

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761039Orig1s000

OTHER ACTION LETTERS



BLA 761039

COMPLETE RESPONSE

Coherus BioSciences, Inc.
Attention: Eva Kras
Executive Director, Regulatory Affairs
333 Twin Dolphin Drive, Suite 600
Redwood City, CA 94065

Dear Ms. Kras:

Please refer to your Biologics License Application (BLA) dated August 9, 2016, received August 9, 2016, submitted under section 351(k) of the Public Health Service (PHS) Act for CHS-1701.

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.

IMMUNOGENICITY

1. In Amendment 41 (received March 21, 2017), for treatment emergent persistent anti-drug antibodies (ADA) with a titer ≥ 2 , you report an ADA incidence of 9.8% in the CHS-1701 arm and an incidence of 5.0% in the US-licensed Neulasta arm. FDA identified an additional subject ^{(b) (6)} as positive in the US-licensed Neulasta arm, which makes the ADA incidence 5.8%. Coherus conducted statistical analysis of ADA incidence yielding a 1-sided upper exact limit of 10%, while the FDA performed independent analysis of your data and obtained a 1-sided upper exact limit of 10.97%. Your observed difference in ADA between groups may not be sufficient to support a demonstration that there are no clinically meaningful differences between CHS-1701 and US-licensed Neulasta. An observed difference at or above the 10% threshold creates residual uncertainty regarding biosimilarity of CHS-1701 to US-licensed Neulasta because the actual baseline immunogenicity rate for pegylated G-CSF products is expected to be lower and the 10% difference was selected to support a feasible study design. In addition, the observed ADA difference needs to be considered in context of other factors that may affect safety and efficacy, such as titers, persistence, and whether the ADA response is against PEG or G-CSF. Provide additional information to address these concerns, such as data that clarifies whether anti-PEG or anti-G-CSF antibodies are driving the observed difference in ADA rates between CHS-1701 and US-licensed Neulasta. Depending on the information provided, further clinical studies may be needed to provide assurance that the difference in ADA rates between CHS-1701 and US-licensed Neulasta

treatment groups do not result in clinically meaningful differences between CHS-1701 and US-licensed Neulasta.

2. You did not provide data on anti-G-CSF antibody titers for subjects confirmed positive for anti-G-CSF antibodies. You also did not provide data for the incidence of neutralizing antibodies. Lack of these two pieces of information creates uncertainty about whether the difference in ADA incidence rates could be due to differences in these two factors. To address this concern provide the following:
 - a) Anti-G-CSF titers for anti-G-CSF positive samples together with time courses for evolution of anti-G-CSF titers.
 - b) We recommend that you test all confirmed positive samples (both anti-PEG and anti-G-CSF) in your neutralizing antibody assay.
3. You provided validation reports for two neutralizing antibody (NAb) assays. The first NAb assay was submitted with the original BLA on August 9, 2016, and the second NAb assay was submitted in an amendment on January 18, 2017. Both NAb assays, are inadequate for the reasons listed below and will not allow for meaningful evaluation of NAb in clinical samples. To resolve the lack of an adequate neutralizing assay, submit a fully validated NAb assay, including the assay validation report and the test method standard operational protocol.

You can revise one of the two NAb assays submitted to the BLA or develop a new NAb assay. In either case, refer to the FDA draft guidance of “*Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Product, April 2016*” for recommendations on assay validation.

Regarding neutralizing antibody assay ((b) (4)) submitted in the original BLA on August 9, 2016:

- a) The CHS-1701 based screening assay shows excessively high intra- and inter-assay variability (%CV). For example, (b) (4)
Due to the high variability of the assay, the validation data generated are deemed unreliable. In addition, you did not provide intra-assay precision for negative control samples (referred to as BTS samples using pooled human plasma in the submission).
- b) In the information request dated December 7, 2016, the Agency asked Coherus to provide the justification or additional data to support using the plating concentration (b) (4)

(b) (4)

Revise the concentration of CHS-1701 so that it is in the linear range of the dosing curve. In addition, revise the concentration of mIL-3 used in the mIL-3 based confirmatory assay so that it yields an outcome similar to that of the CHS-1701.

- c) The condition of the M-NFS-60 cells, including passage number, cell density, and cell viability, may affect the cellular response to CHS-1701 and mIL-3. However, you have not provided developmental data to support these cell related parameters specified in the assay validation report. Provide data to support these key assay parameters used in the assay, including an evaluation of cellular response to CHS-1701 and mIL-3 (dosing curves) when cells are at the low, middle, and high range of the specified passage numbers, cell density, and cell viability. Include sufficient runs to demonstrate the reproducibility of the responses.

- d) (b) (4)

To address this concern, provide information showing that your NAb assay can sensitively detect NAb if they are present.

- e) For the mIL-3 based confirmatory assay, the confirmatory assay cut-point factor was determined by statistical methods to be 0.726 using a parametric method, and 0.817 using a non-parametric method. The statistical methods used to determine the cut-point factor is acceptable. However, it appears that you did not use either of the statistically determined cut-point factors, but instead chose a cut-point factor of 0.829, from the CHS-1701 based screening assay, to be the cut-point factor of the mIL-3 based confirmatory assay. Assay cut-points should be experimentally determined with appropriate statistical methods.
- f) For the immunodepletion confirmatory assay, you chose a cut point factor of 0.829. The cut-points should be experimentally determined with appropriate statistical methods. Determine the cut-point for the immunodepletion confirmatory assay by using a minimum of 30 individual plasma samples tested in the immunodepletion assay on at least 3 different days by at least two analysts.
- g) The assay cut-points were determined from commercially obtained normal human plasma. Processing and storage of plasma can impact assay performance. To ensure that cut-points are appropriate for the specific study population, the cut-points need to

be verified using plasma samples from treatment-naive study subjects. Provide the data confirming the sensitivity and cut-point of your CHS-1701 based screening assay, mIL-3 based confirmatory assay, and immunodepletion confirmatory assay with samples collected and handled the same way as study samples.

- h) You state that sample stability was considered acceptable (b) (4)
(b) (4)
". Your approach is insensitive for the detection of sample degradation (antibody reactivity). Revise the stability acceptance criteria to be based on the comparison of the sample RLU level.

Regarding the neutralizing antibody assay (b) (4) submitted on January 18, 2017:

- i) The drug concentrations used in the NAb assays are (b) (4)
(b) (4)
This indicates the cell growth may be insensitive to the neutralizing effect of anti-drug antibody in the current test method. In order to optimize the assay sensitivity, revise the concentrations of CHS-1701 and mIL-3 so that they are in the linear range of the dosing curves.
- j) (b) (4)
(b) (4)
These data indicate that there might be endogenous stimulators in these plasma samples (b) (6).
Consequently, the assay is less sensitive to detect neutralizing antibody in samples with endogenous stimulators. Provide a plan to identify, test, and interpret data for samples with endogenous stimulator(s) which would interfere with the assay. Alternatively, re-design and re-validate an assay to address this issue. (b) (4)
(b) (4)
(b) (4)
- k) The condition of the M-NFS-60 cells, including passage number, cell density, and cell viability, may affect the cellular response to CHS-1701 and mIL-3. However, you have not provided developmental data to support these cell related parameters specified in the assay validation report. Provide data to support these key assay parameters used in the assay, including an evaluation of cellular response to CHS-1701 and mIL-3 (dosing curves) when cells are at the low, middle, and high range of the specified passage numbers, cell density, and cell viability. Include sufficient runs to demonstrate the reproducibility of the responses.
- l) You initially determined a preliminary low positive control (LPC) using a statistical method, which leads to the rejection of an assay run 1% of the time (Table 6 in

Appendix I). This approach and the concentration of LPC at 631.6ng/mL are acceptable. However, you later increased the concentration of LPC to 1000ng/mL based on the data in Table 7 in Appendix I. The use of LPC at 1000ng/mL is not acceptable because the purpose of LPC is to verify that the assay is running as expected. Based on the PC titration curve (Figure 2 in Appendix I), 1000ng/mL (of PC) is at the mid-point of the linear range of the curve; therefore, 1000ng/mL is not an appropriate concentration for the LPC because it will not adequately demonstrate that the assay is performing as expected.

- m) The statistical method used to determine the screening cut-point (SCP) and confirmatory cut-point (CCP) underestimates data variance, which may increase the risk of false positive detection in both assays. Specifically, the outlier exclusion is calculated on each batch rather than two batches together and cut-point calculation is based on the mean value of the two batches rather than the individual value. We recommend that you revise the statistical method used for cut-point determination and recalculate the SCP and CCP.
- n) The SCP and the CCP were determined from commercially obtained normal human plasma. Processing and storage of plasma can impact assay performance. In order to ensure that cut-points are appropriate for the specific study population, the cut-points need to be verified using plasma samples collected from treatment-naive study subjects and handled in the same way as study samples. Provide the data confirming the sensitivity and cut-points of your assay.
- o) Based on the data reported in Table 11A and 11B of Appendix I for hemolyzed and lipemic plasma interference, it appears that sample hemolysis may increase the risk of false positive detection in the neutralizing assay. Provide a plan to analyze hemolyzed serum samples.
- p) The current acceptance criteria for Negative Control (NC), Variation Control (VC), and Positive Control (PC) samples require only half of the controls to be within the acceptance range. Specifically, (b) (4). Such plate acceptance criteria do not provide adequate control across the entire plate. Revise the plate acceptance criteria to require both sets of NC, VC and PC controls to be within the acceptance range.
- q) You did not provide assay precision for NC samples. See FDA's draft guidance *Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016* regarding recommendations for reporting intra- and inter-assay precision for NC.

PRODUCT QUALITY

3.2.R.1 Analytical Similarity Assessment

1. Adequate physicochemical and functional assessment of degradation profiles of CHS-1701 and US-licensed Neulasta should be performed to provide a direct comparison of CHS-1701 and US-licensed Neulasta. However, you did not evaluate the potency of CHS-1701 and US-licensed Neulasta in the forced degradation study included in the analytical similarity assessment and you did not demonstrate that potency of both products is affected to similar extents when subjected to forced degradation conditions. Provide CHS-1701 and US-licensed Neulasta potency data of samples subjected to forced degradation conditions.
2. You used US-licensed Neulasta lot 1054829 in the CHS-1701-04 clinical study, but you did not include this lot in the Tier 1 analyses of potency due to material limitations. You stated that limited supply of this material has been returned from the clinical site and potency testing for this lot “can be submitted to the BLA upon Agency’s request.” Provide potency data for US-licensed Neulasta lot 1054829.

Drug Substance (DS) & Drug Product (DP) Release and Stability Specifications 3.2.S.4.5 and 3.2.P.5.6 Justification of Specifications

(b) (4)



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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.

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 labels and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated October 12, 2016, which addresses the proposed proprietary name, Udenyca. 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 US-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:

1. Overall, Module 3 of your BLA is not well prepared. Frequently, you refer to information/data in numerous reports, but do not provide an informative summary with your conclusions based on the information. While reports are important to verify some specific information or evaluate raw data, your summaries with interpretations and conclusions form the basis for the Agency's review. Submitting a large number of reports with minimal data interpretation did not allow for an efficient review process. For example, reports related to process characterization and determination of in-process controls were difficult to interpret. Additionally, there are many inconsistencies, missing information, and typographical errors throughout your BLA. We expect that you will address these, and other such issues in any resubmission.

Drug Substance

2.

3.

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5.

(b) (4)

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OTHER

On May 3, 2017, Apotex Inc. and Apobiologix submitted a citizen petition to FDA (Docket No. FDA-2017-P-2803) regarding certain aspects of applications submitted under section 351(k) of the PHS Act referencing Neulasta (pegfilgrastim). The deficiency comments included in this communication reflect only our current thinking and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petition.

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 FDA Guidance for Industry, "*Formal Meetings Between the FDA and Biosimilar Biological 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 Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

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
06/09/2017