CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761091Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761091

COMPLETE RESPONSE

CELLTRION, Inc.
c/o PAREXEL International
Attention: Lotte McNamara, PhD
Principal Consultant
4600 East-West Highway, Suite 350
Bethesda, MD 20814

Dear Dr. McNamara:

Please refer to your Biologics License Application (BLA) dated May 30, 2017, received May 30, 2017, and your amendments, submitted under section 351(k) of the Public Health Service Act for CT-P6.

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

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

PRODUCT QUALITY

2. Per the "Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products" (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm389069.pdf), "In the case of drug products requiring reconstitution, the product should be designed to meet the label claim and acceptable overfill, and allow for correct dosing". **Adjust the Drug Product (DP) release specification of (b) (4) mg/ml to ensure that the recoverable protein content at the lower limit of the acceptance criterion will consistently meet the label claim of 420 mg.**

3. To support the licensure of CT-P6 420 mg/vial, the CT-P6 DP manufacturing process and controls should be set to ensure the appropriate deliverable volume and protein concentration after reconstitution in each DP vial to meet the label claim. Insufficient information and data on the approach and method used to derive the overfill volume ((b) (4)%;

Section 3.2.P.2.2) and fill weight limits ((b) (4) mg; Section 3.2.P.3.4) were provided in the BLA to support fill volume/weight control strategy. Provide additional information (e.g., capability of the filling machine) and data (e.g., from process development results and calculations used to derive the fill weight controls) to support current fill volume/weight limits.

4. The proposed (b) (4) , a critical quality attribute known to adversely affect potency. **Revise the** (b) (4) **that is validated by your manufacturing experience. Alternatively, tighten the DS lot release and stability specifications for** (b) (4) **detected by IEC-HPLC to ensure acceptable product quality upon DP manufacture** at a worst-case scenario (e.g., using DS released at the upper/lower limit and stored through the end of shelf life) in support of the (b) (4) .

5. In the response to an Information Request received on February 16, 2018, your proposed acceptance criterion for (b) (4) is unacceptably broad based on your manufacturing experience. To ensure appropriate (b) (4) of the DP, tighten your acceptance criterion for DS release to (b) (4)

PRESCRIBING INFORMATION

6. 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.

   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

7. We reserve comment on the proposed container label and carton labeling until the application is otherwise adequate. In your resubmission, provide draft carton and container labeling based on our proposed revisions dated February 13, 2018.

PROPRIETARY NAME

8. Please refer to correspondence dated February 14, 2018, which addresses the proposed proprietary name, Herzuma. 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:

CLINICAL PHARMACOLOGY

1. You have submitted 6-month storage stability data for CT-P6 and US-licensed Herceptin in human serum (Project RFHD2). The 6-month storage stability data does not support the sample analysis using ELISA method (ICD546) for Study CT-P6 1.5, which was around 18-months in duration. Submit to the BLA additional long term storage stability data for the duration of the study covering from the date of sample collection to the last sample analysis date.

PRODUCT QUALITY

2. Based on the October 16, 2017, and January 29, 2018, responses to our Information Requests regarding the acceptable ranges for numerous process parameters that have the potential to impact product quality, the limited process characterization and process validation data may not fully justify the criticality ranking of these parameters. The acceptability of these rankings will be a review issue once the entire control strategy is updated and available for review.

3. We acknowledge receipt of your process characterization studies performed in order to establish acceptable ranges for lyophilization process parameters on February 28, 2018. The acceptability of your updated control strategy (process parameters and associated acceptable ranges) for lyophilization will be a review issue that will be addressed in the next review cycle upon receipt of your resubmission.

4. We recommend that you develop a two-tiered reference material system to support the product lifecycle. An appropriately characterized primary reference material that is representative of clinical materials can be used to calibrate or qualify a working reference material and contributes to mitigating the risk of drift in quality attributes over time. Use of a working or secondary reference material calibrated against a single primary reference material for routine release and stability testing of commercial lots provides additional assurance that commercially manufactured product is representative of the clinical trial material.

5. In the response to an Information Request received on February 20, 2018, additional validation data for (b) (4)

6. In your resubmission, provide updated data to the section indicated from the following ongoing studies:

    a. The commercial scale [redacted] chromatography columns (in section 3.2.S.2.5),

    b. The commercial [redacted] lifetime study (in section 3.2.S.2.5),

    c. The ongoing CT-P6 DS and DP stability studies (in sections 3.2.S.7 and 3.2.P.8),

    d. The shipping validation of the finished CT-P6 drug product (in section 3.2.P.3.5),

    e. The stability study on three in-use PS20 lots for up to 12 months, committed in your 2/20/2018 response (in Section 3.2.P.4).

7. [redacted] Feasibility of [redacted] for BWFI has not been determined. In your resubmission, include feasibility studies for [redacted]. Update Section 3.2.P.2 to include a description of the studies as well as the results. If the feasibility studies support the use of [redacted] the manufacturing process for BWFI should be revised accordingly.

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, call Leyish Minie, Regulatory Project Manager, at (301) 796-5522.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
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/

JULIA A BEAVER
03/30/2018