

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761219Orig1s000

OTHER REVIEW(S)

MEMORANDUM
HUMAN FACTORS STUDY RESULTS AND LABEL AND LABELING REVIEW MEMO
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 22, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma [CT-P17] ^a (adalimumab-aaty) ^b Injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Celltrion, Inc.
TTT ID #:	2023-3391-3
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CHES, CPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU) received on May 22, 2023 for Yuflyma. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the IFU for Yuflyma (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to recommendation that we made during a previous human factors study results and label and labeling review and human factors study results and label and labeling review memos.^{c,d,e}

^a CT-P17 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). The proposed proprietary name Yuflyma was found conditionally acceptable by DMEPA.

^b The nonproprietary name, adalimumab-aaty, was found conditionally acceptable on March 10, 2023.

^c Bhalodia, A. Human Factors Study Results and Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 13. TTT ID No.: 2023-3391.

^d Bhalodia, A. Human Factors Study Results and Label and Labeling Review Memo for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 11. TTT ID No.: 2023-3391-1.

^e Bhalodia, A. Human Factors Study Results and Label and Labeling Review Memo for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 19. TTT ID No.: 2023-3391-2.

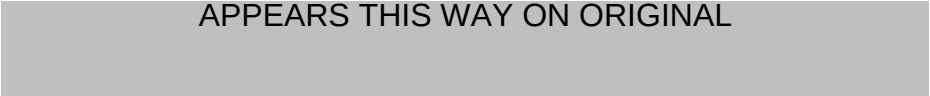
2 CONCLUSION

The Applicant implemented our recommendation and we have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 22, 2023

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05/22/2023 03:11:11 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma (adalimumab-aaty) Injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Celltrion, Inc.
TTT ID #:	2022-2975-3
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on May 18, 2023 for Yuflyma. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised carton labeling for Yuflyma (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Celltrion has revised the color scheme of the two proposed prefilled syringe carton labeling for contrast with the proposed autoinjector carton labeling; no additional revisions to the autoinjector carton labeling are proposed.

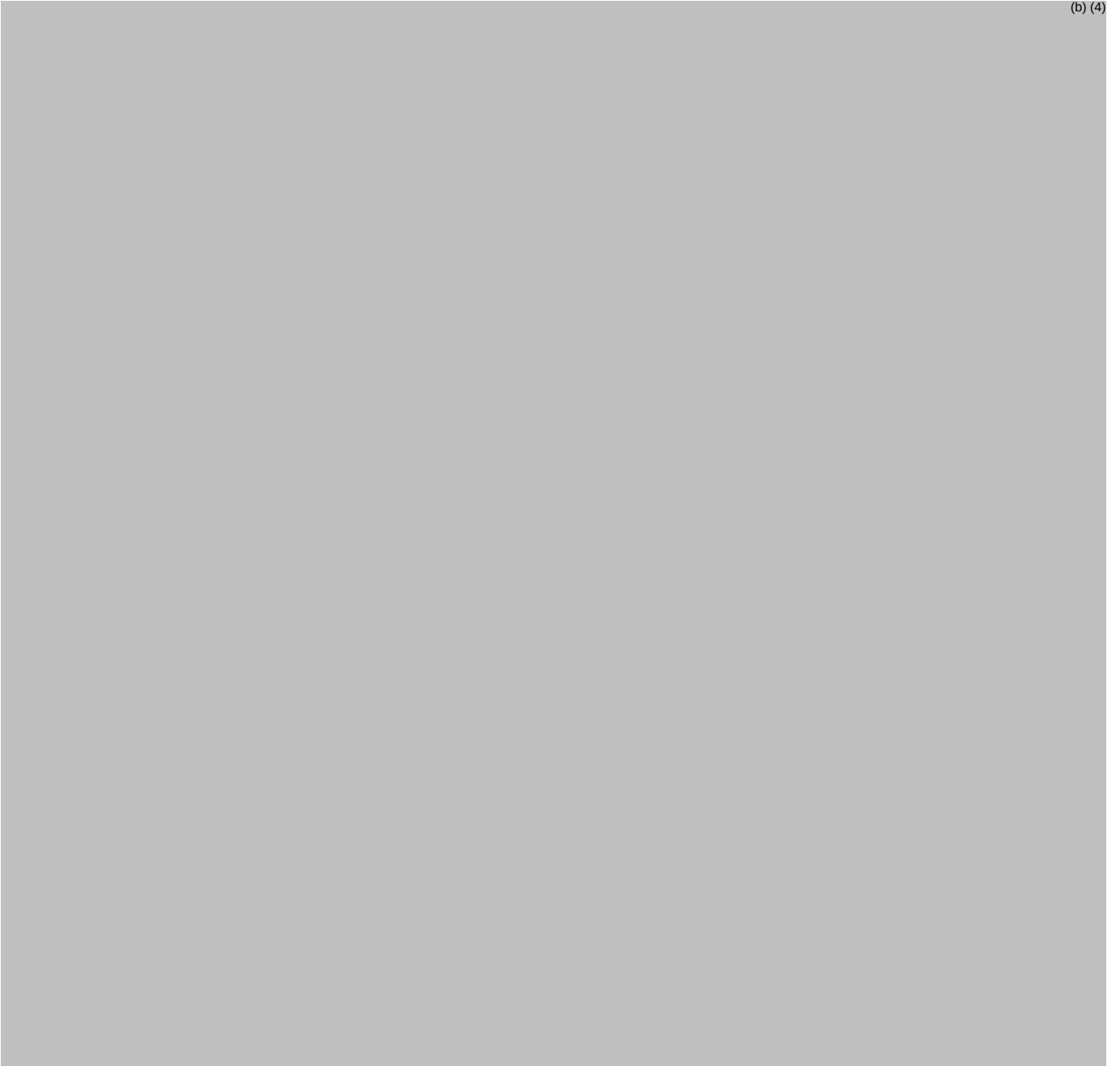
Thus, the Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a McMillan, T. Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 11. TTT ID No.: 2022-2975-2.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 18, 2023

Carton labeling

(b) (4)



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TERESA S MCMILLAN
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IDALIA E RYCHLIK
05/19/2023 01:30:32 PM

MEMORANDUM
HUMAN FACTORS STUDY RESULTS AND LABEL AND LABELING REVIEW MEMO
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma [CT-P17] ^a (adalimumab-aaty) ^b Injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Celltrion, Inc.
TTT ID #:	2023-3391-2
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CHES, CPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU) received on May 15, 2023 for Yuflyma. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the IFU for Yuflyma (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study results and label and labeling review and human factors study results and label and labeling review memo.^{c,d}

2 DISCUSSION AND CONCLUSION

The Applicant implemented all of our recommendations. Regarding our recommendation to include information as to the meaning of the clicks in the autoinjector (AI) instructions for use

^a CT-P17 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). During the writing of this review, the proposed proprietary name Yuflyma was found conditionally acceptable by DMEPA. For the purposes of this review, CT-P17 is used throughout the review to refer to this product.

^b The nonproprietary name, adalimumab-aaty, was found conditionally acceptable on March 10, 2023.

^c Bhalodia, A. Human Factors Study Results and Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 13. TTT ID No.: 2023-3391.

^d Bhalodia, A. Human Factors Study Results and Label and Labeling Review Memo for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 11. TTT ID No.: 2023-3391-1.

(IFU), the Applicant revised the 1st click and 2nd click images in step 10 figure J to include information regarding the meaning of the first click and second click (first click means *“start of injection”* and second click means *“end of injection”*); but the step 10 instruction also includes an image and a phrase *“count slowly to 5”* after the 2nd click image and phrase *“end of injection”*. As such, it was not clear why the user has to count slowly to 5 after the second click if the second click means *“end of injection”* (see image below).



Figure J

Therefore, we sent a clarification request to the Applicant via email on May 17, 2023, to clarify why the user has to *“count slowly to 5”* after the second click if the second click means *“end of injection”*. The Applicant clarified that second click does not always indicate the end of injection as the second click could occur before the end of injection. Additionally, the Applicant noted that they introduced the time difference between the second click and the end of injection as *“≤ 1 sec.”* as an additional functionality test item at batch release based on historical data. As such, the Applicant stated they would like to retain the phrase *“count slowly to 5”* in the IFU to ensure the complete administration of the full dose. Based on the Applicant’s clarification, we agree with retaining the image and the phrase *“count slowly to 5”*. However, we recommend the Applicant revise the phrase *“end of injection”* in the 2nd click image in step 10 figure J to clearly state the meaning of the second click; as the second click does not always indicate the end of injection. For example, the Applicant may consider including a phrase such as *“injection is ongoing”*.

3 RECOMMENDATIONS FOR CELLTRION, INC.

We recommend the following be implemented prior to approval of this BLA:

- A. We note you revised the 2nd click image in step 10 figure J to indicate that second click means “*end of injection*”. In your response to our clarification request sent via email on May 17, 2023, you indicated that second click does not always indicate the end of injection as the second click could occur before the end of injection and provided your rationale for retaining the phrase “*count slowly to 5*” in the IFU. We agree with retaining the image and the phrase “*count slowly to 5*”. However, we recommend that you revise the phrase “*end of injection*” in the 2nd click image in step 10 figure J to clearly state the meaning of the second click; as the second click does not always indicate the end of injection. For example, you may consider including a phrase such as “*injection is ongoing*”.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 15, 2023

Response to Information Request #1: <\\CDSESUB1\EVSPROD\bla761219\0067\m1\us\other-information-amendment-1.pdf>

Response to Information Request #2: <\\CDSESUB1\EVSPROD\bla761219\0067\m1\us\other-information-amendment-2.pdf>

Response to Information Request #3: <\\CDSESUB1\EVSPROD\bla761219\0067\m1\us\other-information-amendment-3.pdf>

Response to Information Request #4: <\\CDSESUB1\EVSPROD\bla761219\0067\m1\us\other-information-amendment-4.pdf>

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 16, 2023

To: Sadaf Nabavian, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for YUFLUMA (adalimumab-aaty) injection, for subcutaneous use

BLA: 761219

Background:

In response to DRTM's consult request dated April 8, 2021, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for YUFLUMA (adalimumab-aaty) injection, for subcutaneous use.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI, Medication Guide, and IFU is based on the draft labeling emailed to OPDP on May 12, 2023, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on May 16, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
05/16/2023 04:38:19 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 11, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma (adalimumab-aaty) Injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Celltrion, Inc.
TTT ID #:	2022-2975-2
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 27, 2023 for Yuflyma. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container label and carton labeling for Yuflyma (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective because the prefilled syringe and autoinjector carton labeling is not adequately differentiated from each other to minimize selection errors. We provide recommendations in Section 3.

^a McMillan, T. Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2023 APR 20. TTT ID No.: 2022-2975-1.

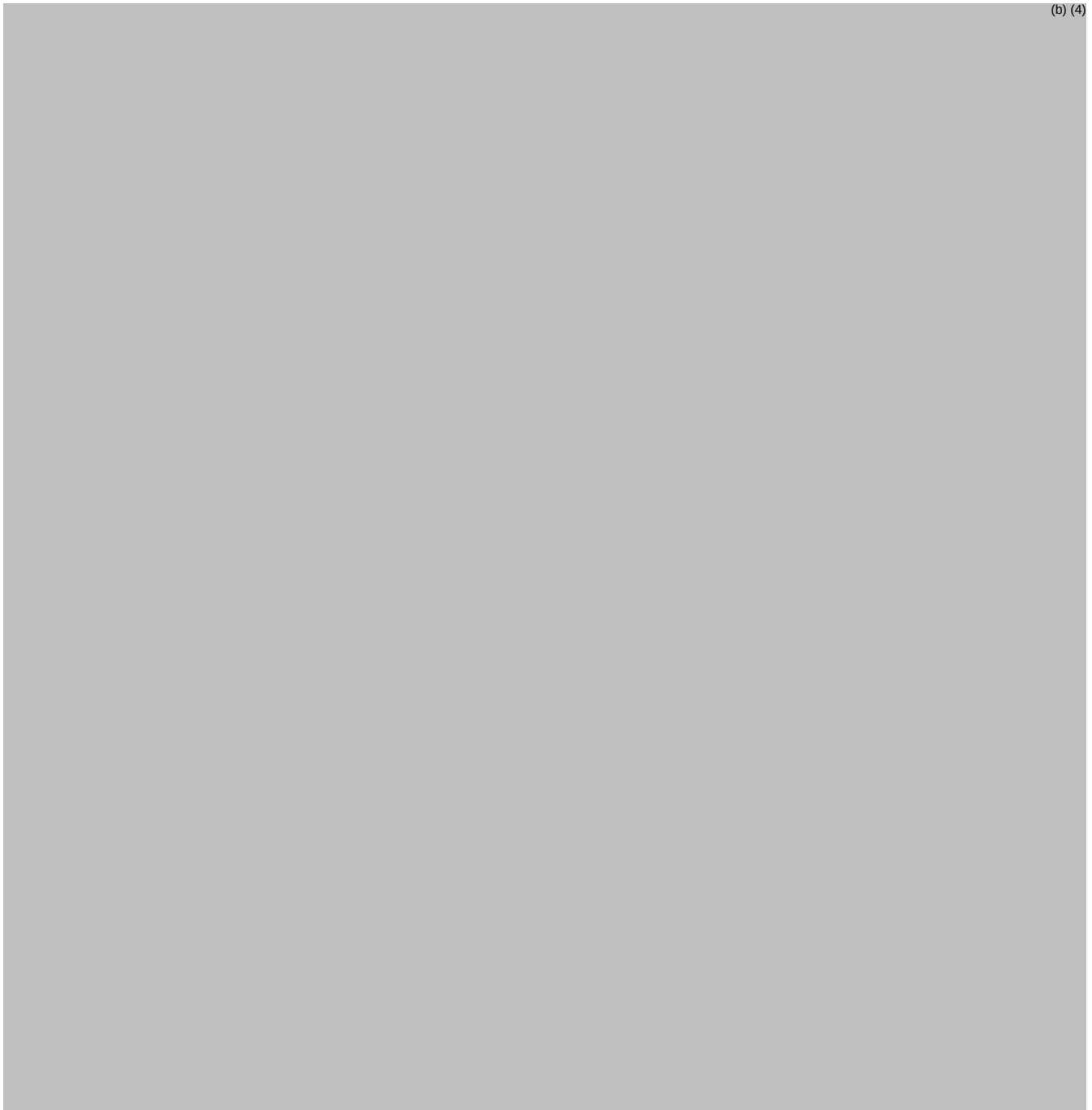
3 RECOMMENDATIONS FOR CELLTRION, INC.

We recommend the following be implemented prior to approval of this BLA supplement:

- A. The same (b) (4) color scheme is used between all presentations [the prefilled syringe (PFS), PFS w/ safety guard and the autoinjector (AI)]. To provide further differentiation and to prevent dispensing errors between these three presentations consider the use of a distinctly different highlight color other than the proposed (b) (4) color on the folds of the carton labeling and on the image of the device for two
- B. out of three of the proposed device carton labeling.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 27, 2023

Carton labeling



(b) (4)

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TERESA S MCMILLAN
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IDALIA E RYCHLIK
05/15/2023 11:53:05 AM

MEMORANDUM

HUMAN FACTORS STUDY RESULTS AND LABEL AND LABELING REVIEW MEMO

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 11, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma [CT-P17] ^a (adalimumab-aaty) ^b Injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Celltrion, Inc.
TTT ID #:	2023-3391-1
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CHES, CPH

1 PURPOSE OF MEMORANDUM

On May 3, 2023, the Applicant submitted revised instructions for use (IFUs) for Yuflyma. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the IFUs for Yuflyma (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study results and label and labeling review.^c

2 DISCUSSION AND CONCLUSION

The Applicant did not implement our recommendation to include information regarding the meaning of the clicks in the autoinjector (AI) instructions for use (IFU). Per the Applicant's cover letter, they indicate that they revised the IFU according to all of FDA comments. We continue to recommend that the Applicant include the meaning of the clicks in step 10 of the AI IFU.

^a CT-P17 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). During the writing of this review, the proposed proprietary name Yuflyma was found conditionally acceptable by DMEPA. For the purposes of this review, CT-P17 is used throughout the review to refer to this product.

^b The nonproprietary name, adalimumab-aaty, was found conditionally acceptable on March 10, 2023.

^c Bhalodia, A. Human Factors Study Results and Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 13. TTT ID No.: 2023-3391.

Regarding our recommendation to label the needle location within the device in the AI IFU, we note that the Applicant added the text, “*because the Needle is inside the Needle Cover*” in step 8; however, they did not label the needle location within the device. As such, we recommend that the Applicant label the needle location within the device in Figure A to ensure users are aware that needle is inside the needle cover.

Regarding our recommendation to “*Revise the statement in Step 11b to correspond with the image in Figure K to show that there is grey color remaining in the window after the injection completion.*”, we note that the Applicant added the statement, “*You may see grey stopper in the window. This is normal.*” in step 11 (see Figure 1 below). However, this statement is not next to the instruction that tells the user to wait until the window turns completely blue. The lack of proximity next to the aforementioned instruction may lead to confusion. As such, we recommend moving the statement “*You may see grey stopper in the Window. This is normal.*” next to second bullet in Step 11 of the AI IFU, “*If the Window has not turned completely blue or if the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.*”

Figure 1

- If the Window has not turned completely blue or if the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.
- Some bleeding may occur.
- **Do not** reuse the Auto-injector.
- **Do not** rub the injection site.
- You may see grey stopper in the Window. This is normal.

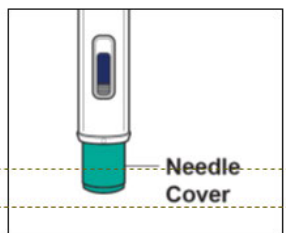


Figure L

Additionally, we note there are three comments in the track change, word version document that are not in English. Specifically, one comment is in PFS-S IFU on page 56 and two comments are in PFS IFU on pages 61 and 64. We request the Applicant clarify what those comments mean.

3 RECOMMENDATIONS FOR CELLTRION, INC.

We recommend the following be implemented prior to approval of this BLA:

- A. We note you did not implement our recommendation to include information regarding the meaning of the clicks in the autoinjector (AI) instructions for use (IFU). In your cover letter, you indicate that you revised the IFU according to all of FDA comments. However, we note that you did not implement abovementioned recommendation. We continue to recommend you include the meaning of the clicks (first click and second click) in step 10 of the AI IFU. For example, the first click means the start of the injection.
- B. Regarding our recommendation to label the needle location within the device AI IFU, we note that you added the text, “*because the Needle is inside the Needle Cover*” in step 8; however, you did not label the needle location within the device. We recommend revising the Figure A to label the needle location within the device to ensure users are

aware that needle is inside the needle cover. For example, consider adding “needle inside” in the parenthesis next to needle cover in Figure A.

- C. Regarding our recommendation to “*Revise the statement in Step 11b to correspond with the image in Figure K to show that there is grey color remaining in the window after the injection completion.*”, we note that you added the statement, “*You may see grey stopper in the window. This is normal.*” in step 11 (see Figure 1 below). However, this statement is not next to the instruction that tells the user to wait until the window turns completely blue. The lack of proximity next to the aforementioned instruction may lead to confusion. As such, we recommend moving the statement “*You may see grey stopper in the Window. This is normal.*” next to second bullet in Step 11 of the AI IFU, “*If the Window has not turned completely blue or if the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.*”

Figure 1

- If the Window has not turned completely blue or if the medicine is still injecting, this means you have not received a full dose. Call your healthcare provider immediately.
- Some bleeding may occur.
- **Do not** reuse the Auto-injector.
- **Do not** rub the injection site.
- You may see grey stopper in the Window.
This is normal.

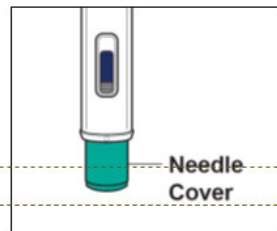


Figure L

- D. Additionally, we note there are three comments in the track change, word version document that are not in English. Specifically, one comment is in PFS-S IFU on page 56 and two comments are in PFS IFU on pages 61 and 64. Please clarify what those comments mean.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 3, 2023

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 20, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma (adalimumab-aaty) Injection, 40 mg/0.4 mL
Applicant/Sponsor Name:	Celltrion, Inc.
TTT ID #:	2022-2975-1
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 17, 2023 for Yuflyma. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container labels and carton labeling for Yuflyma (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective because the prefilled syringe and autoinjector carton labeling is not adequately differentiated from each other to minimize selection errors. We provide recommendations in Section 3.

^a McMillan, T. Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 05. TTT ID No.: 2022-2975.

3 RECOMMENDATIONS FOR CELLTRION, INC.

We recommend the following be implemented prior to approval of this BLA supplement:

- A. We acknowledge your intent to clearly differentiate between the prefilled pens/autoinjector and prefilled syringes carton labeling [REDACTED] (b) (4)

[REDACTED] However, the prefilled pens/autoinjector and prefilled syringes carton labeling is still not adequately differentiated. Increase the prominence of the terms autoinjector/prefilled syringe and the net quantity statements by using different colors, boxing, or some other means to provide adequate differentiation.

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IDALIA E RYCHLIK
04/20/2023 04:01:34 PM

ADDENDUM TO
COMPARATIVE ANALYSES, HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING
REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 13, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form and Strength:	Yuflyma [CT-P17] ^a (adalimumab-aaty) ^b Injection, 40 mg/0.4 mL
Device Constituent	Prefilled autoinjector; prefilled syringe; prefilled syringe with safety guard
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celltrion, Inc.
Submission Date:	November 30, 2022
TTT ID #:	2023-3391
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CHES, CPH
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

^a CT-P17 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). During the writing of this review, the proposed proprietary name Yuflyma was found conditionally acceptable by DMEPA. For the purposes of this review, CT-P17 is used throughout the review to refer to this product.

^b The nonproprietary name, adalimumab-aaty, was found conditionally acceptable on March 10, 2023.

1 PURPOSE OF ADDENDUM

This memorandum serves as an addendum to the comparative analyses, human factors (HF) validation study report and labels and labeling review completed on November 23, 2021.^c This addendum provides revised labels and labeling recommendations based on the HF validation study results submitted on November 24, 2020, and June 30, 2021 (see Appendix A).

1.1 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On April 30, 2019, the Applicant submitted the following under IND 135944:
 - o HF validation study protocol, Use-Related Risk Analysis (URRA) and instructions for use (IFU) for CT-P17 injection, 40 mg/0.4 mL autoinjector (AI). We reviewed the protocol and provided recommendations.^d
 - o URRA for CT-P17 injection, 40 mg/0.4 mL prefilled syringe (PFS) and prefilled syringe with safety guard (PFS-S). The Applicant's proposal was to leverage HF data from CT-P13-SC PFS in lieu of submitting additional HF data to support CT-P17 PFS and PFS-S. We did not agree with the Applicant's proposal since CT-P13-SC PFS was not an approved product at the time.^e As such, we recommended that the Applicant submit their HF validation study protocol for the PFS and PFS-S configurations, for our review.
- On October 29, 2019, the Applicant submitted a follow-up question to the Agency's Human Factors Advice.^e The Applicant's question was unclear, so we issued an information request (IR) asking them to clarify. Subsequently, the Applicant clarified that they would submit separate HF validation studies for CT-P17 PFS and PFS-S, thus, no additional response from the Agency for the submitted follow-up query was required.^f
- On November 24, 2020, the Applicant submitted a biologics license application (BLA) for CT-P17 injection, 40 mg/0.4 mL under BLA 761219. This submission included HF validation study results reports for AI, PFS, and PFS-S. We reviewed the results and had labels and labeling recommendations based on the results and best labeling practices.
- On November 23, 2021, we finalized our HF validation study results reports and labels and labeling review in DARRTS.^c However, our recommendations were not sent to the

^c Bhalodia, A. comparative analyses, human factors study report and labels and labeling review for CT-P17 (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 23. RCM No.: 2020-2472; 2020-2476.

^d Flint, J. Human Factors Validation Study Protocol Review for CT-P17 (IND 135944). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 24. RCM No.: 2019-977.

^e Flint, J. Use-Related Risk Analysis Review for CT-P17 (IND 135944). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 30. RCM No.: 2019-977.

^f Flint, J. Review of Response to Human Factors Advice Memorandum for CT-P17 (IND 135944). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2019 DEC 20. RCM No.: 2019-977-1.

Applicant because the Applicant received a complete response (CR) letter dated November 24, 2021, due to facility issues.^g

- On May 27, 2022, the Applicant resubmitted a BLA for CT-P17 injection, 40 mg/0.4 mL under BLA 761219. This submission did not include the HF validation study results reports as the Applicant had initially submitted these results in their original BLA submission dated November 24, 2020.
- On November 23, 2022, the Applicant received another CR letter due to facility issues.^h
- On November 30, 2022, the Applicant resubmitted a BLA for CT-P17 injection, 40 mg/0.4 mL under BLA 761219. This submission did not include the HF validation study results reports as the Applicant had initially submitted these results in their original BLA submission dated November 24, 2020. As such, the HF validation study results reports submitted on November 24, 2020; is the focus of this memorandum.

2 DISCUSSION AND CONCLUSION

On November 24, 2020, the Applicant submitted a biologics license application (BLA) for CT-P17 injection, 40 mg/0.4 mL under BLA 761219. This submission included human factors (HF) validation study results reports for autoinjector (AI), prefilled syringe (PFS), and prefilled syringe with safety guard (PFS-S). We reviewed the HF validation study results reports and finalized our review in DARRTS on November 23, 2021. In our review, we found the results of the HF validation studies acceptable. Our evaluation of the proposed packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. We recommended the Applicant revise the entire instructions for use (IFU) to align with the reference product US-licensed Humira 40 mg/0.4 mL IFU with appropriate modifications for specific product design differences. At the time of our review, the Agency recommended that Applicants of proposed biosimilars product consider modifying their IFU to align with the reference product IFU with appropriate modifications for specific product design differences. Subsequently, we noted the recommendations in our review dated November 23, 2021, were not sent to the Applicant because the Applicant received a complete response (CR) letter dated November 24, 2021, due to facility issues.^g

On November 30, 2022, the Applicant resubmitted a BLA for CT-P17 injection, 40 mg/0.4 mL under BLA 761219. This submission did not include the HF validation study results reports as the Applicant had initially submitted these results reports in their original BLA submission dated November 24, 2020. Our review was finalized in DARRTS on November 23, 2021; however, our recommendations were not conveyed to the Applicant at that time. Subsequent to finalizing our review, it was determined that we would not request certain changes to the labeling as identified in our November 23, 2021, review.

^g Nabavian, S. Complete Response for CT-P17. Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2021 NOV 24. BLA 761219. Available from: <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af8062c576>.

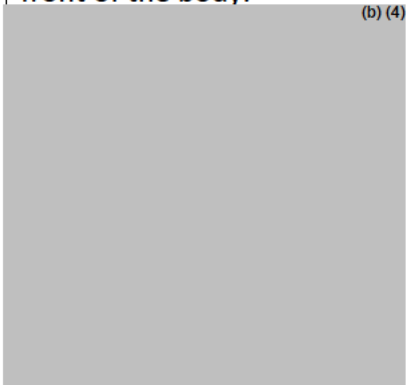
^h Nabavian, S. Complete Response for CT-P17. Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2022 NOV 23. BLA 761219. Available from: <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af8069b884>.

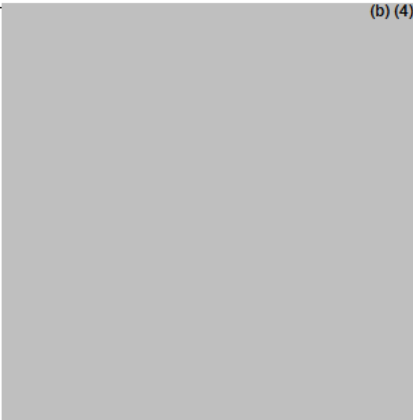
Therefore, we provide revised IFU recommendations based on the HF validation study results and best labeling practices, in Table A: Identified Issues and Recommendations for the Celltrion (the Applicant) below. We ask that the Division of Rheumatology and Transplant Medicine (DRTM) convey Table A in its entirety to the Applicant so that recommendations are implemented prior to approval of this BLA 761219. These changes can be implemented without submitting additional HF validation testing data for Agency review. Additionally, we note that the DMEPA 1 primary review team evaluated product specific label and labeling under separate cover.ⁱ

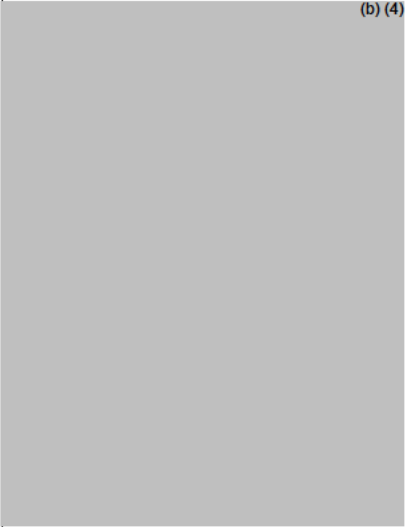
3 RECOMMENDATIONS FOR CELLTRION, INC.

Our evaluation of your human factors (HF) validation study indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised label and labeling for our review. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation data for Agency review.

ⁱ McMillan, T. Label and Labeling Review for Yuflyma (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 5. TTT ID #: 2022-2975.

Table A: Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU) for the Autoinjector (AI), Prefilled Syringe (PFS), Prefilled Syringe with Safety Guard (PFS-S)			
1.	It is unclear if the image in Figure E is depicting the front of the body.  (b) (4) <i>Figure E</i>	Lack of clarity regarding the image in Figure E may lead to wrong injection site selection. The AI and PFS-S Human Factors (HF) validation study results identified subjective feedback that indicated that participants thought the IFU step 5 image in Figure E looked like the back of the person and suggested the image should include more details to show it is the front of the person.	Consider revising the IFU Figure E to clearly depict that it is the front of the person.
2.	The image in Figure G is not clearly depicting that you are supposed to clean the injection site with an alcohol swab.	We are concerned if the user does not clean the injection site with an alcohol swab, there is risk of minor or major infection. The PFS-S HF validation study results identified subjective feedback that indicated that participants interpreted the image in Figure G, as depicting how to place a bandage.	We recommend revising the IFU figure G to clearly depict that you are supposed to clean the injection site with an alcohol swab.

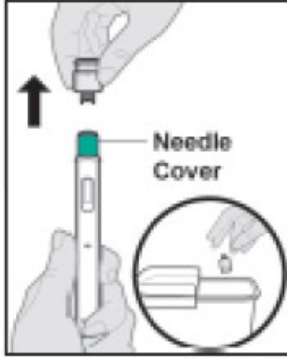
	 (b) (4) <i>Figure G</i>		
3.	Subtasks in Step 2 to inspect the device does not flow naturally. For example, task to check the device for damage is between the tasks to check the label for correct medication and dose and expiration.	Order of the instructions in the device may lead to confusion. The PFS HF validation study results identified subjective feedback that indicated that it was not logical to check the syringe for damage (Step 2b) before checking the expiration date (Step 2c).	We recommend revising the IFU Step 2 by switching the comments in step 2b “Look at the Autoinjector and make sure it is not cracked or damaged.” and “Look at the Prefilled Syringe and make sure it is not cracked or damaged.” with 2c “Check the expiration date on the label of the Autoinjector (<i>see Figure B</i>).” and “Check the expiration date on the label of the Prefilled Syringe (<i>see Figure B</i>).” respectively.
Instructions for Use (IFU) for the PFS and PFS-S			
1.	Instruction to dispose of the cap in Step 8 is not prominent.	We are concerned that due to the formatting of the text in Step 8, instruction to dispose of the cap can be overlooked. The HF validation study results identified subjective feedback that indicated that the participant did not read the “Dispose of the cap...” in Step	We recommend revising the IFU Step 8a to make the instruction to dispose of the cap more prominent, for example by including it as a separate bullet, or some other means.

		8a because there was too much text in Step 8a. The participant stated, "the text did not stand out since it was not its own bullet point."	
2.	The image in Figure I does not clearly depict that skin needs to be pinched. (b) (4)  <i>Figure I</i>	Lack of clarity in the pinching skin step may lead to discomfort. The HF validation study results identified subjective feedback that indicated that Figure I in Step 9 did not clearly depict pinched skin.	We recommend revising IFU Figure I to clearly depict pinching of the skin.
3.	Instruction to not change the position of the PFS is in the wrong location under Step 10 "Give the injection".	We are concerned that changing the position of the PFS after injection has started may lead to partial therapy, delay of therapy, minor injury, major injury, or discomfort. The HF validation study results identified subjective feedback that indicated that a	We recommend revising the IFU to move the warning, "Do not change the position of the pre-filled syringe after the injection has started" from Step 10b to Step 9b.

		participant did not see the warning because it was not located in Step 9.	
Instructions for Use (IFU) for the AI			
1.	Instruction to rotate the injection site in Step 5 is not prominent.	We are concerned due to lack of prominence, information to rotate the injection site can be overlooked. The HF validation study results identified subjective feedback that indicated that participants thought it was not prominent.	We recommend revising the IFU Step 5 to make the instruction to rotate the injection site prominent.
2.	It is unclear where the needle is when removing the cap.	Lack of clarity regarding the needle location within the device may lead to accidental needle stick. The HF validation study results identified subjective feedback that indicated that the participants were unsure where the needle is located when removing the cap. Additionally, participants stated there should be an instruction in the IFU informing the user of the needle location within the device.	We recommend revising the IFU to label the needle location within the device to ensure users are aware that needle is inside the needle cover.
3.	Step 10 and the image in Figure J does not clearly depict how long it would take to administer the injection and the image in Figure J does not include	We are concerned that there is a risk of partial therapy, major injury, or minor injury if user does not hold the device against the skin at the injection site until the second audible click is heard and slowly	We recommend making the following revisions in Step 10: - include the time it takes to complete the injection. - Include information that informs the user to keep holding the AI against the skin

	information regarding the meaning of the clicks.	count to 5 to ensure the full dose has been injected. The HF validation study results identified subjective feedback that indicated that some participants stated that step 10 and the image in Figure J does not clearly depict how long it will take to administer the injection and the image in Figure J does not include information regarding the meaning of the clicks.	between the first and second click, and during the step to “Count slowly to 5” • In Figure J, make the statement “Then, count slowly to 5” more prominent. • In Figure J, include information regarding the meaning of the clicks.
4.	There is discrepancy between the image in Figure K and the instruction in Step 11b regarding filling of the window. The instruction in Step 11b states, "If the window has not turned completely blue or if the medicine is still injecting, this means you have not received a full dose.", however, the image in Figure K depicts a grey color remaining in the window.	This discrepancy regarding filling of the window may lead to confusion. The HF validation study results identified subjective feedback that indicated that participants had difficulty confirming the injection completion because Step 11b tells the user to wait until the window turns completely blue, however, the image in Figure K depicts a grey color remaining in the window.	Revise the statement in Step 11b to correspond with the image in Figure K to show that there is grey color remaining in the window after the injection completion.

	Figure K		
5.	Instructions to confirm injection completion is in the wrong location under Step 11 “Remove the Autoinjector from (b) (4) ”.	We are concerned that there is a risk of partial therapy (one dose) or partial therapy (multiple doses) if the user does not confirm the injection completion. The HF validation study results identified subjective feedback that indicated that a participant did not read step 11a because he thought Step 11 “Remove the Autoinjector from (b) (4) ” only described removing the AI as the title, “Remove the Autoinjector from (b) (4) ” does not convey the need to check the window to confirm injection completion.	We recommend revising the IFU to move the statement in step 11a, “Look at the Autoinjector and make sure that the blue Plunger Rod is filling the Window completely” as Step 10d to ensure that the user reviews the window prior to removing the pen to ensure that the drug content has been delivered.
6.	The instruction to dispose of the cap in Step 8 and the image in Figure H are not prominent.	We are concerned that due to the formatting of the text in Step 8, instruction to dispose of the cap	We recommend revising the IFU Step 8 to make the instruction to dispose of the cap more prominent, for example by including it as a separate bullet, or some other means.

		can be overlooked.  <i>Figure H</i>	Additionally, we recommend revising the image in Figure H to make it clear that it is the FDA cleared sharps container.
7.	Step 11 title does not clearly instruct the user to remove the AI from their skin.	Lack of clarity regarding removing the AI from the skin may lead to confusion.	Consider revising step 11 title to clearly instruct the user to remove the AI from their skin. For example, 11. Remove the Autoinjector from your skin
Instructions for Use (IFU) for the PFS-S			
1.	We note inconsistency in the labeling of the PFS. For example, in the PFS IFU, body of the syringe is labeled in image of Figure A, while in the PFS-S IFU, body of the syringe is not labeled in image of Figure A. PFS:	Lack of consistency between the PFS and PFS-S IFU may lead to confusion.	We recommend revising the IFU to label the image in Figure A (Parts of the Yuflyma pre-filled syringe) with injector body.

1 Page(s) of Draft Label22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT RECEIVED ON
NOVEMBER 24, 2020, AND JUNE 30, 2021

The HF study results report for AI can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761219\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis\5354-other-stud-rep\ct-p17\ct-p17-human-factor-report-ai.pdf>

The HF study results report for PFS can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761219\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis\5354-other-stud-rep\ct-p17\ct-p17-human-factor-report-pfs.pdf>

The HF study results report for PFS-S can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761219\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis\5354-other-stud-rep\ct-p17\ct-p17-human-factor-report-pfs-s.pdf>

The HF study results report for PFS-S – JIA addendum report can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761219\0019\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rheumatoid-arthritis\5354-other-stud-rep\ct-p17\ct-p17-human-factor-report-pfs-s-addendum.pdf>

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AVANI BHALODIA
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JASON A FLINT
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 5, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761219
Product Name, Dosage Form, and Strength:	Yuflyma (adalimumab-aaty) Injection, 40 mg/0.4 ML
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celltrion, Inc.
FDA Received Date:	November 30, 2022
TTT ID #:	2022-2975
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Yuflyma (adalimumab-aaty) Injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Yuflyma prescribing information (PI), Instructions for Use (IFU), and the Medication Guide (MG), carton labels, and container labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

BLA 761219 is a proposed biosimilar to US-licensed Humira (adalimumab) originally submitted on November 24, 2020. However, BLA 761219 received a Complete Response (CR) letter on November 24, 2021^a. Subsequently, Celltrion submitted a Class 2 Resubmission on May 27, 2022. However, BLA 761219 received a CR letter again on November 23, 2022^b. Thus, Celltrion submitted a Class 2 Resubmission on November 30, 2022.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

^a Nikolov, N.P. Complete Response (BLA 7611219). Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2021 Nov 24.

^b Nikolov, N.P. Complete Response (BLA 7611219). Silver Spring (MD): FDA, CDER, OND, DRTM (US); 2022 Nov 23.

3 CONCLUSION AND RECOMMENDATIONS

Our review of the proposed Instructions for Use (IFU) and the Medication Guide (MG) did not identify areas of vulnerability that may lead to medication errors. However, prescribing information, the carton labels, and container labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and Section 5 for Celltrion, Inc.

DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE (DRTM)

Table 2. Identified Issues and Recommendations for Division of Rheumatology and Transplant Medicine (DRTM)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The nonproprietary name suffix placeholder “xxx” has not been defined.	An undefined nonproprietary name suffix placeholder may lead to identification medication errors.	Per our Nonproprietary Name Suffix Advice letter dated March 2, 2023, the nonproprietary name, adalimumab-aaty, was found conditionally acceptable. Revise the nonproprietary name to read “adalimumab-aaty” throughout the labels and labeling.
2.	The abbreviation ‘AI’ is utilized as a descriptor and follows the Proprietary name Yuflyma throughout the prescribing information.	The use of abbreviations as descriptors may be misleading. Additionally, the placement of this abbreviated descriptor follows the proprietary name as if being utilized as a modifier and does not align with the presentation of the Proprietary name on the carton and container.	Spell out the intended meaning of the descriptor AI throughout the PI. Revise Yuflyma AI to Yuflyma autoinjector.

5 RECOMMENDATIONS FOR CELLTRION, INC.

Table 3. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling (all)			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	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.
2.	The nonproprietary name suffix placeholder “xxxx” has not been defined.	An undefined nonproprietary name suffix placeholder may lead to identification medication errors.	Per our Nonproprietary Name Suffix Advice letter dated March 2, 2023, the nonproprietary name, adalimumab-aaty, was found

Table 3. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			conditionally acceptable. Revise the nonproprietary name to read “adalimumab-aaty” throughout the labels and labeling.
3.	The barcode has not been defined and appears as the following: (b) (4)	An undefined barcode may lead to identification medication errors.	Remove “barcode” placeholder and replace it with the actual barcode.
4.	The prefilled syringe and prefilled autoinjector container labels and carton labeling are not adequately differentiated.	Lack of adequate differentiation may contribute to selection errors amongst product presentations.	We are aware of reported medication selection errors with prefilled pens/autoinjectors and prefilled syringes as reported by ISMP. ^c These errors may result in a delay in therapy or the user’s inability to operate the device. Therefore, it is recommended all presentations labels/labeling are clearly differentiated from each other to minimize medication selection errors. Consider the use of different colors, boxing, or some other

^c Community/Ambulatory Care ISMP Medication Safety Alert: “Look-alike cartons: Potential for wrong specialty product to be dispensed”. FEBRUARY 2002: VOLUME 21: ISSUE 2.

Table 3. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			means to provide adequate differentiation between all proposed presentations.
Container Label(s) [all]			
1.	It is not clear what the empty box outline/code on the container label is meant to represent. (b) (4)	Unidentifiable codes and/or empty boxes may lead to confusion.	Please clarify the purpose of the empty box outline/code.
2.	The container label barcode appears to be in a horizontal orientation.	Barcodes placed in a horizontal position may not scan due to vial curvature.	Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode.
3.	The container label does not include a 2D data matrix barcode.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act. ^{18d} . The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.

^d [Product Identifiers under the Drug Supply Chain Security Act](#)

Table 3. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		and homogenous case of a product.	
Carton Labeling			
1.	The dosage form has been omitted from the principal display panel (PDP).	Omitting the dosage form may lead to wrong formulation errors.	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.
2.	The “Dispense the enclosed Medication Guide to each patient” statement has been omitted.	Inclusion of this statement is required per 21 CFR 208.24(d) and 21 CFR 610.60(a)(7).	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”
3.	The recommended dosage statement is inconsistent with the Prescribing Information.	Inconsistent dosage statements may lead to dosing medication errors.	For consistency, revise the “(b) (4)” statement to “Recommended Dosage: See prescribing information.”
4.	The 2D data matrix barcode has not been defined.	Undefined 2D data matrix barcode may lead to identification errors.	Replace the barcode placeholder with the actual 2D matrix barcode.

Table 3. Identified Issues and Recommendations for Celltrion, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	The prefilled syringe and autoinjector images are no prominent.	Lack of prominence of these images can lead to selection medication errors.	Increase the prominence of the prefilled syringe and autoinjector images on the principal display panel taken into account not to compete with the prominence of other important information such as the proprietary and proper names, dosage form, strength, and route of administration.
6.	The back panel of the autoinjector carton labeling has the following statement: (b) (4) (b) (4)	Inaccurate information regarding the content of the carton may lead to confusion.	Revise carton labeling back panel for 1 pack AI to state “1 Single-dose Autoinjector”.

Additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Yuflyma that Celltrion, Inc. submitted on May 27, 2022.

Table 4. Relevant Product Information for Yuflyma	
Initial Approval Date	N/A
Nonproprietary name	Adalimumab-aaty
Indication	• Rheumatoid Arthritis (RA): reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile Idiopathic Arthritis (JIA): reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older. • Psoriatic Arthritis (PsA): reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • Ankylosing Spondylitis (AS): reducing signs and symptoms in adult patients with active AS. • Crohn's Disease (CD): treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older. • Ulcerative Colitis (UC): treatment of moderately to severely active ulcerative colitis in adults. <u>Limitations of Use:</u> Effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque Psoriasis (Ps): treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. • Hidradenitis Suppurativa (HS): treatment of adult patients with moderate to severe hidradenitis suppurativa.
Route of Administration	Subcutaneous

Dosage Form	Injection								
Strength	40 mg/0.4 mL								
Dose and Frequency	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: • <i>Adults</i>: 40 mg every other week. • Some patients with RA not receiving methotrexate may benefit from increasing the dosage to 40 mg every week or 80 mg every other week. Juvenile Idiopathic Arthritis: • ≥ 30 kg (66 lbs): 40 mg every other week Crohn's Disease: • <i>Adults</i>: 160 mg on Day 1 (given in one day or split over two consecutive days); 80 mg on Day 15; and 40 mg every other week starting on Day 29. • <i>Pediatric Patients 6 Years of Age and Older</i>: <table border="1"><thead><tr><th rowspan="2">Pediatric Weight</th><th colspan="2">Recommended Dosage</th></tr><tr><th>Days 1 through 15</th><th>Starting on Day 29*</th></tr></thead><tbody><tr><td>40 kg (88 lbs) and greater</td><td>Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg</td><td>40 mg every other week</td></tr></tbody></table> *Continue the recommended pediatric dosage in patients who turn 18 years of age and who are well-controlled on their YUFLYMA regimen. Ulcerative Colitis: • <i>Adults</i>: 160 mg on Day 1 (given in one day or split over two consecutive days), 80 mg on Day 15 and 40 mg every other week starting on Day 29. Discontinue in patients without evidence of clinical remission by eight weeks (Day 57). Plaque Psoriasis: • 80 mg initial dose followed by 40 mg every other week starting one week after initial dose. Hidradenitis Suppurativa : • <i>Adults</i>: Day 1: 160 mg (given in one day or split over two consecutive days) Day 15: 80 mg Day 29 and subsequent doses: 40 mg every week or 80 mg every other week	Pediatric Weight	Recommended Dosage		Days 1 through 15	Starting on Day 29*	40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week
Pediatric Weight	Recommended Dosage								
	Days 1 through 15	Starting on Day 29*							
40 kg (88 lbs) and greater	Day 1: 160 mg (single dose or split over two consecutive days) Day 15: 80 mg	40 mg every other week							
How Supplied	YUFLYMA (adalimumab-xxxx) is supplied as a preservative-free, sterile, clear to opalescent, and colorless to pale brown solution for subcutaneous administration. The following packaging configurations are available. • YUFLYMA AI Carton - 40 mg/0.4 mL 1 pack YUFLYMA is supplied in a carton containing two alcohol preps and a single-dose prefilled auto-injector, containing a 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, providing 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4)								

	• YUFLYMA AI Carton - 40 mg/0.4 mL 2 pack YUFLYMA is supplied in a carton containing two alcohol preps and two single-dose prefilled auto-injectors, each containing a 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, providing 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • YUFLYMA AI Carton - 40 mg/0.4 mL 4 pack YUFLYMA is supplied in a carton containing four alcohol preps and four single-dose prefilled auto-injectors, each containing a 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, providing 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • YUFLYMA AI Carton - 40 mg/0.4 mL 6 pack YUFLYMA is supplied in a carton containing six alcohol preps and six single-dose prefilled auto-injectors, each containing a 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, providing 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe with Safety Guard Carton - 40 mg/0.4 mL 1 pack YUFLYMA is supplied in a carton containing two alcohol preps and a single-dose prefilled syringe with safety guard, 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, providing 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe with Safety Guard Carton - 40 mg/0.4 mL 2 pack YUFLYMA is supplied in a carton containing two alcohol preps and two single-dose prefilled syringes with safety guard, each containing 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, and 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe with Safety Guard Carton - 40 mg/0.4 mL 4 pack YUFLYMA is supplied in a carton containing four alcohol preps and four single-dose prefilled syringes with safety guard, each containing 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, and 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4)
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	• Prefilled Syringe with Safety Guard Carton - 40 mg/0.4 mL 6 pack YUFLYMA is supplied in a carton containing six alcohol preps and six single-dose prefilled syringes with safety guard, each containing 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, and 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe Carton - 40 mg/0.4 mL 1 pack YUFLYMA is supplied in a carton containing two alcohol preps and a single-dose prefilled syringe, 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, providing 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe Carton - 40 mg/0.4 mL 2 pack YUFLYMA is supplied in a carton containing two alcohol preps and two single-dose prefilled syringes, each containing 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, and 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe Carton - 40 mg/0.4 mL 4 pack YUFLYMA is supplied in a carton containing four alcohol preps and four single-dose prefilled syringes, each containing 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, and 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4) • Prefilled Syringe Carton - 40 mg/0.4 mL 6 pack YUFLYMA is supplied in a carton containing six alcohol preps and six single-dose prefilled syringes, each containing 1 mL prefilled syringe with a fixed thin wall, ½ inch needle, and 40 mg/0.4 mL of YUFLYMA. The NDC number is (b) (4)
Storage	Do not use beyond the expiration date on the container. YUFLYMA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, YUFLYMA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 30 days, with protection from light. YUFLYMA should be discarded if not used within the 30-day period. Record

	the date when YUFLYMA is first removed from the refrigerator in the spaces provided on the carton and dose pack. Do not store YUFLYMA in extreme heat or cold.
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APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 26, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Yuflyma. Our search identified one previous review^e, and we confirmed that our previous recommendations were implemented.

^e Bhalodia, A. COMPARATIVE ANALYSES, HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW for Yuflyma (CT-P17) (adalimumab-aaty) (BLA 761219). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 23. RCM No.: 2020-2472; 2020-2476.

APPENDIX C. ISMP NEWSLETTERS-N/A

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)-N/A

APPENDIX E. N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Yuflyma labels and labeling submitted by Celltrion, Inc..

- Container label(s) received on May 27, 2022
- Carton labeling received on May 27, 2022
- Prescribing Information, Instructions for Use, and Medication Guide (Image not shown) received on October 18, 2022, available from <\\CDSESUB1\EVSPROD\bla761219\0056\m1\us\draft-labeling-text-clean.docx>

F.2 Label and Labeling Images- 40 mg/0.4 mL prefilled syringe and autoinjector

Container label(s)



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^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

TERESA S MCMILLAN
04/05/2023 02:19:25 PM

IDALIA E RYCHLIK
04/05/2023 03:14:21 PM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	11/2/2022		
To:	Anh-Thy Ly		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division: DRBPMI/RBPMB1	Other
From:	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Division): *optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	ICCR00850377 (Engineering review) and ICCR00850390 (Facilities review) ICC2200484 (Engineering review) and ICC2200485 (Facilities review) BLA761219 CT-P17		
Recommendation:	☒ Engineering review: Firm's response to additional comments 3 and 4 appear to be adequate. ☒ Facilities Pre-approval Inspection: Adequacy of firm's responses to device inspection observations not yet determined; therefore, additional comment recommended in CDER's recommended CR letter.		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (optional)

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#00850377 and ICCR00850390
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/5003d000003HXCvAAO/view https://force-dsc.lightning.force.com/lightning/r/Case/5003d000003HYFvAAO/view
ICC tracking #	ICC2200484 and ICC2200485
Submission Number	BLA761219
Sponsor	CELLTRION INC
Drug/Biologic	CT-P17
Indications for Use	Rheumatoid Arthritis same as Humira
Device Constituent	PFS, PFS w/ needle safety device, Auto-injector
Related Files	Appendix 1: ICC20011114 (CDRH original review- with PAI and PMC recommendations) Appendix 2: BLA761219 Type 1 meeting comments, 02/10/22 Appendix 3: Complete Response Letter

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, DRBPMI:	This application received a Complete response due to facility. CDRH also have 2 comments for the action letter. 3. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification. 4. (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.
Device Presentation(s) being evaluated:	PFS, PFS w/ needle safety device, Auto-injector

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	(b) (4) • Formulation in the devices is identical, with dose of 40 mg in 0.4 mL volume. • The primary container is a (b) (4) 1 mL (b) (4) glass syringe, ½ inch (29 G thin wall) staked SS needle with rigid needle shield and (b) (4) stopper. • The secondary container for the PFS and PFS-S consist of finger flange, plunger rod; (b) (4) –a Letter of Authorization (LOA) was provided in response to our IR, in Sequence 0005. The LOA references the (b) (4) • The secondary container for the (b) (4) consists of 2 subassembly units, syringe unit and drive unit. The (b) (4) is customized for CT-P17 and there is no LOA associated with it. *Refer to Appendix 1 for complete device description and use steps.
Objective of this Memo:	• Facilities Review: Confirm PAI recommendation from CDRH review 12/28/2020 or provide new inspection recommendation and provide approvability recommendation based on inspection results. • Engineering Review: Determine adequacy in CR responses to “additional comments” 3 and 4.
Review Comments: <u>Original CDRH Review (December 2020):</u> Background: CDRH reviewed the proposed combination product(s) in December 2020 (ICC2001114) and concluded the following: Original facilities inspection (ICC2001114): (b) (4) A pre-approval inspection was recommended. <i>The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part. The inspection that took place in (b) (4) was conducted in support of the BLA for</i>	

(b) (4) a PFS product. The inspection was requested by OPQ and appeared to be mostly focused on the drug substance manufacturing, however Quality Systems was covered. Since this inspection resulted in an OAI, and device inspection was not the focus, an inspection is recommended.

Original engineering review (ICC2001114): A post market commitment/requirement is recommended for 2 device deficiencies which are as follows:

1. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification.
2. (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.

*For complete original review memo, refer to Appendix 1 below.

Note, while CDRH recommended a PMR/PMC, CDER recommended a CRL. Therefore, CDRH PMR/PMC was converted into an additional comment in the Complete Response Letter. This review is to determine if CDRH still recommends a PAI and if the firm's response to the CRL is adequate for approval or a subsequent recommendation of PMR/PMC.

*For complete CRL, refer to Appendix 3 below.

Type 1 Meeting Request for CR Deficiencies (December 27, 2021):

The following excerpt pertains to the device "additional comments" included in the CR letter. Note all other questions in the CR letter were unrelated to the device and therefore not considered for this review.

Question 2:

There are additional comments in the Complete Response Letter (Reference ID: 4894531) that are not approvability issues. Does the Agency agree that a re-submission of CT-P17 BLA is possible if we provide responses to these issues and include commitments as to when the reports will be provided during review period?

FDA Response to Question 2:

Yes, responses to the additional comments may be provided during the resubmission of the BLA. We recommend that the timing of report submissions should facilitate a complete review during the BLA resubmission review cycle.

*For complete meeting minutes, refer to Appendix 2 below

CDRH Device CR Response Review (November 1, 2022):

Engineering review (This ICC, ICC200484):

Filing review: The firm's response to additional comments 2 and 3 were technically considered "incomplete" as the firm stated they are planning to respond to comment 3 in September 2022/during review and the response to comment 4 is unclear. However, in a type 1 meeting request the firm asked if they could provide a response to the additional comments during the review and FDA agreed that approach was okay per the excerpt below. Additionally, both CDRH

deficiencies were recommended as a PMR/PMC, therefore when the file was determined to be CR by CDER, CDER converted the PMR/PMC deficiencies as additional comments and not CR deficiencies. For consistency as the CDRH deficiencies are not considered CR deficiencies, but additional comments per the type 1 meeting agreement, Information Requests were issued about the unclear response for comment 4 and the device responses were considered fileable. The sponsor submitted a response to the device information request 1, relating to additional comment 4 on 08/30/2022. The sponsor submitted a response to the device additional comment 3 on 09/27/2022.

	Date Sent (CRL): 12/24/2021	Date/Sequence Received (CR Response): 5/27/2022						
Complete Response Additional Comments 3	You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification. Please note, this CR additional comment was a result of information request 5 that was issued during the original review (refer to Appendix 2) that was determined to be inadequately addressed. The initial IR from the original review and the sponsor's initial response is as follows: <table border="1"> <tr> <th></th><th>Date Sent: 4/21/2021</th><th>Date/Sequence Received: 5/11/2021</th></tr> <tr> <td>Information Request #5</td><td colspan="2"> Provide verification data for your AI device verifying audible feedback at the end of the dose. Include information regarding your requirements on sound volume, timing relative to the end of dose (i.e., +/- x seconds from end of dose) and residual volume after the sound. This information is required in order to ensure a complete dose is delivered at the same time as the audible feedback. </td></tr> </table>			Date Sent: 4/21/2021	Date/Sequence Received: 5/11/2021	Information Request #5	Provide verification data for your AI device verifying audible feedback at the end of the dose. Include information regarding your requirements on sound volume, timing relative to the end of dose (i.e., +/- x seconds from end of dose) and residual volume after the sound. This information is required in order to ensure a complete dose is delivered at the same time as the audible feedback.	
	Date Sent: 4/21/2021	Date/Sequence Received: 5/11/2021						
Information Request #5	Provide verification data for your AI device verifying audible feedback at the end of the dose. Include information regarding your requirements on sound volume, timing relative to the end of dose (i.e., +/- x seconds from end of dose) and residual volume after the sound. This information is required in order to ensure a complete dose is delivered at the same time as the audible feedback.							

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	(b) (4) <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Sponsor Response</td> <td></td> </tr> <tr> <td>Reviewer Comments</td> <td>PMC will be sent. See Section 13.3.2 for review.</td> </tr> <tr> <td>Response Adequate:</td> <td>☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.</td> </tr> </table>	Sponsor Response		Reviewer Comments	PMC will be sent. See Section 13.3.2 for review.	Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
Sponsor Response							
Reviewer Comments	PMC will be sent. See Section 13.3.2 for review.						
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.						
Related Meeting Request (SDN40, received 12/27/21)	<u>Question 2:</u> <i>There are additional comments in the Complete Response Letter (Reference ID: 4894531) that are not approvability issues. Does the Agency agree that a re-submission of CT-P17 BLA is possible if we provide responses to these issues and include commitments as to when the reports will be provided during review period?</i> <u>FDA Response to Question 2:</u> Yes, responses to the additional comments may be provided during the resubmission of the BLA. We recommend that the timing of report submissions should facilitate a complete review during the BLA resubmission review cycle.						
Sponsor Response (CR initial response, received 05/27/22)	<i>CELLTRION acknowledges the Agency's concern that it should be ensured that the full dose be always delivered to patient. For this, the implementation of analytical testing using the device specific equipment including software modification and method validation is undergoing. CELLTRION commits to define specification to ensure full dose delivery based on the click sound, and the established method and specification will be provided by the end of September 2022.</i>						
Sponsor Response (SDN54, received 09/27/22)	<i>In order to implement the requested additional AI functionality test and specification, CELLTRION communicated with the vendor of auto-injector test machine (b) (4). Based on the communications, a feasible way to control the full dose delivery based on the 2nd click sound time was identified. (b) (4)</i> (b) (4) <i>Accordingly, the associated test program was modified for reporting 2nd click timing results using source data (end of emission time, 2nd click sound generation time) by vendor.</i>						

CELLTRION conducted a historical data assessment using the process validation lots and additional commercial lots for EU markets manufactured at (b) (4) to define a specification and acceptance criterion for 2nd click timing based on sufficient data. The commercial AI lots for the EU market are also representative of CT-P17 AI for US market as they are manufactured using the same device components and assembly process. Unlike initial studies using testing of only 10 samples of CT-P17 autoinjector (AI), there were some cases where the 2nd click sound was occurred prior to the end of emission in the historical data assessment, albeit the time gap was very small.

(b) (4)

Taking into account the instruction in proposed label (refer to draft-labelling-text) to continue holding the CT-P17 AI after the 2nd click and slowly count to 5 and this instruction was validated by the human factor validation study results as user error rate was mitigated in Use scenario 2: IFU Mandatory compared to Use scenario 1: IFU optional use (refer to Section 5.3.5.4 human factor-report-ai). Therefore, CELLTRION believes that the proposed specification for 2nd click timing can guarantee the full dose injection of CT-P17 AI.

Following sections are revised accordingly;

- [Section 3.2.P.5.1](#)
- [Section 3.2.P.5.2](#)
- [Section 3.2.P.5.3](#)
- [Section 3.2.P.5.4](#)
- [Section 3.2.P.5.6 and Appendix 2 of Section 3.2.P.5.6](#)
- [Section 3.2.P.8.1](#)
- [Section 3.2.P.8.3](#)

Data excerpt from Table 3.2.P.8.3- Stability-data:

Table 3.2.P.8.3-56: CT-P17 Drug Product Long-term Stability Study (5±3 °C) of Functionality Testing, Lot No. CTP17PV2A1

Test Item	Acceptance Criterion	Time Point (Months)																				
		0			3			6			9			12			18			24		
		Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min
Dose Accuracy	(b) (4)	0.4 mL	0.4 mL	0.4 mL	-	-	-	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Actuation Force		8 N	8 N	7 N	-	-	-	7 N	8 N	7 N	7 N	8 N	7 N	7 N	8 N	6 N	7 N	8 N	7 N	7 N	8 N	7 N
Injection Depth		5.85 mm	6.07 mm	5.63 mm	-	-	-	5.74 mm	5.95 mm	5.39 mm	5.73 mm	5.91 mm	5.55 mm	5.78 mm	5.41 mm	6.01 mm	5.71 mm	5.97 mm	5.53 mm	5.77 mm	5.94 mm	5.32 mm
Injection Time		3 sec	4 sec	3 sec	-	-	-	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec
2 nd Click Timing		-	0 sec	-	-	-	-	0 sec	-	-	0 sec	-	-	1 sec	-	-	0 sec	-	-	0 sec	-	

Table 3.2.P.8.3-57: CT-P17 Drug Product Long-term Stability Study (5±3 °C) of Functionality Testing, Lot No. CTP17PV3A2

Test Item	Acceptance Criterion	Time Point (Months)																				
		0			3			6			9			12			18			24		
		Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min
Dose Accuracy	(b) (4)	0.4 mL	0.4 mL	0.4 mL	-	-	-	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Actuation Force		8 N	8 N	7 N	-	-	-	7 N	8 N	7 N	7 N	8 N	6 N	7 N	8 N	7 N	7 N	8 N	7 N	7 N	8 N	7 N
Injection Depth		5.82 mm	6.03 mm	5.36 mm	-	-	-	5.82 mm	6.04 mm	5.52 mm	5.68 mm	5.86 mm	5.28 mm	5.79 mm	5.97 mm	5.55 mm	5.71 mm	5.94 mm	5.55 mm	5.79 mm	5.95 mm	5.58 mm
Injection Time		3 sec	3 sec	3 sec	-	-	-	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec
2 nd Click Timing		-	0 sec	-	-	-	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-

Table 3.2.P.8.3-58: CT-P17 Drug Product Long-term Stability Study (5±3 °C) of Functionality Testing, Lot No. CTP17PV4A3

Test Item	Acceptance Criterion	Time Point (Months)																				
		0			3			6			9			12			18			24		
		Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min
Dose Accuracy	(b) (4)	0.4 mL	0.4 mL	0.4 mL	-	-	-	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Actuation Force		8 N	8 N	7 N	-	-	-	8 N	8 N	7 N	7 N	8 N	7 N	8 N	8 N	7 N	8 N	8 N	7 N	8 N	8 N	7 N
Injection Depth		5.81 mm	6.04 mm	5.65 mm	-	-	-	5.70 mm	5.98 mm	5.42 mm	5.72 mm	5.95 mm	5.48 mm	5.67 mm	6.01 mm	5.30 mm	5.66 mm	5.83 mm	5.42 mm	5.70 mm	5.98 mm	5.59 mm
Injection Time		3 sec	3 sec	3 sec	-	-	-	3 sec	4 sec	3 sec	4 sec	4 sec	3 sec	4 sec	4 sec	3 sec	3 sec	4 sec	3 sec	4 sec	4 sec	3 sec
2 nd Click Timing		-	0 sec	-	-	-	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-

Reviewer Comments

The firm's response appears to be reasonable as they have defined the time between the end of dose delivery and 2nd click to be (b) (4) second and they have validated the method and provided real time test data from stability samples (3 lots) over the proposed shelf life and test data from accelerated aged stability samples (1 lot) over the proposed shelf life.

Additionally, in the original review of this submission, the sponsor addressed concerns with the second click occurring concurrently to dose delivery with a correlation being made to the presence of an air bubble that should be considered during measurement of a complete dose as opposed to the end of plunger movement. For additional discussion, refer to the original review memo in appendix 2 below, pages 72 to 74 of 81. The sponsor responded with labeling controls and HF validation for IFU labeling for users to continue to hold the injector in place and count to 5 after the second click as a control to potentially prevent premature device removal which could result in an incomplete dose. Additionally, the device has a viewing window and colored plunger rod that moves as the dose is delivered to indicate a dose delivery (i.e., there is a passive end of dose indication). Testing submitted in this CR response considers the air bubble and the specification has been defined and verified per the CR additional comment 3 request, and there labeling controls in place as well as a visual feedback to indicate a complete dose. Therefore, the deficiency is considered adequately addressed.

Response Adequate:

☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

Date Sent (CRL):

12/24/2021

Date/Sequence Received (CR Response):

5/27/2022

Complete Response Additional

(b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after

Comments 4	simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.									
	Please note, this CR additional comment was a result of an "Information Request to (b) (4)" that was issued during the original review (refer to Appendix 2) that was determined to be inadequately addressed. The initial IR from the original review and the sponsor's initial response is as follows:									
	<table border="1"> <tr> <td data-bbox="302 422 553 474"></td><td data-bbox="553 422 878 474">Date Sent: 4/15/2021</td><td data-bbox="878 422 1398 474">Date/Sequence Received: 4/22/2021</td></tr> <tr> <td data-bbox="302 474 553 684">Information Request to (b) (4)</td><td colspan="2" data-bbox="553 474 1398 684"> Provide verification data on the needle safety device's lockout force and activation force through end of shelf-life and after shipping per ASTM 4169-16. For activation force, specify whether CT-P17 final PFS product was included in the testing. Also, specify whether the manufacturing process that was used on the device before testing is the same manufacturing process that is used for the final drug product. </td></tr> <tr> <td data-bbox="302 684 553 1003">Sponsor Response</td><td colspan="2" data-bbox="553 684 1398 1003"> Verification testing for the needle safety device was performed with consideration to the following FDA guidance documents, special controls and/or recognized standards: • ISO 23908:2011 Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling • Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (August 2005) Verification testing, which may include the use of a prefilled syringe or not, was performed on the (b) (4) device constituent alone. It is the responsibility of the CT-P17 applicant to </td></tr> </table>		Date Sent: 4/15/2021	Date/Sequence Received: 4/22/2021	Information Request to (b) (4)	Provide verification data on the needle safety device's lockout force and activation force through end of shelf-life and after shipping per ASTM 4169-16. For activation force, specify whether CT-P17 final PFS product was included in the testing. Also, specify whether the manufacturing process that was used on the device before testing is the same manufacturing process that is used for the final drug product.		Sponsor Response	Verification testing for the needle safety device was performed with consideration to the following FDA guidance documents, special controls and/or recognized standards: • ISO 23908:2011 Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling • Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (August 2005) Verification testing, which may include the use of a prefilled syringe or not, was performed on the (b) (4) device constituent alone. It is the responsibility of the CT-P17 applicant to	
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	determine how this verification testing can apply to the final CT-P17 PFS with safety device product. The (b) (4) device is composed of a clear needle guard, white plunger rod and optional white add-on finger flange. The plunger rod and add-on finger flange can further undergo customization to support combination product differentiation through color changes. The other components (body and guard) remain transparent and do not undergo color customization. Design verification testing summarized in the table below and presented in the report ERD20193829 was performed for the (b) (4) device constituent components. A tabular summary of the design verification related to performance of the safety feature performed on the device constituent components is presented below (see table following this review box)									
	<table border="1"> <tr> <td data-bbox="302 1535 553 1854">Reviewer Comments</td><td data-bbox="553 1535 1429 1854"> Response acceptable. It is unclear if the manufacturing used at (b) (4) is the final manufacturing process of the DP. Further, lockout force should be verified after shipping per ASTM 4169 on the final product using the Sponsor's packaging design. This was not conducted. The following PMC will be sent: (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, <i>Standard Practice for Performance Testing of Shipping Containers and Systems</i> on the final finished device in the final packaging. </td></tr> </table>	Reviewer Comments	Response acceptable. It is unclear if the manufacturing used at (b) (4) is the final manufacturing process of the DP. Further, lockout force should be verified after shipping per ASTM 4169 on the final product using the Sponsor's packaging design. This was not conducted. The following PMC will be sent: (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, <i>Standard Practice for Performance Testing of Shipping Containers and Systems</i> on the final finished device in the final packaging.							
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	<table border="1"> <tr> <td data-bbox="302 1860 553 1883">Response Adequate:</td><td data-bbox="553 1860 1429 1883"> ☒ Yes ☐ No, but PMC will be sent to address gaps. </td></tr> </table>	Response Adequate:	☒ Yes ☐ No, but PMC will be sent to address gaps.							
Response Adequate:	☒ Yes ☐ No, but PMC will be sent to address gaps.									

Sponsor Response	<i>The shipping validation for CT-P17 PFS-S finished drug product was completed including Temperature Mapping Study, Container/Closure Integrity (CCI), Function Test and Quality Test under Maximum Load as per P2-SVP-1A190 and the shipping validation report was provided as Appendix 8 of Section 3.2.P.3.5 in the initial BLA (SN0001).</i> <i>To verify that the lockout force of CT-P17 PFS-S in the final packaging is unaffected after simulated shipping, samples were taken from the additional real-time shipping study conducted for stopper movement which used the loading configuration and shipment route as described in P2-SVP-1A190 (refer to the Response to Information Request #1 in SN0030).</i> <i>The acceptance criteria for compression force (to override the activated locked guard, to the unactivated position i.e., lockout force) is (b) (4) N, as shown in the customer quality specification of (b) (4) (Attachment #1). Samples after shipping were subjected to the lockout force (compression force) test with the same acceptance criteria. The lockout force test results are presented in Table 1 and the shipping validation data for the lockout force test are updated in Section 3.2.P.3.5.1.3. The shipping validation report is also provided as Appendix 12 of Section 3.2.P.3.5.</i> <i>The data show that shipping had no adverse effect on the lockout force (compression force needed to override the activated locked guard, to the un-activated position), and all final finished device samples in the final packaging met the acceptance criteria of (b) (4) N for lockout force after shipping.</i> Table 1: Results of Lockout Force Tests from Real-Time Shipping Study (PFS-S) <table border="1" data-bbox="293 1003 1443 1161"> <thead> <tr> <th>Shipment</th><th>Result¹</th></tr> </thead> <tbody> <tr> <td>Run 1</td><td>≥ 95.15 N</td></tr> <tr> <td>Run 2</td><td>≥ 94.89 N</td></tr> <tr> <td>Run 3</td><td>≥ 95.10 N</td></tr> </tbody> </table> ¹Minimum value of the measured lockout force.	Shipment	Result ¹	Run 1	≥ 95.15 N	Run 2	≥ 94.89 N	Run 3	≥ 95.10 N
Shipment	Result ¹								
Run 1	≥ 95.15 N								
Run 2	≥ 94.89 N								
Run 3	≥ 95.10 N								
Reviewer Comments	Shipping validation report was provided as Appendix 8 of Section 3.2.P.3.5 in the initial BLA (SN0001): The shipping validation study solely focuses on measurement of the temperature and any possible excursions and does not include any testing of EPRs (i.e., needle safety override force). The test report is sufficient to validation the simulated shipping method; however, it does not address the CR deficiency. Response to Information Request #1 in SN0030: It is unclear how response to Information request 1 in SN00030 relates to this deficiency as it solely focuses on assessment of stopper movement and does not appear to include test data of lockout force. Shipping validation report is also provided as Appendix 12 of Section 3.2.P.3.5 and lock out force testing per Table 1 in the firm's response: The table does not provide sufficient information to determine adequacy of lockout force testing. The validation report in Appendix 12 is illegible and does not appear to include pertinent information such as the sample size, min, mean, and max, data assessment (e.g., k factor analysis), and indicate whether or not there were any deviations with rationale for acceptability of data.								
Response Adequate:	☐ Yes ☒ No, See IR # Sent on 8/26/2022								
Follow-On Deficiency	Date Sent: 8/25/2022	Date/Sequence Received: 8/30/2022							

Information Request #1	Your response to additional comment 4 appears to be incomplete as we are unable to locate lockout force data within your submission. You refer to Appendix 8 of Section 3.2.P.3.5 in the initial BLA (SN0001) which is a report for shipping validation but does not include test data for lockout confirmation. Additionally, you refer to your response to information request #1 in SN0030; however, it does not appear to address lockout confirmation as it appears to focus on stopper movement testing. Lastly, you refer to Appendix 12 of Section 3.2.P.3.5 and table 1 that you have included in your response; however, the table does not provide sufficient information to determine adequacy of lockout force testing and the validation report in Appendix 12 is illegible and does not appear to include pertinent information such as the sample size, minimum, mean, and maximum, data assessment (e.g., k factor analysis), and indicate whether or not there were any deviations with rationale for acceptability of data. Please provide a verification report for lockout force after shipping that details the test method used, results (i.e., sample size, minimum, mean, maximum, and standard deviation), data assessment (e.g., k factor analysis), and indicate whether or not there were any deviations with rationale for acceptability of data in the event of deviations.
Sponsor Response	<i>For the BLA submission and during the review procedure, CELLTRION conducted following shipping validations for CT-P17 drug product;</i> • Initial BLA, Section 3.2.P.3.5.1.3 (SN0001): initial shipping validation for CT-P17 assembled DP and finished DP (PFS, PFS-S, AI) • Response to information request #1 (SN0030): additional shipping validation for CT-P17 fDP (PFS and PFS-S) to provide data for stopper movement testing. • Response to complete response additional comment #4 (SN0042): additional data for CT-P17 PFS-S lockout force testing. Available samples from the previous shipment for stopper movement testing was implemented for this additional testing. <i>Among these submission, only the last submission included in the BLA re-submission (SN0042) relates to the data for lockout force of CT-P17 PFS-S and CELLTRION mentioned all these references in previous submission in an attempt to show the applied shipping routes were same. CELLTRION appreciates the Agency's request and the submitted Appendix 12 of Section 3.2.P.3.5 indeed had a problem in scan quality and thereby, is replaced with an improved version in this submission, Appendix 12 of Section 3.2.P.3.5. The location of pertinent information on lockout force testing from this report is the last page (p. 26) where the analytical report is attached. In the response to complete response additional comment #4, The lockout force results of sampled CT-P17 PFS-S from 3 separate shipping runs were presented in a table with minimum value of each run only.</i> <i>Therefore, CELLTRION would like to provide detailed information for the previously submitted reports to support that the lockout force of CT-P17 PFS-S remains unaffected after worst-case shipping described below.</i> Refer to the Sequence number 0053, module 1.11.1 for complete response from sponsor.
Reviewer Comments	The sponsor provided a more legible test report for testing of needle safety override after shipping. While the data showed passing results with all samples to override according to specification (b) (4) N, the sample size is inadequate. The sponsor tested 2 samples from 3 runs, totaling 6 samples which is not statistically relevant. Additionally, the sponsor did not provide rationale for the sample size, considering the desired confidence and

	reliability of device performance that impacts safety which should be at a minimum 95/99% C/R. However, in the sponsor's original submission they provided test data from the component supplier, (b) (4). The data demonstrated that the safety guard maintains sufficient lockout force (Compression force, i.e., lockout force (b) (4) N) after aging for up to 5 years in real time conditions and shipping based on a study of 102 samples (refer to Appendix 11 of Section 3.2.R.7). Additionally, the needle guard component does not undergo customization and is unchanged in material, color, and manufacturing independent of the supplier's customer (e.g., Celltrion). Therefore, considering the least burdensome approach and given the combination of data provided by the sponsor and the sponsor's supplier (b) (4), the sponsor appears to sufficiently demonstrate adequate needle safety override force for the proposed combination product.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

Facilities review (This ICC, ICC2200485): FEI# (b) (4) A pre-approval inspection is recommended.

Form 356h for SDN 42 (this response) confirms the manufacturers and responsibilities remain the same where FEI# (b) (4) is responsible for *Production of CT-P17 drug product (uDP), Labeling and assembly of CT-P17 drug product (PFS, PFS-S and AI), Cartoning of CT-P17 drug product (PFS, PFS-S and AI), Release testing of CT-P17 drug product*. Therefore, the recommendation from the original review of a PAI is verified to remain as the recommendation.

ORA conducted a one overall inspection of the sponsor, Celltrion's contract manufacturer, (b) (4). The inspection included a for-cause inspection initiated by CDER and a pre-approval inspection recommended by CDRH. The inspection resulted in 9 observations, 3 of which were for the device constituent part of the proposed combination product. CDER categorized the inspection as POAI with a possible downgrade to VAI as CDER is still conducting their EIR review. CDRH is also still conducting the EIR review and assessing the sponsor's responses to each violation and has not yet determined the supportability of each potential regulatory violation nor adequacy of response. Therefore, CDRH has not categorized the PAI device portion of the inspection and cannot provide an approvability recommendation at this time. However, as CDER is recommended CR due to the for-cause portion of the inspection observations, CDRH would like to include an additional comment as it relates to the device observations. CDRH will provide a recommendation for categorization of the inspection and determine adequacy in the sponsor's response to the observations was the EIR review is complete. CDRH will provide an approvability recommendation once the submission once the sponsor has responded to the CR hold.

Review Recommendation:	Engineering review: Firm's response to additional comments 3 and 4 appear to be adequate. Facilities Inspection: Adequacy of firm's responses to PAI device inspection observations not yet determined; therefore, additional comment recommended in CDER's recommended CR letter. Device additional comment 1: FDA conducted an inspection of your contract manufacturing organization (CMO), (b) (4). During the inspection, the inspector noted the following observations:
--------------------------------------	---

ICC#2200484, ICC#2200485

BLA761219, CT-P17

Celltrion Inc.

(b) (4)



---END OF REVIEW---



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	12/28/2020		
To:	Anh-thy Ly		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Choose an item.
From	Suzanne Hudak OPEQ/OHT3/DHT3C		
Through (Division)	Rumi Young, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761219 , CT-P17 ICC 2001114 Case 00048134, 00048140		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Facilities Recommendation: PAI (b) (4) Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 7/1/2021 ☐ Device Constituent Parts of the Combination Product are Approvable. ☒ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761219
Sponsor	Celltrion
Drug/Biologic	CT-P17
Indications for Use	Rheumatoid Arthritis same as Humira
Device Constituent	PFS, PFS with SD, Auto-Injector
Related Files	ICC2000184, ICC2000851

Review Team		
Lead Device Reviewer	Suzanne Hudak	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	7/2/2021
Interim Due Dates	
Filing	1/8
74-Day Letter	2/5
Mid-Cycle	
Primary Review	5/3
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☒ Approvable with PMC or PMR, [See Section 2.3](#)
- ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	x			
Labeling	x			
Design Controls	x			
Risk Analysis	x			
Design Verification	x			
Consultant Discipline Reviews			x	
Clinical Validation	x			
Human Factors Validation			x	
Facilities & Quality Systems	x			

2.1. **Comments to the Review Team**

- ☒ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

2.2. **Complete Response Deficiencies**

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market Commitments or Requirements	☒
CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

1. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification.

2. ^{(b) (4)} has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper

functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, *Standard Practice for Performance Testing of Shipping Containers and Systems* on your final finished device in the final packaging.

APPEARS THIS WAY ON ORIGINAL

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3. PURPOSE/BACKGROUND

3.1. Scope

Celltrion is requesting approval of CT-P17. The device constituent of the combination product is a PFS, FPS with SD, AI.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

CT-P17

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device performance, device design control, device quality systems

This review will not cover the following review areas:

All other

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
CT-P17	Rheumatoid Arthritis same as Humira
Choose an item.	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	2.3
	3.2.P.7
	In Regional information 7: 3.2.R.7.9.1 and.2 (functionality testing)
	3.2.P.8.3 (Stability
	3.2.P.5.1 and 5.6 (Specifications)
	1.14.1.1 and 1.14.1.3 (Labeling & IFU)

4. DEVICE DESCRIPTION

4.1. Device Description

Section 2.3 and 3.2.P.7

There are 3 devices in the submission:

- PFS
- PFS-S

v05.02.2019

Page 7 of 81

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

(b) (4)

- Formulation in the devices are identical, with dose of 40 mg in 0.4 mL volume.
- The primary container is a (b) (4) 1 mL (b) (4) glass syringe, ½ inch (29 G thin wall) staked SS needle with rigid needle shield and (b) (4) stopper.
- The secondary container for the PFS and PFS-S consist of finger flange, plunger rod; (b) (4) – a LOA was provided in response to our IR, in Sequence 0005. The LOA references the (b) (4)
- The secondary container for the (b) (4) consists of 2 subassembly units, syringe unit and drive unit. The (b) (4) is customized for CT-P17 and there is no LOA associated with it.

4.2. Steps for Using the Device

For AI:

- Remove cap
- Place at 90 degree angle at injection site
- Press the AI firmly against skin
- When injection starts, you will hear 1st click
- Hold and listen for 2nd click
- Count to 5 after 2nd click
- Remove AI from skin

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> Device was appropriately described.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review ☒ Finalize Filing Review Section	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist			
Description	Present		
	Yes	No	N/A
Description of Device Constituent	X		
Device Constituent Labeling	X		
Letters of Authorization	X		
Essential Performance Requirements defined by the application Sponsor	X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor	X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor	X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities			
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)		X
	Reliability	X	
	Biocompatibility		X
	Sterility		X
	Software		X
	Cybersecurity		X
	Electrical Safety		X
	EMC/RF Wireless		X
	MR Compatibility		X
	Human Factors	X	
	Shelf Life, Aging and Transportation	X	
	Clinical Validation	X	
	Human Factors Validation	X	
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X	
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X	
	CAPA Procedure	X	
	Control Strategy provided for EPRs	X	

Reviewer Comment

-LOAs are missing
-Design verification summaries were provided. Reports were not provided.

-Need some clarification on Management responsibility. (b) (4) manufactures DP, but the relationship is not described. Will send boilerplate on site responsibility clarification, management responsibility and acceptance activities.

-Risk analysis is described but not provided.

The missing information would not result in a refuse to accept.

Device IRs:

1. Please provide LOAs for the (b) (4)
2. Please provide your design verification reports for the AI.
3. Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design.

QS IRs:

Clarification on Site Responsibilities

1. Your submission has identified Celltrion as the application holder, and at least one facility as involved in the manufacturing of the combination product. Please identify the facility or facilities responsible for designing, fabricating, assembling, labeling, packaging, holding, and storing the finished combination product.
2. Please identify the firm(s) responsible for establishing and maintaining a quality policy, performing quality planning, providing adequate resources, and reviewing the suitability and effectiveness of the quality system, as it pertains to the combination product.
3. Please identify the firm(s) responsible for conducting design and development planning, establishing and maintaining design inputs/design outputs, performing design reviews, and performing design verification/validation, as it pertains to the combination product. Also, please identify the firm(s) authorized to perform any changes to the combination product design, if/when required.
4. If components or constituent parts are used to design and manufacture the finished combination product, please identify the firm(s) responsible for obtaining those components or constituent parts. Also, please identify the firm(s) responsible for evaluating suppliers and for maintaining records of acceptable suppliers.
5. When quality problems are identified with the finished combination product, please identify the firm(s) responsible for establishing and maintaining procedures for implementing corrective and preventive action, which may include investigating the cause of nonconformities, identifying the action(s) needed to correct and prevent recurrence, verifying or validating the corrective and preventive action, implementing and recording changes in methods and procedures, submitting relevant information for management review, and documenting all activities.

Management Responsibility (21 CFR 820.20)

6. Please provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20. Please also provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

Acceptance Activities

7. Please explain how the manufacturing site will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. Please specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. Please also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

See Sections 8, 9 and 12.4 for response review. All IRs resolved.

5.2. Facilities Information

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Production of CT-P17 drug product (uDP), Labeling and assembly of CT-P17 drug product (PFS, PFS-S and AI), Cartonning of CT-P17 drug product (PFS, PFS-S and AI), Release testing of CT-P17 drug product
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☒ Inspection was conducted (b) (4). The inspection covered drug CGMP and was classified OAI. This inspection was requested by OPQ for the Drug Product (b) (4). Another inspection was conducted (b) (4). This inspection was for the product (b) (4). The result of this inspection was VAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation: ☒ A pre-approval inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part. The inspection that took place in (b) (4) was conducted in support of the BLA for (b) (4) a PFS product. The inspection was requested by OPQ and appeared to be mostly focused on the drug substance manufacturing, however Quality Systems was covered. Since this inspection resulted in an OAI, and device inspection was not the focus, an inspection is recommended. ☐ An inspection is not required because Choose an item.	

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Release testing of CT-P17 drug product – no functionality testing conducted.
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item.. ☒ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation: ☐ A pre-approval inspection is required because:	

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm **has not been performed**.

☒ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

The following manufacturing sites were not reviewed for inspection requirements as activities do not relate to CDRH review:

- 1) (b) (4) Responsible for production of MCB and WCB
- 2) (b) (4) Responsible for Testing of MCB
- 3) (b) (4) Responsible for testing of unprocessed bulk

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☒ Yes ☐ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation:	
☒ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	

Site(s) needing inspection: (b) (4)
<u>Reviewer Comments</u>
Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A
74-Day Letter Deficiencies: ☒ Yes ☐ No ☐ N/A

	Date Sent: 1/11/2021	Date/Sequence Received: 2/5/2021
Information Request #1	Please provide LOAs for the (b) (4)	
Sponsor Response	Reviewed in Design Verification , Section 9. Resolved.	

	Date Sent: 1/11/2021	Date/Sequence Received: 2/5/2021
Information Request #2	Please provide your design verification reports for the AI.	
Sponsor Response	Reviewed in Design Verification , Section 9. Resolved	

	Date Sent: 1/11/2021	Date/Sequence Received: 2/5/2021
Information Request #3	Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design.	
Sponsor Response	Reviewed in Risk Analysis , Section 8. Resolved	

6. LABELING

PFS:

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(b) (4)

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		

Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications			x
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors	x		
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. DESIGN CONTROL [SUMMARY](#)

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial	x		
Bioequivalence Study utilized to-be-marketed device	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	x		
Traceability demonstrated for specifications to performance data		x	

Reviewer Comments

The risk analysis review is acceptable, see section 8.
Design verification document in Appendix 16, Section 3.2.R.7 includes design requirements , including EPRs.
Traceability reports could not be located. IR was sent. See Section 13.3.2 for review. Resolved.

7.2. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Actual shipping used
IEC 60601-1-2:2014	n/a
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	n/a
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	n/a
Applying Human Factors and Usability Engineering to Medical Devices	n/a

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2014	Y	Y
ISO 11608-5:2012	Y	Y

7.3. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	Please provide the following documents that you have referenced in your submission: - GR-RD-20-289, Traceability Matrix for CT-P17 (40mg/0.4mL) Auto-injector (AI) - GR-RD-20-291 Traceability, Matrix for CT-P17 (40 mg/0.4 mL) Prefilled Syringe with Safety Guard (PFS-S).	
Sponsor Response		
Reviewer Comments	See Section 13.3.2 for review	

Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
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8. RISK ANALYSIS

IR: Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design. The Sponsor responded:

The risk assessment used for device design of CT-P17 drug product has been performed as a part of risk management activities during the device design and development process. The risk management activities in device component level were performed by the device component suppliers and the risk management activities in the final drug product level were performed by CELLTRION. The summary of risk management activities for the design of CT-P17 prefilled syringe (PFS), prefilled syringe with safety guard (PFS-S) and auto injector (AI) are provided [Table 1](#) to [Table 3](#) below.

Device (PFS-S)		Summary of Risk Management Activities	Report/ Statement
Device Components	(b) (4) Glass Syringe	A risk management plan has been developed and implemented to evaluate the current risk acceptability associated to the use of the (b) (4) staked needle syringe and to identify the needs for risk control measures that will be addressed through further product and process design work. The risk management activity performed for this purpose are Use, Design and Manufacturing Failure Mode Effect Analysis (FMEA) compiled into (b) (4) Risk Management Files. (b) (4) has identified several residual risk of product failure, which were concluded acceptable as intended for subcutaneous injections of a non-emergency Biopharmaceutical drugs.	Appendix 1
	(b) (4)	A risk management plan has been developed and implemented to evaluate the current risk acceptability associated to the use of the (b) (4) product and to identify the needs for risk control measures that has been addressed through further product and process design work. The risk management activity performed for this purpose are Use, Design and Manufacturing Failure Mode Effect Analysis (FMEA) compiled into (b) (4) Risk Management Files. Overall risk assessment has been performed reviewing risks per hazardous situation and per effect and no residual risks were found after conducting risk management activities on (b) (4) products.	Appendix 5
CT-P17 Final Combination Drug Product (PFS-S)		As a final drug product, CELLTRION conducted uFMEA for CT-P17 PFS-S and found 149 potential failure cases. Among 149 potential failure cases, 63 potential failure cases were evaluated as unacceptable risk. Throughout the risk control process, the initial 63 unacceptable risks were mitigated to an acceptable level. Therefore, no unacceptable residual risk were determined in overall residual risk assessment.	Risk Assessment (Appendix 6) Risk Control (Appendix 7)

Appendix 6 – DP PFS-S

Sponsor provides analysis method, including probability classification, harm severity classification and a risk acceptability matrix. Risk level is probability x severity.

Risks were analyzed to determine acceptability. If above the acceptability threshold, the risks are mitigated to lower the risk level. Risks related to needle safety device, such as premature activation and failure to activate are included as risks. The probability of each were deemed low and mitigation was not needed for NSD.

Appendix 7 – DP PFS-S

Risk control measures are found here

Table 3: Summary of Risk Management Activities of CT-P17 Auto Injector (AI)

Device (AI)		Summary of Risk Management Activities	Report/ Statement
Device Components	(b) (4) Glass Syringe	A risk management plan has been developed and implemented to evaluate the current risk acceptability associated to the use of the (b) (4) staked needle syringe and to identify the needs for risk control measures that will be addressed through further product and process design work. The risk management activity performed for this purpose are Use, Design and Manufacturing Failure Mode Effect Analysis (FMEA) compiled into (b) (4) (b) (4) Risk Management Files. (b) (4) has identified several residual risk of product failure, which were	Appendix 1

	(b) (4)	concluded acceptable as intended for subcutaneous injections of a non-emergency Biopharmaceutical drugs.	
	(b) (4)	For the device design and development of sub-assemblies, total 3 FMEAs have been performed by device supplier, (b) (4). The Application-FMEA lists 55 failures, the Design-FMEA lists 76 failures and the Process-FMEA lists 83 failures for low-volume assembly and 84 failures for high-volume assembly. As a result, none of the evaluated failures and use errors have a Risk Priority Number (RPN) greater than or equal to 100 after taking into account all implemented mitigation measures. Therefore, the residual risks are considered acceptable.	Appendix 8
CT-P17 Final Combination Drug Product (AI)		As a final drug product, CELLTRION conducted uFMEA for CT-P17 AI and found 122 potential failure cases. Among 122 potential failure cases, 45 potential failure cases were evaluated as unacceptable risk. Throughout the risk control process, the initial 45 unacceptable risks were mitigated to an acceptable level. Therefore, no unacceptable residual risk were determined in overall residual risk assessment.	Risk Assessment (Appendix 9) Risk Control (Appendix 10)

81	User unintentionally activates the injection - loss of dose, Delay therapy (multiple dose)	3	2	6	2019-10-24
82	User unintentionally activates the injection - drug contacts skin, Delay therapy (one dose)	1	1	1	2019-10-24

Appendix 9 – AI

Sponsor provides analysis method, including probability classification, harm severity classification and a risk acceptability matrix. Risk level is probability x severity.

Risks were analyzed to determine acceptability. If above the acceptability threshold, the risks are mitigated to lower the risk level. Risks related to device, such as failure to remove cap and accidental activation are included. Major risks seem to be captured.

Appendix 10 – AI

Risk control measures are found here. Risk control measures are acceptable, for example acceptance criteria is set to ensure proper functionality, and IFU states how to do steps.

Reviewer Comments Risk analysis and mitigation measures are acceptable.

8.1. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design.	
Sponsor Response	See above.	
Reviewer Comments	Requested data meets our expectations.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	You have provided your risk assessment in Sequence 0005. It is unclear how you determined the probability for each risk. Please clarify how probabilities are determined. State whether they are based on actual data, and if so, is the data set size sufficiently large for determining probability. If probability is not based on data, explain your method for determining probability and provide justification.	
Sponsor Response		
Reviewer Comments	See Section 13.3.2 for review.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9. DESIGN VERIFICATION REVIEW

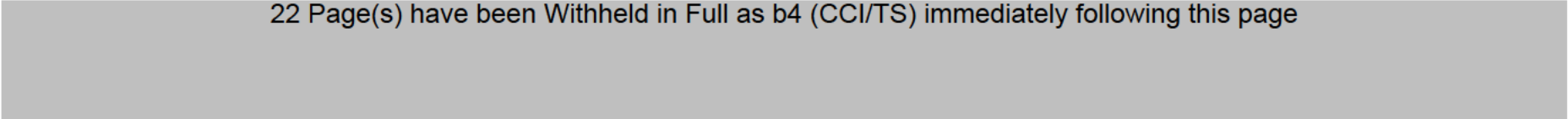
9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

(b) (4)



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10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
☒ There are clinical studies for review

This information was obtained from the following [documents](#):

Study Name	Phase 1, randomised, open-label, two-arm, parallel group, singledose study in healthy male and female subjects
Study Type	PK study between CT-P17 AI and CT-P17 PFS
Objectives/Endpoints	To demonstrate the PK similarity
Drug/Device Studied	AI and PFS
Number and Type of Subjects	N=193, (95 PFS, 98 AI). Healthy male or female subjects.
Results	Equivalent results between CT-P17 AI or PFS, SC administration was well tolerated
Device Related Comments	No Comments
Reviewer Comments	No Comments
Reviewer Conclusion	Comparable results of AI vs PFS

Study Name	Phase 3, randomised, activecontrolled, double-blind , multicenter study in patients with moderate to severe active RA
Study Type	Confirmatory efficacy and safety study
Objectives/Endpoints	To demonstrate similarity of efficacy
Drug/Device Studied	CT-P17 PFS and Humira PFS
Number and Type of Subjects	N=648, n=324 for each device, male or female with moderate to severe RA
Results	Efficacy and PK results similar between CT-P17 and Humira No significant difference between CT-P17 and Humira in PD results
Device Related Comments	No Comments

Reviewer Comments	No Comments
Reviewer Conclusion	Comparable results of CT-P17 PFS and Humira PFS

Study Name	Phase 3, open-label, single-arm, multiple-dose study in patients with moderate to severe active RA
Study Type	AI usability study
Objectives/Endpoints	The usability as assessed by patients rating using PRE- and POST-Self-Injection Assessment
Drug/Device Studied	CT-P17 AI
Number and Type of Subjects	N=62, male or female with moderate to severe RA
Results	CT-P17 delivered by SC AI was successfully administered with high usability in moderate to severe active RA patients.
Device Related Comments	No Comments
Reviewer Comments	No Comments
Reviewer Conclusion	AI injection was successful among RA patients

Reviewer Comment

Study with PFS vs AI conducted, and AI usability study. Devices validated.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☒
CDRH Facilities Inspection Review was not conducted	☐

Facility Regulatory History Review	
Firm Name:	(b) (4)
Address & FEI:	
Responsibilities:	Production of CT-P17 drug product (uDP), Labeling and assembly of CT-P17 drug product (PFS, PFS-S and AI), Cartonning of CT-P17 drug product (PFS, PFS-S and AI), Release testing of CT-P17 drug product
Site Inspection Recommendation:	VAI.

<u>Reviewer Comments</u>	
Reported inspectional coverage included: production premises (	(b) (4)
, utilities, packaging, storage, GMP-relevant documentation and related activities. Areas not inspected included Quality control and shipping and distribution.	
Inspection elements covered included:	(b) (4)
There were no critical or major deficiencies. However, seven (7) Other deficiencies were noted that included:	
For the minor issues, the firm sent a CAPA response that was deemed adequate. A GMP certificate was issued and this was closed as a VAI.	

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☐ No

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
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<<END OF REVIEW>>

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/s/

ANH-THY LY
11/10/2022 08:32:02 AM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	11/2/2022		
To:	Anh-Thy Ly		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division: DRBPMI/RBPMB1	Other
From:	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Division): *optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	ICCR00850377 (Engineering review) and ICCR00850390 (Facilities review) ICC2200484 (Engineering review) and ICC2200485 (Facilities review) BLA761219 CT-P17		
Recommendation:	☒ Engineering review: Firm's response to additional comments 3 and 4 appear to be adequate. ☒ Facilities Pre-approval Inspection: Adequacy of firm's responses to device inspection observations not yet determined; therefore, additional comment recommended in CDER's recommended CR letter.		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (optional)

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#00850377 and ICCR00850390
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/5003d000003HXCvAAO/view https://force-dsc.lightning.force.com/lightning/r/Case/5003d000003HYFvAAO/view
ICC tracking #	ICC2200484 and ICC2200485
Submission Number	BLA761219
Sponsor	CELLTRION INC
Drug/Biologic	CT-P17
Indications for Use	Rheumatoid Arthritis same as Humira
Device Constituent	PFS, PFS w/ needle safety device, Auto-injector
Related Files	Appendix 1: ICC20011114 (CDRH original review- with PAI and PMC recommendations) Appendix 2: BLA761219 Type 1 meeting comments, 02/10/22 Appendix 3: Complete Response Letter

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, DRBPMI:	This application received a Complete response due to facility. CDRH also have 2 comments for the action letter. 3. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification. 4. (b) (4) has provided testing on the PFS-S device's lockout force , however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.
Device Presentation(s) being evaluated:	PFS, PFS w/ needle safety device, Auto-injector

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

	(b) (4) • Formulation in the devices is identical, with dose of 40 mg in 0.4 mL volume. • The primary container is a (b) (4) 1 mL (b) (4) glass syringe, ½ inch (29 G thin wall) staked SS needle with rigid needle shield and (b) (4) stopper. • The secondary container for the PFS and PFS-S consist of finger flange, plunger rod; (b) (4) (b) (4) –a Letter of Authorization (LOA) was provided in response to our IR, in Sequence 0005. The LOA references the (b) (4) (b) (4). • The secondary container for the (b) (4) consists of 2 subassembly units, syringe unit and drive unit. The (b) (4) is customized for CT-P17 and there is no LOA associated with it. *Refer to Appendix 1 for complete device description and use steps.
Objective of this Memo:	• Facilities Review: Confirm PAI recommendation from CDRH review 12/28/2020 or provide new inspection recommendation and provide approvability recommendation based on inspection results. • Engineering Review: Determine adequacy in CR responses to “additional comments” 3 and 4.
Review Comments: <u>Original CDRH Review (December 2020):</u> Background: CDRH reviewed the proposed combination product(s) in December 2020 (ICC2001114) and concluded the following: Original facilities inspection (ICC2001114): FEI# (b) (4) A pre-approval inspection was recommended.	

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part. The inspection that took place in (b) (4) was conducted in support of the BLA for (b) (4) a PFS product. The inspection was requested by OPQ and appeared to be mostly focused on the drug substance manufacturing, however Quality Systems was covered. Since this inspection resulted in an OAI, and device inspection was not the focus, an inspection is recommended.

Original engineering review (ICC2001114): A post market commitment/requirement is recommended for 2 device deficiencies which are as follows:

1. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification.
2. (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.

*For complete original review memo, refer to Appendix 1 below.

Note, while CDRH recommended a PMR/PMC, CDER recommended a CRL. Therefore, CDRH PMR/PMC was converted into an additional comment in the Complete Response Letter. This review is to determine if CDRH still recommends a PAI and if the firm's response to the CRL is adequate for approval or a subsequent recommendation of PMR/PMC.

*For complete CRL, refer to Appendix 3 below.

Type 1 Meeting Request for CR Deficiencies (December 27, 2021):

The following excerpt pertains to the device "additional comments" included in the CR letter. Note all other questions in the CR letter were unrelated to the device and therefore not considered for this review.

Question 2:

There are additional comments in the Complete Response Letter (Reference ID: 4894531) that are not approvability issues. Does the Agency agree that a re-submission of CT-P17 BLA is possible if we provide responses to these issues and include commitments as to when the reports will be provided during review period?

FDA Response to Question 2:

Yes, responses to the additional comments may be provided during the resubmission of the BLA. We recommend that the timing of report submissions should facilitate a complete review during the BLA resubmission review cycle.

*For complete meeting minutes, refer to Appendix 2 below

CDRH Device CR Response Review (November 1, 2022):

Engineering review (This ICC, ICC200484):

Filing review: The firm's response to additional comments 2 and 3 were technically considered "incomplete" as the firm stated they are planning to respond to comment 3 in September 2022/during review and the response to comment 4 is unclear. However, in a type 1 meeting request the firm asked if they could provide a response to the additional comments during the review and FDA agreed that approach was okay per the excerpt below. Additionally, both CDRH deficiencies were recommended as a PMR/PMC, therefore when the file was determined to be CR by CDER, CDER converted the PMR/PMC deficiencies as additional comments and not CR deficiencies. For consistency as the CDRH deficiencies are not considered CR deficiencies, but additional comments per the type 1 meeting agreement, Information Requests were issued about the unclear response for comment 4 and the device responses were considered fileable. The sponsor submitted a response to the device information request 1, relating to additional comment 4 on 08/30/2022. The sponsor submitted a response to the device additional comment 3 on 09/27/2022.

	Date Sent (CRL): 12/24/2021	Date/Sequence Received (CR Response): 5/27/2022						
Complete Response Additional Comments 3	You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification. Please note, this CR additional comment was a result of information request 5 that was issued during the original review (refer to Appendix 2) that was determined to be inadequately addressed. The initial IR from the original review and the sponsor's initial response is as follows: <table border="1"> <tr> <th></th><th>Date Sent: 4/21/2021</th><th>Date/Sequence Received: 5/11/2021</th></tr> <tr> <td>Information Request #5</td><td colspan="2"> Provide verification data for your AI device verifying audible feedback at the end of the dose. Include information regarding your requirements on sound volume, timing relative to the end of dose (i.e., +/- x seconds from end of dose) and residual volume after the sound. This information is required in order to ensure a complete dose is delivered at the same time as the audible feedback. </td></tr> </table>			Date Sent: 4/21/2021	Date/Sequence Received: 5/11/2021	Information Request #5	Provide verification data for your AI device verifying audible feedback at the end of the dose. Include information regarding your requirements on sound volume, timing relative to the end of dose (i.e., +/- x seconds from end of dose) and residual volume after the sound. This information is required in order to ensure a complete dose is delivered at the same time as the audible feedback.	
	Date Sent: 4/21/2021	Date/Sequence Received: 5/11/2021						
Information Request #5	Provide verification data for your AI device verifying audible feedback at the end of the dose. Include information regarding your requirements on sound volume, timing relative to the end of dose (i.e., +/- x seconds from end of dose) and residual volume after the sound. This information is required in order to ensure a complete dose is delivered at the same time as the audible feedback.							

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4) <table border="1" data-bbox="402 905 1484 993"> <tr> <td>Sponsor Response</td> <td></td> </tr> <tr> <td>Reviewer Comments</td> <td>PMC will be sent. See Section 13.3.2 for review.</td> </tr> <tr> <td>Response Adequate:</td> <td>☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.</td> </tr> </table>	Sponsor Response		Reviewer Comments	PMC will be sent. See Section 13.3.2 for review.	Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
Sponsor Response							
Reviewer Comments	PMC will be sent. See Section 13.3.2 for review.						
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.						
Related Meeting Request (SDN40, received 12/27/21)	<u>Question 2:</u> <i>There are additional comments in the Complete Response Letter (Reference ID: 4894531) that are not approvability issues. Does the Agency agree that a re-submission of CT-P17 BLA is possible if we provide responses to these issues and include commitments as to when the reports will be provided during review period?</i> <u>FDA Response to Question 2:</u> Yes, responses to the additional comments may be provided during the resubmission of the BLA. We recommend that the timing of report submissions should facilitate a complete review during the BLA resubmission review cycle.						
Sponsor Response (CR initial response, received 05/27/22)	<i>CELLTRION acknowledges the Agency's concern that it should be ensured that the full dose be always delivered to patient. For this, the implementation of analytical testing using the device specific equipment including software modification and method validation is undergoing. CELLTRION commits to define specification to ensure full dose delivery based on the click sound, and the established method and specification will be provided by the end of September 2022.</i>						
Sponsor Response (SDN54, received 09/27/22)	<i>In order to implement the requested additional AI functionality test and specification, CELLTRION communicated with the vendor of auto-injector test machine (b) (4). Based on the communications, a feasible way to control the full dose delivery based on the 2nd click sound time was identified. (b) (4)</i> <i>(b) (4)</i> <i>(b) (4)</i> <i>(b) (4)</i> <i>(b) (4)</i> <i>Accordingly, the associated test program was modified for reporting 2nd click timing results using source data (end of emission time, 2nd click sound generation time) by vendor.</i>						

CELLTRION conducted a historical data assessment using the process validation lots and additional commercial lots for EU markets manufactured at (b) (4) to define a specification and acceptance criterion for 2nd click timing based on sufficient data. The commercial AI lots for the EU market are also representative of CT-P17 AI for US market as they are manufactured using the same device components and assembly process. Unlike initial studies using testing of only 10 samples of CT-P17 autoinjector (AI), there were some cases where the 2nd click sound was occurred prior to the end of emission in the historical data assessment, albeit the time gap was very small.

(b) (4)

(b) (4)

Taking into account the instruction in proposed label (refer to draft-labelling-text) to continue holding the CT-P17 AI after the 2nd click and slowly count to 5 and this instruction was validated by the human factor validation study results as user error rate was mitigated in Use scenario 2: IFU Mandatory compared to Use scenario 1: IFU optional use (refer to Section 5.3.5.4 human factor-report-ai). Therefore, CELLTRION believes that the proposed specification for 2nd click timing can guarantee the full dose injection of CT-P17 AI.

Following sections are revised accordingly;

- [Section 3.2.P.5.1](#)
- [Section 3.2.P.5.2](#)
- [Section 3.2.P.5.3](#)
- [Section 3.2.P.5.4](#)
- [Section 3.2.P.5.6 and Appendix 2 of Section 3.2.P.5.6](#)
- [Section 3.2.P.8.1](#)
- [Section 3.2.P.8.3](#)

Data excerpt from Table 3.2.P.8.3- Stability-data:

Table 3.2.P.8.3-56: CT-P17 Drug Product Long-term Stability Study (5±3 °C) of Functionality Testing, Lot No. CTP17PV2A1

Test Item	Acceptance Criterion	Time Point (Months)																				
		0			3			6			9			12			18			24		
		Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min
Dose Accuracy	(b) (4)	0.4 mL	0.4 mL	0.4 mL	-	-	-	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Actuation Force		8 N	8 N	7 N	-	-	-	7 N	8 N	7 N	7 N	8 N	7 N	7 N	8 N	6 N	7 N	8 N	7 N	7 N	8 N	7 N
Injection Depth		5.85 mm	6.07 mm	5.63 mm	-	-	-	5.74 mm	5.95 mm	5.39 mm	5.73 mm	5.91 mm	5.55 mm	5.78 mm	5.41 mm	6.01 mm	5.71 mm	5.97 mm	5.53 mm	5.77 mm	5.94 mm	5.32 mm
Injection Time		3 sec	4 sec	3 sec	-	-	-	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec
2 nd Click Timing		-	0 sec	-	-	-	-	0 sec	-	-	0 sec	-	-	1 sec	-	-	0 sec	-	-	0 sec	-	-

Table 3.2.P.8.3-57: CT-P17 Drug Product Long-term Stability Study (5±3 °C) of Functionality Testing, Lot No. CTP17PV3A2

Test Item	Acceptance Criterion	Time Point (Months)																				
		0			3			6			9			12			18			24		
		Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min
Dose Accuracy	(b) (4)	0.4 mL	0.4 mL	0.4 mL	-	-	-	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Actuation Force		8 N	8 N	7 N	-	-	-	7 N	8 N	7 N	7 N	8 N	6 N	7 N	8 N	7 N	7 N	8 N	7 N	7 N	8 N	7 N
Injection Depth		5.82 mm	6.03 mm	5.36 mm	-	-	-	5.82 mm	6.04 mm	5.52 mm	5.68 mm	5.86 mm	5.28 mm	5.79 mm	5.97 mm	5.55 mm	5.71 mm	5.94 mm	5.55 mm	5.79 mm	5.95 mm	5.58 mm
Injection Time		3 sec	3 sec	3 sec	-	-	-	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec	3 sec	4 sec	3 sec
2 nd Click Timing		-	0 sec	-	-	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	

Table 3.2.P.8.3-58: CT-P17 Drug Product Long-term Stability Study (5±3 °C) of Functionality Testing, Lot No. CTP17PV4A3

Test Item	Acceptance Criterion	Time Point (Months)																				
		0			3			6			9			12			18			24		
		Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min
Dose Accuracy	(b) (4)	0.4 mL	0.4 mL	0.4 mL	-	-	-	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Actuation Force		8 N	8 N	7 N	-	-	-	8 N	8 N	7 N	7 N	8 N	7 N	8 N	8 N	7 N	8 N	8 N	7 N	8 N	8 N	7 N
Injection Depth		5.81 mm	6.04 mm	5.65 mm	-	-	-	5.70 mm	5.98 mm	5.42 mm	5.72 mm	5.95 mm	5.48 mm	5.67 mm	6.01 mm	5.30 mm	5.66 mm	5.83 mm	5.42 mm	5.70 mm	5.98 mm	5.59 mm
Injection Time		3 sec	8 sec	3 sec	-	-	-	3 sec	4 sec	3 sec	4 sec	4 sec	3 sec	4 sec	4 sec	3 sec	3 sec	4 sec	3 sec	4 sec	4 sec	3 sec
2 nd Click Timing		-	0 sec	-	-	-	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-	-	0 sec	-

Reviewer Comments

The firm's response appears to be reasonable as they have defined the time between the end of dose delivery and 2nd click to be (b) (4) second and they have validated the method and provided real time test data from stability samples (3 lots) over the proposed shelf life and test data from accelerated aged stability samples (1 lot) over the proposed shelf life.

Additionally, in the original review of this submission, the sponsor addressed concerns with the second click occurring concurrently to dose delivery with a correlation being made to the presence of an air bubble that should be considered during measurement of a complete dose as opposed to the end of plunger movement. For additional discussion, refer to the original review memo in appendix 2 below, pages 72 to 74 of 81. The sponsor responded with labeling controls and HF validation for IFU labeling for users to continue to hold the injector in place and count to 5 after the second click as a control to potentially prevent premature device removal which could result in an incomplete dose. Additionally, the device has a viewing window and colored plunger rod that moves as the dose is delivered to indicate a dose delivery (i.e., there is a passive end of dose indication). Testing submitted in this CR response considers the air bubble and the specification has been defined and verified per the CR additional comment 3 request, and there labeling controls in place as well as a visual feedback to indicate a complete dose. Therefore, the deficiency is considered adequately addressed.

Response Adequate:

☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

Date Sent (CRL):

12/24/2021

Date/Sequence Received (CR Response):

5/27/2022

Complete Response

(b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging

Additional Comments
4

design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, Standard Practice for Performance Testing of Shipping Containers and Systems on your final finished device in the final packaging.

Please note, this CR additional comment was a result of an “Information Request to (b) (4) that was issued during the original review (refer to Appendix 2) that was determined to be inadequately addressed. The initial IR from the original review and the sponsor’s initial response is as follows:

	Date Sent: 4/15/2021	Date/Sequence Received: 4/22/2021
Information Request to (b) (4)	Provide verification data on the needle safety device’s lockout force and activation force through end of shelf-life and after shipping per ASTM 4169-16. For activation force, specify whether CT-P17 final PFS product was included in the testing. Also, specify whether the manufacturing process that was used on the device before testing is the same manufacturing process that is used for the final drug product.	
Sponsor Response	Verification testing for the needle safety device was performed with consideration to the following FDA guidance documents, special controls and/or recognized standards: • ISO 23908:2011 Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling • Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (August 2005) Verification testing, which may include the use of a prefilled syringe or not, was performed on the (b) (4) device constituent alone. It is the responsibility of the CT-P17 applicant to	

	determine how this verification testing can apply to the final CT-P17 PFS with safety device product. The (b) (4) device is composed of a clear needle guard, white plunger rod and optional white add-on finger flange. The plunger rod and add-on finger flange can further undergo customization to support combination product differentiation through color changes. The other components (body and guard) remain transparent and do not undergo color customization. Design verification testing summarized in the table below and presented in the report ERD20193829 was performed for the (b) (4) device constituent components. A tabular summary of the design verification related to performance of the safety feature performed on the device constituent components is presented below (see table following this review box)	
	Reviewer Comments Response acceptable. It is unclear if the manufacturing used at (b) (4) is the final manufacturing process of the DP. Further, lockout force should be verified after shipping per ASTM 4169 on the final product using the Sponsor's packaging design. This was not conducted. The following PMC will be sent: (b) (4) has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, <i>Standard Practice for Performance Testing of Shipping Containers and Systems</i> on the final finished device in the final packaging.	
	Response Adequate: ☒ Yes ☐ No, but PMC will be sent to address gaps.	
Sponsor Response	<i>The shipping validation for CT-P17 PFS-S finished drug product was completed including Temperature Mapping Study, Container/Closure Integrity (CCI), Function Test and Quality Test under Maximum Load as per P2-SVP-1A190 and the shipping validation report was provided as Appendix 8 of Section 3.2.P.3.5 in the initial BLA (SN0001).</i> <i>To verify that the lockout force of CT-P17 PFS-S in the final packaging is unaffected after simulated shipping, samples were taken from the additional real-time shipping study conducted for stopper movement which used the loading configuration and shipment route as described in P2-SVP-1A190 (refer to the Response to Information Request #1 in SN0030).</i> <i>The acceptance criteria for compression force (to override the activated locked guard, to the unactivated position i.e., lockout force) is (b) (4) N, as shown in the customer quality specification of (b) (4) (Attachment #1). Samples after shipping were subjected to the lockout force (compression force) test with the same acceptance criteria. The lockout force test results are presented in Table 1 and the shipping validation data for the lockout force test are updated in Section 3.2.P.3.5.1.3. The shipping validation report is also provided as Appendix 12 of Section 3.2.P.3.5.</i> <i>The data show that shipping had no adverse effect on the lockout force (compression force needed to override the activated locked guard, to the un-activated position), and all final finished device samples in the final packaging met the acceptance criteria of (b) (4) N for lockout force after shipping.</i>	

Table 1: Results of Lockout Force Tests from Real-Time Shipping Study (PFS-S)	
Shipment	Result ¹
Run 1	≥ 95.15 N
Run 2	≥ 94.89 N
Run 3	≥ 95.10 N

¹Minimum value of the measured lockout force.

Reviewer Comments	Shipping validation report was provided as Appendix 8 of Section 3.2.P.3.5 in the initial BLA (SN0001): The shipping validation study solely focuses on measurement of the temperature and any possible excursions and does not include any testing of EPRs (i.e., needle safety override force). The test report is sufficient to validate the simulated shipping method; however, it does not address the CR deficiency. Response to Information Request #1 in SN0030: It is unclear how response to Information request 1 in SN0030 relates to this deficiency as it solely focuses on assessment of stopper movement and does not appear to include test data of lockout force. Shipping validation report is also provided as Appendix 12 of Section 3.2.P.3.5 and lock out force testing per Table 1 in the firm's response: The table does not provide sufficient information to determine adequacy of lockout force testing. The validation report in Appendix 12 is illegible and does not appear to include pertinent information such as the sample size, min, mean, and max, data assessment (e.g., k factor analysis), and indicate whether or not there were any deviations with rationale for acceptability of data.
Response Adequate:	☐ Yes ☒ No, See IR # Sent on 8/26/2022

Follow-On Deficiency	Date Sent: 8/25/2022	Date/Sequence Received: 8/30/2022
Information Request #1	Your response to additional comment 4 appears to be incomplete as we are unable to locate lockout force data within your submission. You refer to Appendix 8 of Section 3.2.P.3.5 in the initial BLA (SN0001) which is a report for shipping validation but does not include test data for lockout confirmation. Additionally, you refer to your response to information request #1 in SN0030; however, it does not appear to address lockout confirmation as it appears to focus on stopper movement testing. Lastly, you refer to Appendix 12 of Section 3.2.P.3.5 and table 1 that you have included in your response; however, the table does not provide sufficient information to determine adequacy of lockout force testing and the validation report in Appendix 12 is illegible and does not appear to include pertinent information such as the sample size, minimum, mean, and maximum, data assessment (e.g., k factor analysis), and indicate whether or not there were any deviations with rationale for acceptability of data. Please provide a verification report for lockout force after shipping that details the test method used, results (i.e., sample size, minimum, mean, maximum, and standard deviation), data assessment (e.g., k factor analysis), and indicate whether or not there were any deviations with rationale for acceptability of data in the event of deviations.	
Sponsor Response	For the BLA submission and during the review procedure, CELLTRION conducted following shipping validations for CT-P17 drug product; Initial BLA, Section 3.2.P.3.5.1.3 (SN0001): initial shipping validation for CT-P17 assembled DP and finished DP (PFS, PFS-S, AI)	

	• Response to information request #1 (SN0030): additional shipping validation for CT-P17 fDP (PFS and PFS-S) to provide data for stopper movement testing. • Response to complete response additional comment #4 (SN0042): additional data for CT-P17 PFS-S lockout force testing. Available samples from the previous shipment for stopper movement testing was implemented for this additional testing. Among these submission, only the last submission included in the BLA re-submission (SN0042) relates to the data for lockout force of CT-P17 PFS-S and CELLTRION mentioned all these references in previous submission in an attempt to show the applied shipping routes were same. CELLTRION appreciates the Agency's request and the submitted Appendix 12 of Section 3.2.P.3.5 indeed had a problem in scan quality and thereby, is replaced with an improved version in this submission, Appendix 12 of Section 3.2.P.3.5. The location of pertinent information on lockout force testing from this report is the last page (p. 26) where the analytical report is attached. In the response to complete response additional comment #4, The lockout force results of sampled CT-P17 PFS-S from 3 separate shipping runs were presented in a table with minimum value of each run only. Therefore, CELLTRION would like to provide detailed information for the previously submitted reports to support that the lockout force of CT-P17 PFS-S remains unaffected after worst-case shipping described below. Refer to the Sequence number 0053, module 1.11.1 for complete response from sponsor.
Reviewer Comments	The sponsor provided a more legible test report for testing of needle safety override after shipping. While the data showed passing results with all samples to override according to specification (b) (4) N, the sample size is inadequate. The sponsor tested 2 samples from 3 runs, totaling 6 samples which is not statistically relevant. Additionally, the sponsor did not provide rationale for the sample size, considering the desired confidence and reliability of device performance that impacts safety which should be at a minimum 95/99% C/R. However, in the sponsor's original submission they provided test data from the component supplier, (b) (4). The data demonstrated that the safety guard maintains sufficient lockout force (Compression force, i.e., lockout force (b) (4) N) after aging for up to 5 years in real time conditions and shipping based on a study of 102 samples (refer to Appendix 11 of Section 3.2.R.7). Additionally, the needle guard component does not undergo customization and is unchanged in material, color, and manufacturing independent of the supplier's customer (e.g., Celltrion). Therefore, considering the least burdensome approach and given the combination of data provided by the sponsor and the sponsor's supplier (b) (4) the sponsor appears to sufficiently demonstrate adequate needle safety override force for the proposed combination product.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

Facilities review (This ICC, ICC2200485): FEI# (b) (4). A pre-approval inspection is recommended.

Form 356h for SDN 42 (this response) confirms the manufacturers and responsivities remain the same where FEI# (b) (4) is responsible for Production of CT-P17 drug product (uDP), Labeling and assembly of CT-P17 drug

product (PFS, PFS-S and AI), Carttoning of CT-P17 drug product (PFS, PFS-S and AI), Release testing of CT-P17 drug product. Therefore, the recommendation from the original review of a PAI is verified to remain as the recommendation.

ORA conducted a one overall inspection of the sponsor, Celltrion's contract manufacturer, (b) (4). The inspection included a for-cause inspection initiated by CDER and a pre-approval inspection recommended by CDRH. The inspection resulted in 9 observations, 3 of which were for the device constituent part of the proposed combination product. CDER categorized the inspection as POAI with a possible downgrade to VAI as CDER is still conducting their EIR review. CDRH is also still conducting the EIR review and assessing the sponsor's responses to each violation and has not yet determined the supportability of each potential regulatory violation nor adequacy of response. Therefore, CDRH has not categorized the PAI device portion of the inspection and cannot provide an approvability recommendation at this time. However, as CDER is recommended CR due to the for-cause portion of the inspection observations, CDRH would like to include an additional comment as it relates to the device observations. CDRH will provide a recommendation for categorization of the inspection and determine adequacy in the sponsor's response to the observations was the EIR review is complete. CDRH will provide an approvability recommendation once the submission once the sponsor has responded to the CR hold.

Review**Recommendation:**

Engineering review: Firm's response to additional comments 3 and 4 appear to be adequate.
Facilities Inspection: Adequacy of firm's responses to PAI device inspection observations not yet determined; therefore, additional comment recommended in CDER's recommended CR letter.

Device additional comment 1:

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

(b) (4)

ICC#2100611
BLA021172, NovoLog Mix 70/30
Novo Nordisk Inc.

(b) (4)



---END OF REVIEW---



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	12/28/2020		
To:	Anh-thy Ly		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Choose an item.
From	Suzanne Hudak OPEQ/OHT3/DHT3C		
Through (Division)	Rumi Young, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761219 , CT-P17 ICC 2001114 Case 00048134, 00048140		
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Facilities Recommendation: PAI for Catalent Belgium SA, FEI#3007647000 Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 7/1/2021 ☐ Device Constituent Parts of the Combination Product are Approvable. ☒ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761219
Sponsor	Celltrion
Drug/Biologic	CT-P17
Indications for Use	Rheumatoid Arthritis same as Humira
Device Constituent	PFS, PFS with SD, Auto-Injector
Related Files	ICC2000184, ICC2000851

Review Team		
Lead Device Reviewer	Suzanne Hudak	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	7/2/2021
Interim Due Dates	
Filing	1/8
74-Day Letter	2/5
Mid-Cycle	
Primary Review	5/3
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
- ☒ Approvable with PMC or PMR, [See Section 2.3](#)
- ☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	x			
Labeling	x			
Design Controls	x			
Risk Analysis	x			
Design Verification	x			
Consultant Discipline Reviews			x	
Clinical Validation	x			
Human Factors Validation			x	
Facilities & Quality Systems	x			

2.1. **Comments to the Review Team**

- ☒ CDRH does not have any further comments to convey to the review team.
- ☐ CDRH has the following comments to convey to the review team:

2.2. **Complete Response Deficiencies**

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- ☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market Commitments or Requirements	☒
CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

1. You have provided testing on 10 samples to demonstrate that the full dose is delivered prior to the sound of the second click. However, to ensure that you adequately control the design so that the full dose is always delivered prior to the sound of the second click, please define specifications for the end of injection click timing, and verify the new specification.

2. ^{(b) (4)} has provided testing on the PFS-S device's lockout force, however in order to be representative this test should be conducted after simulated shipping on the final finished device with your packaging design. In order to ensure proper

ICC 2001114
BLA 761219 ,CT-P17
Celltrion

functioning of the PFS-S lockout force, provide testing after simulated shipping per ASTM 4169-16, *Standard Practice for Performance Testing of Shipping Containers and Systems* on your final finished device in the final packaging.

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3. PURPOSE/BACKGROUND

3.1. Scope

Celltrion is requesting approval of CT-P17. The device constituent of the combination product is a PFS, FPS with SD, AI.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

CT-P17

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device performance, device design control, device quality systems

This review will not cover the following review areas:

All other

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
CT-P17	Rheumatoid Arthritis same as Humira
Choose an item.	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	2.3
	3.2.P.7
	In Regional information 7: 3.2.R.7.9.1 and.2 (functionality testing)
	3.2.P.8.3 (Stability
	3.2.P.5.1 and 5.6 (Specifications)
	1.14.1.1 and 1.14.1.3 (Labeling & IFU)

4. DEVICE DESCRIPTION

4.1. Device Description

Section 2.3 and 3.2.P.7

There are 3 devices in the submission:

- PFS
- PFS-S

v05.02.2019

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

(b) (4)

- Formulation in the devices are identical, with dose of 40 mg in 0.4 mL volume.
- The primary container is a (b) (4) 1 mL (b) (4) glass syringe, ½ inch (29 G thin wall) staked SS needle with rigid needle shield and (b) (4) stopper.
- The secondary container for the PFS and PFS-S consist of finger flange, plunger rod; (b) (4) – a LOA was provided in response to our IR, in Sequence 0005. The LOA references the (b) (4)
- The secondary container for the (b) (4) consists of 2 subassembly units, syringe unit and drive unit. The (b) (4) is customized for CT-P17 and there is no LOA associated with it.

4.2. Steps for Using the Device

For AI:

- Remove cap
- Place at 90 degree angle at injection site
- Press the AI firmly against skin
- When injection starts, you will hear 1st click
- Hold and listen for 2nd click
- Count to 5 after 2nd click
- Remove AI from skin

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> Device was appropriately described.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review ☒ Finalize Filing Review Section	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities				
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability	X		
	Biocompatibility			X
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

-LOAs are missing
-Design verification summaries were provided. Reports were not provided.

-Need some clarification on Management responsibility. (b) (4) manufactures DP, but the relationship is not described. Will send boilerplate on site responsibility clarification, management responsibility and acceptance activities.

-Risk analysis is described but not provided.

The missing information would not result in a refuse to accept.

Device IRs:

1. Please provide LOAs for the (b) (4).
2. Please provide your design verification reports for the AI.
3. Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design.

QS IRs:

Clarification on Site Responsibilities

1. Your submission has identified Celltrion as the application holder, and at least one facility as involved in the manufacturing of the combination product. Please identify the facility or facilities responsible for designing, fabricating, assembling, labeling, packaging, holding, and storing the finished combination product.
2. Please identify the firm(s) responsible for establishing and maintaining a quality policy, performing quality planning, providing adequate resources, and reviewing the suitability and effectiveness of the quality system, as it pertains to the combination product.
3. Please identify the firm(s) responsible for conducting design and development planning, establishing and maintaining design inputs/design outputs, performing design reviews, and performing design verification/validation, as it pertains to the combination product. Also, please identify the firm(s) authorized to perform any changes to the combination product design, if/when required.
4. If components or constituent parts are used to design and manufacture the finished combination product, please identify the firm(s) responsible for obtaining those components or constituent parts. Also, please identify the firm(s) responsible for evaluating suppliers and for maintaining records of acceptable suppliers.
5. When quality problems are identified with the finished combination product, please identify the firm(s) responsible for establishing and maintaining procedures for implementing corrective and preventive action, which may include investigating the cause of nonconformities, identifying the action(s) needed to correct and prevent recurrence, verifying or validating the corrective and preventive action, implementing and recording changes in methods and procedures, submitting relevant information for management review, and documenting all activities.

Management Responsibility (21 CFR 820.20)

6. Please provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20. Please also provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

Acceptance Activities

7. Please explain how the manufacturing site will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. Please specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. Please also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

See Sections 8, 9 and 12.4 for response review. All IRs resolved.

5.2. Facilities Information

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Production of CT-P17 drug product (uDP), Labeling and assembly of CT-P17 drug product (PFS, PFS-S and AI), Cartonning of CT-P17 drug product (PFS, PFS-S and AI), Release testing of CT-P17 drug product
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☒ Inspection was conducted (b) (4). The inspection covered drug CGMP and was classified OAI. This inspection was requested by OPQ for the Drug Product (b) (4). Another inspection was conducted (b) (4). This inspection was for the product (b) (4). The result of this inspection was VAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation: ☒ A pre-approval inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part. The inspection that took place in (b) (4) was conducted in support of the BLA for (b) (4) a PFS product. The inspection was requested by OPQ and appeared to be mostly focused on the drug substance manufacturing, however Quality Systems was covered. Since this inspection resulted in an OAI, and device inspection was not the focus, an inspection is recommended. ☐ An inspection is not required because Choose an item.	

Firm Name:	(b) (4)
Address:	(b) (4)
FEI:	(b) (4)
Responsibilities:	Release testing of CT-P17 drug product – no functionality testing conducted.
Inspectional History An analysis of the firm's inspection history over the past 2 years: ☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item.. ☒ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product	
Inspection Recommendation: ☐ A pre-approval inspection is required because:	

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm **has not been performed**.

☒ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

The following manufacturing sites were not reviewed for inspection requirements as activities do not relate to CDRH review:

- 1) (b) (4) Responsible for production of MCB and WCB
- 2) (b) (4), Responsible for Testing of MCB
- 3) (b) (4) Responsible for testing of unprocessed bulk

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☒ Yes ☐ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation:	
☒ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	

Site(s) needing inspection: (b) (4)
Reviewer Comments
Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A
74-Day Letter Deficiencies: ☒ Yes ☐ No ☐ N/A

	Date Sent: 1/11/2021	Date/Sequence Received: 2/5/2021
Information Request #1	Please provide LOAs for the (b) (4)	
Sponsor Response	Reviewed in Design Verification , Section 9. Resolved.	

	Date Sent: 1/11/2021	Date/Sequence Received: 2/5/2021
Information Request #2	Please provide your design verification reports for the AI.	
Sponsor Response	Reviewed in Design Verification , Section 9. Resolved	

	Date Sent: 1/11/2021	Date/Sequence Received: 2/5/2021
Information Request #3	Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design.	
Sponsor Response	Reviewed in Risk Analysis , Section 8. Resolved	

6. LABELING

PFS:

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immediately following this page

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		

Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications			x
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors	x		
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			x
RF/Wireless Labeling/Symbols			x

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. DESIGN CONTROL [SUMMARY](#)

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial	x		
Bioequivalence Study utilized to-be-marketed device	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	x		
Traceability demonstrated for specifications to performance data		x	

Reviewer Comments

The risk analysis review is acceptable, see section 8.
Design verification document in Appendix 16, Section 3.2.R.7 includes design requirements , including EPRs.
Traceability reports could not be located. IR was sent. See Section 13.3.2 for review. Resolved.

7.2. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Actual shipping used
IEC 60601-1-2:2014	n/a
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	n/a
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	n/a
Applying Human Factors and Usability Engineering to Medical Devices	n/a

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2014	Y	Y
ISO 11608-5:2012	Y	Y

7.3. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	Please provide the following documents that you have referenced in your submission: - GR-RD-20-289, Traceability Matrix for CT-P17 (40mg/0.4mL) Auto-injector (AI) - GR-RD-20-291 Traceability, Matrix for CT-P17 (40 mg/0.4 mL) Prefilled Syringe with Safety Guard (PFS-S).	
Sponsor Response		
Reviewer Comments	See Section 13.3.2 for review	

Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
--------------------	--

8. RISK ANALYSIS

IR: Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design. The Sponsor responded:

The risk assessment used for device design of CT-P17 drug product has been performed as a part of risk management activities during the device design and development process. The risk management activities in device component level were performed by the device component suppliers and the risk management activities in the final drug product level were performed by CELLTRION. The summary of risk management activities for the design of CT-P17 prefilled syringe (PFS), prefilled syringe with safety guard (PFS-S) and auto injector (AI) are provided [Table 1](#) to [Table 3](#) below.

Device (PFS-S)		Summary of Risk Management Activities	Report/ Statement
Device Components	(b) (4) Glass Syringe	A risk management plan has been developed and implemented to evaluate the current risk acceptability associated to the use of the (b) (4) staked needle syringe and to identify the needs for risk control measures that will be addressed through further product and process design work. The risk management activity performed for this purpose are Use, Design and Manufacturing Failure Mode Effect Analysis (FMEA) compiled into (b) (4) Risk Management Files. (b) (4) has identified several residual risk of product failure, which were concluded acceptable as intended for subcutaneous injections of a non-emergency Biopharmaceutical drugs.	Appendix 1
	(b) (4)	A risk management plan has been developed and implemented to evaluate the current risk acceptability associated to the use of the (b) (4) product and to identify the needs for risk control measures that has been addressed through further product and process design work. The risk management activity performed for this purpose are Use, Design and Manufacturing Failure Mode Effect Analysis (FMEA) compiled into (b) (4) Risk Management Files. Overall risk assessment has been performed reviewing risks per hazardous situation and per effect and no residual risks were found after conducting risk management activities on (b) (4) products.	Appendix 5
CT-P17 Final Combination Drug Product (PFS-S)		As a final drug product, CELLTRION conducted uFMEA for CT-P17 PFS-S and found 149 potential failure cases. Among 149 potential failure cases, 63 potential failure cases were evaluated as unacceptable risk. Throughout the risk control process, the initial 63 unacceptable risks were mitigated to an acceptable level. Therefore, no unacceptable residual risk were determined in overall residual risk assessment.	Risk Assessment (Appendix 6) Risk Control (Appendix 7)

Appendix 6 – DP PFS-S

Sponsor provides analysis method, including probability classification, harm severity classification and a risk acceptability matrix. Risk level is probability x severity.

Risks were analyzed to determine acceptability. If above the acceptability threshold, the risks are mitigated to lower the risk level. Risks related to needle safety device, such as premature activation and failure to activate are included as risks. The probability of each were deemed low and mitigation was not needed for NSD.

Appendix 7 – DP PFS-S

Risk control measures are found here

Table 3: Summary of Risk Management Activities of CT-P17 Auto Injector (AI)

Device (AI)		Summary of Risk Management Activities	Report/ Statement
Device Components	(b) (4) Glass Syringe	A risk management plan has been developed and implemented to evaluate the current risk acceptability associated to the use of the (b) (4) stake needle syringe and to identify the needs for risk control measures that will be addressed through further product and process design work. The risk management activity performed for this purpose are Use, Design and Manufacturing Failure Mode Effect Analysis (FMEA) compiled into (b) (4) (b) (4) Risk Management Files. (b) (4) has identified several residual risk of product failure, which were	Appendix 1

	(b) (4)	concluded acceptable as intended for subcutaneous injections of a non-emergency Biopharmaceutical drugs.	
	(b) (4)	For the device design and development of sub-assemblies, total 3 FMEAs have been performed by device supplier, (b) (4) The Application-FMEA lists 55 failures, the Design-FMEA lists 76 failures and the Process-FMEA lists 83 failures for low-volume assembly and 84 failures for high-volume assembly. As a result, none of the evaluated failures and use errors have a Risk Priority Number (RPN) greater than or equal to 100 after taking into account all implemented mitigation measures. Therefore, the residual risks are considered acceptable.	Appendix 8
CT-P17 Final Combination Drug Product (AI)		As a final drug product, CELLTRION conducted uFMEA for CT-P17 AI and found 122 potential failure cases. Among 122 potential failure cases, 45 potential failure cases were evaluated as unacceptable risk. Throughout the risk control process, the initial 45 unacceptable risks were mitigated to an acceptable level. Therefore, no unacceptable residual risk were determined in overall residual risk assessment.	Risk Assessment (Appendix 9) Risk Control (Appendix 10)

81	User unintentionally activates the injection - loss of dose, Delay therapy (multiple dose)	3	2	6	2019-10-24
82	User unintentionally activates the injection - drug contacts skin, Delay therapy (one dose)	1	1	1	2019-10-24

Appendix 9 – AI

Sponsor provides analysis method, including probability classification, harm severity classification and a risk acceptability matrix. Risk level is probability x severity.

Risks were analyzed to determine acceptability. If above the acceptability threshold, the risks are mitigated to lower the risk level. Risks related to device, such as failure to remove cap and accidental activation are included. Major risks seem to be captured.

Appendix 10 – AI

Risk control measures are found here. Risk control measures are acceptable, for example acceptance criteria is set to ensure proper functionality, and IFU states how to do steps.

Reviewer Comments
Risk analysis and mitigation measures are acceptable.

8.1. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	Please provide your risk analysis assessment used for the design of your final drug product with respect to the device design.	
Sponsor Response	See above.	
Reviewer Comments	Requested data meets our expectations.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #	You have provided your risk assessment in Sequence 0005. It is unclear how you determined the probability for each risk. Please clarify how probabilities are determined. State whether they are based on actual data, and if so, is the data set size sufficiently large for determining probability. If probability is not based on data, explain your method for determining probability and provide justification.	
Sponsor Response		
Reviewer Comments	See Section 13.3.2 for review.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9. DESIGN VERIFICATION REVIEW

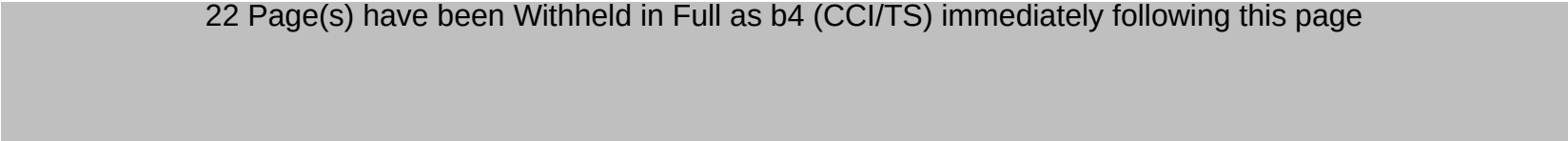
9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

(b) (4)



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10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
☒ There are clinical studies for review

This information was obtained from the following [documents](#):

Study Name	Phase 1, randomised, open-label, two-arm, parallel group, singledose study in healthy male and female subjects
Study Type	PK study between CT-P17 AI and CT-P17 PFS
Objectives/Endpoints	To demonstrate the PK similarity
Drug/Device Studied	AI and PFS
Number and Type of Subjects	N=193, (95 PFS, 98 AI). Healthy male or female subjects.
Results	Equivalent results between CT-P17 AI or PFS, SC administration was well tolerated
Device Related Comments	No Comments
Reviewer Comments	No Comments
Reviewer Conclusion	Comparable results of AI vs PFS

Study Name	Phase 3, randomised, activecontrolled, double-blind , multicenter study in patients with moderate to severe active RA
Study Type	Confirmatory efficacy and safety study
Objectives/Endpoints	To demonstrate similarity of efficacy
Drug/Device Studied	CT-P17 PFS and Humira PFS
Number and Type of Subjects	N=648, n=324 for each device, male or female with moderate to severe RA
Results	Efficacy and PK results similar between CT-P17 and Humira No significant difference between CT-P17 and Humira in PD results
Device Related Comments	No Comments

Reviewer Comments	No Comments
Reviewer Conclusion	Comparable results of CT-P17 PFS and Humira PFS

Study Name	Phase 3, open-label, single-arm, multiple-dose study in patients with moderate to severe active RA
Study Type	AI usability study
Objectives/Endpoints	The usability as assessed by patients rating using PRE- and POST-Self-Injection Assessment
Drug/Device Studied	CT-P17 AI
Number and Type of Subjects	N=62, male or female with moderate to severe RA
Results	CT-P17 delivered by SC AI was successfully administered with high usability in moderate to severe active RA patients.
Device Related Comments	No Comments
Reviewer Comments	No Comments
Reviewer Conclusion	AI injection was successful among RA patients

Reviewer Comment

Study with PFS vs AI conducted, and AI usability study. Devices validated.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☒
CDRH Facilities Inspection Review was not conducted	☐

Facility Regulatory History Review	
Firm Name:	(b) (4)
Address & FEI:	
Responsibilities:	Production of CT-P17 drug product (uDP), Labeling and assembly of CT-P17 drug product (PFS, PFS-S and AI), Cartonning of CT-P17 drug product (PFS, PFS-S and AI), Release testing of CT-P17 drug product
Site Inspection Recommendation:	VAI.

Reviewer Comments
Reported inspectional coverage included: production premises (b) (4) (b) (4) utilities, packaging, storage, GMP-relevant documentation and related activities. Areas not inspected included Quality control and shipping and distribution.
Inspection elements covered included: (b) (4) (b) (4)
There were no critical or major deficiencies. However, seven (7) Other deficiencies were noted that included: (b) (4) (b) (4)
For the minor issues, the firm sent a CAPA response that was deemed adequate. A GMP certificate was issued and this was closed as a VAI.

Facilities Review Conclusion	
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes ☐ No

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.
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<<END OF REVIEW>>

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/s/

ANH-THY LY
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