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*APPLICATION NUMBER:*

**125544Orig1s000**

**OTHER ACTION LETTERS**



BLA 125544

**COMPLETE RESPONSE**

Celltrion, Inc.  
c/o Parexel International  
4600 East-West Highway, Suite 350  
Bethesda, MD 20814

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) dated August 8, 2014, received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13.

We acknowledge receipt of your amendments dated September 5, and 22, October 1, 20, 27, and 28, November 5, 13, 14, and 28, December 5, 23, and 26, 2014, January 15, 22, and 27, February 11 (2), 13, and 24, March 9, 23, and 31, April 2, 17 (3), May 6, and 7, and June 3, 2015.

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.

**PRODUCT QUALITY**

1. You provided data from a limited number of lots showing lower levels of subvisible particulates in the range of 1 to 5 microns in US-licensed Remicade compared to both CT-P13 and EU-approved Remicade. The observed differences may be due to the limited number of lots of CT-P13, US-licensed Remicade and EU-approved Remicade used to perform the analysis. However, these results suggest that analytical differences may exist between US-licensed Remicade and EU-approved Remicade, which, if confirmed, could impact the assessment of the adequacy of the analytical bridge between the three products. To address this concern, provide results of subvisible particulate analysis from an adequate number of additional CT-P13, US-licensed Remicade and EU-approved Remicade lots.
2. You evaluated the analytical similarity of CT-P13 and US-licensed Remicade using a variety of functional assays. Your data generated using a standard NK-cell based killing ADCC assay suggest that CT-P13 has ~20% lower ADCC activity compared to the reference product US-licensed Remicade, which correlates with differences in FcγRIIIa binding. The difference in ADCC leads to residual uncertainty about whether CT-P13 is highly similar to US-licensed Remicade, as the role of ADCC remains uncertain in the

clinical activity of the reference product (e.g., in the setting of inflammatory bowel disease). Furthermore, you did not adequately justify the impact of the difference in ADCC on the analytical similarity assessment and did not identify the structural basis underlying this difference. For example, you should determine whether the H2L1 variant that is present at relatively high levels in CT-P13 compared to US-licensed Remicade plays a role in decreasing NK-dependent ADCC activity. On the other hand, the Agency has not excluded the possibility that analysis of additional lots of CT-P13, US-licensed Remicade, and EU-approved Remicade lots could overcome a statistical anomaly due to the analysis of a limited number of lots. To this point, we note that prior differences in glycan patterns were reduced when additional lots of CT-P13, US-licensed Remicade and EU-approved Remicade were analyzed. To address the current deficiency with respect to differences in ADCC activity, we recommend that you repeat the evaluation of ADCC using additional lots to determine whether the ADCC difference you have reported was due to small sample size and decreases when additional lots are evaluated. If the difference in ADCC persists following analysis of additional lots, you should identify and demonstrate control of the product quality attributes that underlie ADCC activity in CT-P13 (e.g., glycan pattern, contribution of H2L1 variant, etc.) and provide an adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity.

### **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](#) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 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>

### **PROPRIETARY NAME**

Please refer to correspondence dated, February 23, 2015, which addresses the proposed proprietary name, Inflectra. 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. You are advised to contact the Division of Pulmonary, Allergy, and Rheumatology Products regarding the extent and format of your safety update prior to responding to this letter.

### **ADDITIONAL COMMENTS**

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

1. You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade, and differences were observed in immunogenicity incidence rates between these products. This single dose, healthy volunteer study suggests a potential trend towards increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved Remicade [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. Differences are also observed in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 3.42 vs 2.63, respectively). To address these observations, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.
2. The current drug product stability data using Process B batches of CT-P13 support an expiry date of 42, not <sup>(b) (4)</sup> months. To address this concern, adjust your proposed expiry dating to reflect existing data and provide a stability protocol to support post-approval expiry extension.
3. We acknowledge the plan outlined in your April 17, 2015, letter to develop and validate a revised version of the visible particle test for reconstituted drug product. The revised test will use <sup>(b) (4)</sup> and visual inspection of 20 reconstituted vials. Data supporting the assay revision have not been provided to the BLA. To address this concern, submit the assay SOP, validation report and revised specification to the Agency for review.

### **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. 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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.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 Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BADRUL A CHOWDHURY  
06/08/2015