked glycosylation site (Asn301) in the CH2 domain of the heavy chain which can facilitates Fc-effector function.

- Mechanism of Action (MoA):

  TNFα is a cytokine produced mainly by macrophages which has both immunostimulatory and immunosuppressive effects. Elevated levels of TNFα are associated with the pathologic inflammation and joint destruction in patients with rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis ankylosing spondylitis and psoriasis plaques. Adalimumab can suppress TNFα-induced pro-inflammatory activities by binding to soluble TNFα and blocking its interaction with cell surface TNF receptors (p55/TNFRI and p75/TNFRII). Adalimumab may also bind to transmembrane TNFα (tmTNFα) which can facilitate inhibition of tmTNFα-mediated effector function, induction of regulatory macrophages by FcγR crosslinking and destruction of TNFα-bearing cells by antibody-dependent cellular cytotoxicity (ADCC), reverse signaling and complement-dependent cytotoxicity.

- Potency Assay:

  In vitro hTNFα Neutralization Assay

  Potency of CT-P17 is assessed using a quantitative cell-based hTNFα neutralization assay which utilizes hTNFα and the TNF-sensitive mouse sarcoma cell line, WEHI164. Serial dilutions of CT-P17 test articles and reference standard, in addition to hTNFα, are added to 96-well plates containing WEHI164 cells. Upon incubation, cellular metabolic activity is measured as an indicator of cell viability using a colorimetric method (absorbance at 450 nm and 650 nm). The 4-paramter logistic curves of the reference standard and test article are fitted with 10 concentration points and optical density values. The relative potency of test articles is measured by its ability to bind hTNFα and neutralize TNFα-mediated cytotoxicity relative to the CT-P17 reference standard.

  FcγRIIIa (V type) Binding Affinity Assay

  Potency of CT-P17 is assessed by a surface plasmon resonance (SPR) assay that utilizes FcγRIIIa ligand immobilized on a CM5 chip via amine coupling reaction. The method evaluates the relative binding affinity of the Fc region of CT-P17 test articles to the immobilized FcγRIIIa ligand in comparison with the reference standard. Binding affinity is measured in response units and the equilibrium association (dissociation/KD) constants are calculated based on a fitted model of the response curves.

- Reference Materials:

(b) (4)

(b) (4)

- **Critical starting materials or intermediates:**

(b) (4)

- **Manufacturing process summary:**

CT-P17 DS is manufactured at Celltrion, Inc., Plant (b) (4), Incheon, Republic of Korea. (b) (4)

(b) (4)

- **Container closure:**

  The DS container closure system is comprised of (b) (4) .

- **Dating period and storage conditions**:

  The dating period for CT-P17 DS is (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Yuflyma] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

The following table provides a summary of the identification, risk, and lifecycle knowledge management for the drug product CQAs that derive from (b) (4) process and general drug product attributes.

CQA (type)	Risk	Origin	Control Strategy	Other
Particulate matter (visible and subvisible) (Product or process related impurities)	Safety/immunogenicity	Manufacturing process and container closure system	(b) (4)	N/A
Extractable Volume/ Dose Accuracy (general)	Efficacy/dosing	Manufacturing process		(b) (4)

				accuracy.
Device Functionality (general)	Efficacy/dosing	Manufacturing Process	(b) (4)	Review of the device functionality control strategy is deferred to the CDRH assessor.
Leachables (process related impurities)	Safety	Manufacturing equipment and container closure		Long-term leachable study results for the DP container closure system were only available during the review cycle through 12 months at 5 ± 3°C. A post-market commitment will be issued upon the BLA resubmission for providing updated study results annually in the BLA Annual Report and to submit the final study report, including the toxicological risk evaluation, to the BLA.
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process		N/A
Endotoxin (Contaminant)	Safety, Purity, Raw materials, manufacturing process	Controlled by the bioburden control and sterility-assurance strategies.		N/A
Container closure integrity	Safety (sterility assurance)	Container closure breaches during storage. May be impacted by storage conditions.		N/A

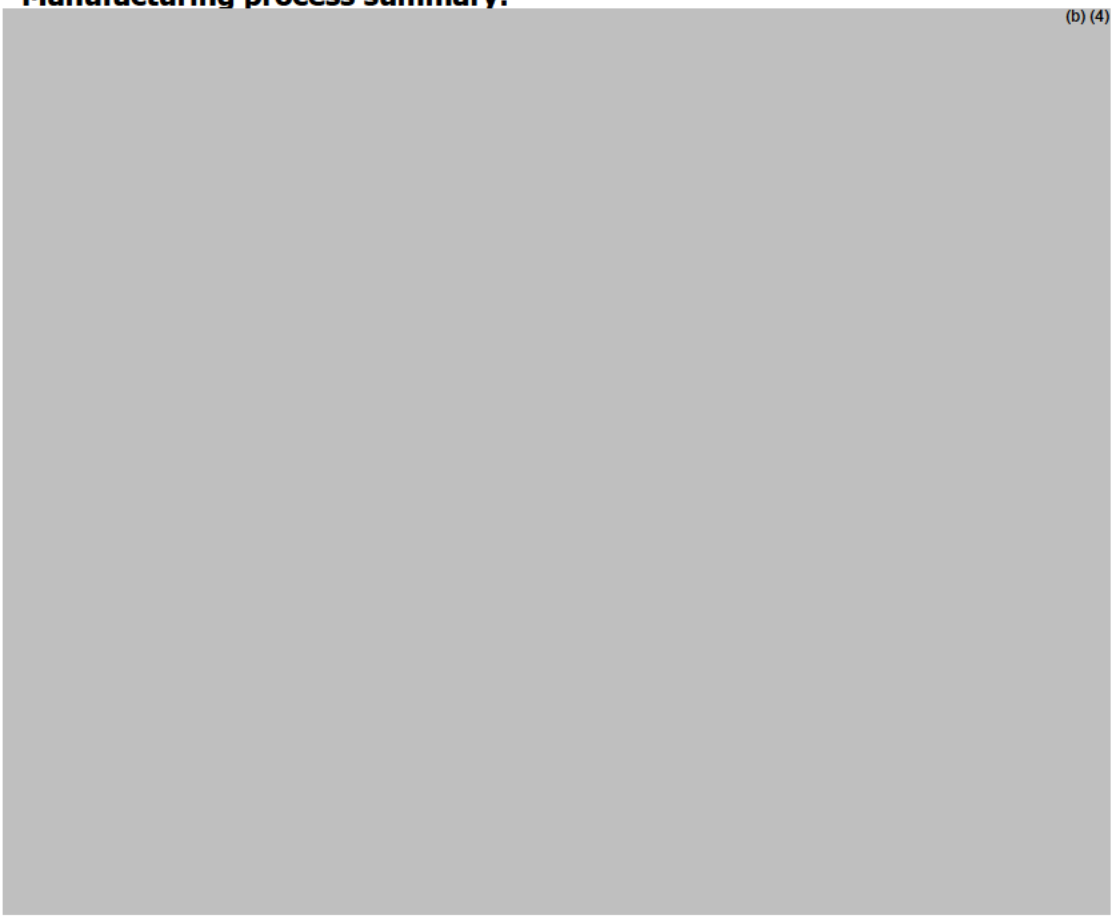
- Potency and Strength:
  Yuflyma is supplied at a strength of 40 mg/0.4 mL (100 mg/mL). Potency is

defined as the percent hTNFα neutralization activity relative to the current adalimumab-aaty WRS. The potency assay is the same as described for DS.

- **Summary of Product Design:**
  Yuflyma is a sterile, preservative-free, clear to opalescent, colorless to pale brown solution supplied in a single-dose PFS, PFS-S or AI. Yuflyma is intended for administration by subcutaneous injection. The single-dose PFS, PFS-S and AI contains 0.4 mL extractable volume (40 mg dose) of 100 mg/mL adalimumab-aaty, 10 mM sodium acetate, 250 mM glycine, 0.10% polysorbate 80, pH 5.2.

- **List of Excipients:**
  Sodium acetate, glycine and polysorbate 80 are all compendial excipients.

- **Reference Materials:**
  The same reference material is used for DS and DP.

- **Manufacturing process summary:**
  (b) (4)
  

- **Container closure:**
  The DP primary container closure system is comprised of a 1-mL (b) (4) glass syringe with a ½ -inch (29G thin wall) stacked stainless steel needle (b) (4) The syringe is closed with a (b) (4) elastomeric plunger stopper (b) (4) with a (b) (4) elastomeric rigid

needle shield.

- Dating period and storage conditions:
  The dating period for assembled Yuflyma PFS, PFS-S and AI is (b) (4) months from the date of the filling when stored at 5 ± 3°C, protected from light. The assembled Yuflyma PFS, PFS-S and AI may be stored up to 30 days at 25±2°C/ 60±5% RH, protected from light.

- List of co-packaged components, if applicable: N/A

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall recommendation: *Withhold*					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, DS in-process testing, unprocessed bulk testing, DS release/stability testing, MCB/WCB testing/storage, DS release	CELLTRION, Inc., Plant (b) (4), Yeonsu-gu, Incheon, 22014, Republic of Korea	3005241015/ 688836030	704(a) document review.	None	Approve
MCB/WCB production, storage and testing	(b) (4)		No Evaluation Necessary	N/A	No Evaluation Necessary
MCB testing			No Evaluation Necessary	N/A	No Evaluation Necessary
MCB testing			No Evaluation Necessary	N/A	No Evaluation Necessary

MCB testing	(b) (4)	No Evaluation Necessary	N/A	No Evaluation Necessary
Unprocessed bulk testing		Approved based on profile	N/A	Approve
Unprocessed bulk testing		Approved based on profile	N/A	Approve

DRUG PRODUCT

Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
uDP manufacture, labeling/assembly/ packaging (PFS, PFS-S, AI), in-process testing, release testing, DP holding/storage, incoming device component controls	(b) (4)		Pre-approval Inspection	OAI	Withhold
Incoming device components controls, design controls, release/stability testing, in-process testing, DP release	CELLTRION, Inc., Plant (b) (4), Yeonsu-gu, Incheon, 22014, Republic of Korea	3005241015/ 688836030	Acceptable based on Profile	N/A	Approve
Release testing	(b) (4)		Acceptable based on Profile	N/A	Approve

G. Facilities:

Celltrion, Inc. (FEI 3005241015) is responsible for drug substance (DS) manufacturing. A review of requested manufacturing site records under Section 704(a)(4) (FDASIA Sec. 706) was conducted in lieu of an onsite pre-license inspection (PLI). The Agency requested audit documents for drug substance manufacturing, testing (including comparative analytical assessment), and storage on February 25, 2021 and April 2, 2021. No objectionable issues were identified. The Agency determined that the proposed drug substance manufacturing and testing facility is acceptable to support approval of BLA 761219.

A withhold is recommended for this application based on the outcome of the preapproval inspection of the DP manufacturer, (b) (4) A pre-license inspection by FDA from (b) (4), that resulted in an initial field recommendation of withhold the application. The objectionable conditions included: multiple (b) (4) failures in the (b) (4) manufacturing areas; failure to adequately investigate numerous environmental monitoring excursions for the GMP drug product manufacturing areas; failure to adequately validate the CT-P17 drug product manufacturing process; equipment and facilities used in the manufacture of drug product are not adequately maintained; deficient standard operating procedures; inadequate procedures and validation of procedures designed to prevent contamination of products during (b) (4). A PLI review was conducted by OPMA/DBM. The firm's responses and corrective actions to the FDA Form 483 observations #1-3 are inadequate. Consequently, DBM concurs with the field recommendation to withhold the application based firm's readiness for commercial manufacturing.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
N/A

ii. Outstanding review issues/residual risk:
N/A

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
N/A

ii. Outstanding review issues/residual risk:
N/A

iii. Future inspection points to consider: None

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/s/

WILLIE N WILSON
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