CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761088Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761088

COMPLETE RESPONSE

CELLTRION, Inc.
c/o PAREXEL International Corporation
Attention: Jeffrey Fairbairn
Senior Director, Integrated Product Development
4600 East-West Highway, Suite 350
Bethesda, MD 20814

Dear Mr. Fairbairn:

Please refer to your Biologics License Application (BLA) dated April 28, 2017, received April 28, 2017, and your amendments, submitted under section 351(k) of the Public Health Service Act for CT-P10.

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

During a recent inspection of the Celltrion, Inc. (FEI 3005241015) manufacturing facility, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of the deficiencies is required before this BLA may be approved.

CLINICAL

You have not provided adequate information and scientific justification that Study CT-P10 3.3, in patients with advanced follicular lymphoma, is adequate to detect differences between the products, should they exist, to support a demonstration of no clinically meaningful differences between CT-P10 and US-licensed Rituxan in terms of the safety, purity, and potency of the product. You will need to provide additional information and justification to address the uncertainty raised by observed differences, specifically in objective response rate (ORR) and adverse events, in Study CT-P10 3.3.

PRODUCT QUALITY

1. The cell culture process (b) (4) . However, the characterization and

assessment of (b) (4) Therefore, your control over (b) (4) during manufacture is inadequate. To ensure product quality and cell culture process consistency,

(b) (4)

2. Your proposed ranges for certain process parameters are unacceptable, given that their values exceed those evaluated during process validation and that adequate process characterization data supporting their limits were not provided. For the following parameters, revise sections 3.2.S.2.2 to limit the proposed acceptable ranges for the commercial process to the validation ranges or to commercial manufacturing experience. Alternatively, provide additional process characterization data to justify the proposed ranges for these parameters.

(b) (4)

3. In the responses received on November 21 and 28, 2017, to the Agency's information request (IR) comments 1e, 1f, 1i and 16 dated November 13, 2017, Celltrion included descriptions of certain process parameters. However, section 3.2.S.2.2 which describes the conditions of routine manufacture was not updated to reflect this information. Update section 3.2.S.2.2 to be consistent with the information received on November 21 and 28, 2017, for the following parameters:

(b) (4)

4. In the response received on November 28, 2017, to our IR regarding the acceptable ranges for the (b) (4) for the chromatography columns, Celltrion stated that these ranges are based on (b) (4)

[redacted] This does not provide sufficient control for consistency during routine manufacture. Parameters associated with [redacted] should be assigned for the target values set in the [redacted] and justified using data obtained in the PPQ and commercial manufacturing runs. If wider ranges are desired than those established during PPQ and commercial manufacturing runs, data should be provided to justify the proposed ranges.

5. Product fragments are identified as a critical quality attribute (CQA) for CT-P10 and monitored [redacted]. However, the impact of the [redacted] process on product fragment levels was not assessed during process development. Therefore, it is not clear if proposed critical process parameters are sufficient to control levels of fragments during routine manufacture. To adequately control for product fragments:
   a. Identify [redacted] process unit operations that impact the levels of product fragments,
   b. [redacted]
   c. Provide a complete summary and description of your control strategy for product fragments.
6. Deamidation at the heavy chain Asn55 (HC Asn55) site is identified as a CQA and controlled by the [redacted] To support the proposed control strategy, provide data showing that changes in deamidation at HC Asn55 can be reliably detected by the [redacted] method.
7. The data provided in section 3.2.R.4.1.5 *Afucosylation* show that increased afucosylated glycans (G0+G1) can affect FcγRIIIa binding and, consequently ADCC activity of CT-P10. Therefore, the proposed DS specification for glycans of G0 = [redacted]% and Unidentified Peaks [redacted]% does not provide adequate control of ADCC, as it does not provide sufficient control of G1 content. Provide the BLA with the following:
   a. Propose DS specifications with acceptance criteria to control all main afucosylated glycans,
   b. Provide assay validation data to confirm the suitability of the oligosaccharide profile test for the proposed specifications for afucosylated glycans,
   c. Provide all available DS lot release and stability data to justify the revised specifications and the acceptance criteria.
8. In the response to IR comment 4 received on January 3, 2018, Celltrion described the stability testing plan and specifications for the CT-P10 master and working cell banks; however, the information was not submitted in relevant section of Module 3. Update section 3.2.S.2.3.2 with the information provided in the response.
9. FcγRIIIa binding affinity is included in the DS release and stability specifications to control CT-P10 ADCC activity. Celltrion states that testing of DS is sufficient to ensure FcγRIIIa binding affinity of CT-P10 DP throughout its shelf life. However, no data is

provided for FcγRIIIa binding affinity for DP stored under the long term storage condition of 5±3°C. Celltrion should provide data for FcγRIIIa binding affinity during DP storage to support the current testing strategy, or alternatively, include FcγRIIIa binding affinity testing in the DP stability program.

10. In the IR response received on January 3, 2018, you proposed an acceptance criterion of polysorbate 80 (PS80) concentration [redacted] Provide data to support the adequacy of the proposed PS80 lower limit.

11. The response received on January 3, 2018, to the Agency's IR comment 26 dated December 21, 2017, indicates that a small portion of the 100 mg CT-P10 DP vials from the PPQ and commercial runs fail based on [redacted] fill weight check and these vials do not meet the requirement of extractable volume per USP<1>. Section 3.2.P.3.5 should be revised to reflect that these vials are quarantined and discarded.

12. The media fill simulation provided in the BLA was not conducted using the primary container closure system specific for the CT-P10 100-mg process (10-mL [redacted] glass vial and 20mm [redacted] rubber stopper). Conduct three media fill simulations using the CT-PT10 100-mg primary container closure system and include the study report upon resubmission.

13. Vials used as positive controls in the dye penetration container closure integrity test were breached using a 34-gauge needle (80-190 µm). The positive control breach size is approximately 12-fold larger than the test method limit of detection. Modify the container closure integrity test to include positive controls with breach size close to the limit of detection.

14. Information and data supporting the use of the drug product sterilizing filter is insufficient. The bacterial retention study data included in the BLA showed a loss in cell viability after 8 hours of contact with the drug product. Therefore, the study was conducted by inoculating the bacteria during the last 8 hours of total contact time [redacted]. However, no evidence is provided to indicate that cell viability is maintained throughout the 8-hour challenge period. Provide bacterial growth study data to demonstrate consistent growth of *B. diminuta* for up to 8 hours of contact time with the drug product.

15. The equipment sterilization validation data to support [redacted] sterilization of the [redacted] were not sufficiently described. [redacted]

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* 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 draft guidance for industry: Labeling for Biosimilar Products at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

We reserve comment on the proposed container label and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, July 26, 2017, which addresses the proposed proprietary name, Truxima. This name was found 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.

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 patient 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.

ADDITIONAL COMMENTS

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

PRODUCT QUALITY

1. In 3.2.R.3.2.1.5 *Peptide Mapping by LC-MS* Celltrion stated that the peptide sequence coverage was 100% for both the heavy chain and light chain for all samples. Additionally, you state that "MS/MS data (data not shown) confirmed that the amino acid sequences of Rituxan, CT-P10, and MabThera matched and sequence coverage by MS/MS was also 100% (data not shown)." We note the summarized information in Table 3.2.R.3-6 described the trypsin- and Asp-N- digested peptides. However, the heavy chain residues 419 and 420 were not provided. Clarify this discrepancy.
2. In the complete response submission, provide updated data from the following studies that are ongoing:
   a. (b) (4)
   b.
   c. The ongoing CT-P10 DS and DP stability studies (in sections 3.2.S.7 and 3.2.P.8),

d. The leachable study on 100 mg DP lots committed in your January 3, 2018 response to IR comment 21,

e. The stability study on three [redacted] (b) (4) lots for up to 12 months, committed in your January 3, 2018 response to IR comment 8. Provide the control strategy of [redacted] (b) (4) used in the manufacturing of CT-P10.

3. Results from the endotoxin spiking study indicate that the CT-P10 drug product is affected by low endotoxin recovery (LER) when tested using the kinetic chromogenic method. Therefore, the applicant submitted data to qualify the Gel Clot method as an alternative method for endotoxin detection. The data submitted in Amendment 0028 demonstrates that no LER effects are observed when the Gel Clot method is used. Update the BLA to include the use of the gel clot method as a release test. A description of the method, specifications, and method qualification studies should be included in the appropriate sections of the application.

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 FDA Guidance for Industry, "*Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants,*" November 2015 at https://www.fda.gov/downloads/drugs/guidances/ucm345649.pdf.

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, please call Esther Park, Regulatory Project Manager, at (301) 796-2811.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
02/28/2018