CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761219Orig1s000

OTHER ACTION LETTERS

FDA U.S. FOOD & DRUG ADMINISTRATION

BLA 761219

COMPLETE RESPONSE

Celltrion, Inc.
c/o Parexel International
2520 Meridian Parkway Suite 200
Durham, NC 27713

Attention: Ryan Zettle, PharmD, MBA
Manager, Regulatory Affairs

Dear Dr. Zettle:

Please refer to your biologics license application (BLA) dated and received November 24, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for CT-P17.

We acknowledge receipt of your amendment dated May 27, 2022, which constituted a complete response to our November 24, 2021, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTION DEFICIENCY

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

ADDITIONAL COMMENTS

We also have the following comment that is not an approvability issue:

Center for Devices and Radiological Health

FDA conducted an inspection of your contract manufacturing organization (CMO), (b) (4) manufacturing facility for this application from (b) (4) During the inspection three device observations were noted. At the time of your response to this CR letter, provide an update on the corrections and corrective actions the CMO has taken to address all observations.

PRESCRIBING INFORMATION

(1) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[3]

In addition, we encourage you to review the draft guidance for industry *Labeling for Biosimilar Products.*

CARTON AND CONTAINER LABELING

(2) We reserve comment on the proposed labeling until the application is otherwise adequate.

Please refer to correspondence dated, August 11, 2022, which addresses the proposed proprietary name, Yuflyma, in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

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[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
- Present tabulations of the new safety data combined with the original BLA data.
- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

(3) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

(6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

NIKOLAY P NIKOLOV
11/23/2022 10:50:22 AM

U.S. FOOD & DRUG ADMINISTRATION

BLA 761219

COMPLETE RESPONSE

Celltrion, Inc.
c/o Parexel International
2520 Meridian Parkway
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Attention: Ryan Zettle, PharmD, MBA
Manager, Regulatory Affairs

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We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS DEFICIENCIES

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

PRODUCT QUALITY

1. Implement (b) (4) limits validated by bacterial retention study.

2. The endotoxin limit for the (b) (4) exceeds the endotoxin limit for release. This may allow for the production of a batch that may meet (b) (4) limits but exceeds the specification for release. Update the endotoxin (b) (4) limit and/or the release specification.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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.

PRESCRIBING INFORMATION

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CARTON AND CONTAINER LABELING

(2) We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, February 22, 2021, which addresses the proposed proprietary name, Yuflyma. This name was found conditionally

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
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acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

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immunogenicity. Include an updated estimate of use for this product marketed in other countries.

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BsUFA II APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They

will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

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/

NIKOLAY P NIKOLOV
11/24/2021 02:27:22 PM