CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761039Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115573

MEETING MINUTES

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

Dear Ms. Kras:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CHS-1701.

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2016. The purpose of the meeting was to discuss the format and content of a biosimilar biologic product application to be submitted under section 351(k) of the PHS act for the proposed biosimilar biologic product, CHS-1701, and the reference product, US licensed Neulasta® (US), for the purpose of obtaining licensure under section 351(k) of the PHS Act.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Natasha Kormanik, Regulatory Health Project Manager at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	Biological Product Development (BPD) Type 4
Meeting Date and Time:	August 8, 2016 from 1:00-2:00 PM (ET)
Meeting Location:	FDA White Oak Building 10903 New Hampshire Avenue White Oak Building 22, Room 1309 Silver Spring, MD 20903
Application Number:	IND 115573
Proposed Indication:	CHS-1701 is being developed for the same indications as approved for US-licensed Neulasta
Sponsor/Applicant Name:	Coherus Biosciences, Inc.
Meeting Chair:	Nicole Gormley, MD
Meeting Recorder:	Natasha Kormanik, MSN, RN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Ann Farrell, MD – Division Director
Albert Deisseroth, MD, PhD – Clinical Team Lead
Nicole Gormley, MD – Acting Clinical Lead
Bindu Kanapuru, MD – Clinical Reviewer
Theresa Carioti, MPH – Chief, Project Management Staff
Thomas Iype, PharmD – Regulatory Project Manager
Alycia Anderson, CCRP – Regulatory Project Manager
Natasha Kormanik, MSN, RN, OCN – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology
Brenda Gehrke, PhD – Reviewer
Michael Manning, PhD – Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD –Team Lead
Vicky Hsu, PhD – Reviewer
Sarah Schrieber, PharmD- Reviewer

Office of Biostatistics
Jingjing Ye, PhD – Biostatistics Reviewer
Xiaoyu (Cassie) Dong, PhD – CMC Statistics Reviewer

Office of Pharmaceutical Quality (OPQ)/ Office of Biotechnology Products/ Division of Biotechnology Research and Review IV
Gibbes Johnson, PhD – Acting Division Director
Serge Beaucage, PhD – Team Lead
Jacek Cieslak, PhD – Reviewer

OPQ/ Office of Process and Facilities/ Division of Microbiology Assessment
Patricia Hughes, PhD – Acting Branch Chief, Product Quality Microbiology
Maria Candau-Chacon, PhD – Acting Quality Assessment Lead
Lakshmi Narasimhan, PhD – Reviewer

Office of Surveillance and Epidemiology (OSE)/ Division of Medication Error Prevention and Analysis
Lubna Merchant, PharmD – Deputy Director
Hina Mehta, PharmD – Acting Team Lead
Nicole Garrison, PharmD, BCPS – Safety Evaluator
Sarah Harris, PharmD – Safety Regulatory Project Manager

Division of Pediatric and Maternal Health
John Alexander, MD, MPH – Deputy Director
Erica Radden, MD – Medical Officer

Office of New Drugs Therapeutic Biologics and Biosimilars Staff
Sue Lim, MD – Senior Staff Fellow
Lanre Okusanya, PharmD, MS – Reviewer

Office of Regulatory Policy/ Division of Regulator Policy I (DRP 1)
Patrick Raulerson, JD – Regulatory Counsel

SPONSOR ATTENDEES

Coherus Biosciences, Inc.
Eva Kras, MS – Senior Directory Regulatory Affairs
Lisa Bell, PhD – EVP, Regulatory Affairs
Barbara Finck, MD - Chief Medical Officer
Karen Miller, PhD – VP, Analytical and Pharmaceutical Sciences
Vladimir Vexler, PhD – SVP, Translational and Developmental Sciences
Vince Anicetti, MS – SVP, Quality and Compliance
Peter Watler, PhD – Chief Technical Officer
Helen Tang – Senior Director, Biostatistics
Dennis Lanfear – Chief Executive Officer and President

1.0 BACKGROUND

The Sponsor states that CHS-1701 is a covalent conjugate of recombinant methionyl human granulocyte colony stimulating factor (G-CSF) and 20 kDa monomethoxypolyethylene glycol (PEG). The proposed indication for CHS-1701 is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia and to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). However, we remind you that US-licensed Neulasta has orphan drug exclusivity for the latter indication (i.e., H-ARS), which precludes approval of a biosimilar to US-licensed Neulasta for this indication until that sponsor's period of exclusivity expires (subject to certain exceptions listed at 21 CFR section 316.31).

(b) (4)

On October 9, 2014, the Sponsor and the Agency had a BPD type 2 meeting to discuss the quality, nonclinical and clinical aspects of the development program to support licensure of CHS-1701 as a proposed biosimilar to US-licensed Neulasta under section 351(k) of the PHS Act.

On September 29, 2015, the Sponsor and the Agency had a BPD type 2 meeting to discuss Coherus' definitive analytical similarity package.

On December 1, 2015, the Sponsor and the Agency had a BPD type 3 meeting with a purpose of gaining an in-depth data review and advice meeting regarding the ongoing BPD clinical program for CHS-1701.

On March 21, 2016, the Sponsor and the Agency had a BPD type 1 meeting to discuss the design and analysis of a proposed comparative PK similarity study using comparing the proposed biosimilar biologic product, CHS-1701, and the reference product, US-licensed Neulasta, to support licensure under section 351(k) of the Public Health Service (PHS) Act.

On May 22, 2016, the Sponsor requested a BPD type 4 meeting to discuss the format and content of a biosimilar biologic product application to be submitted under section 351(k) of the PHS act for the proposed biosimilar biologic product, CHS-1701, and the reference product, US licensed Neulasta® (US), for the purpose of obtaining licensure under section 351(k) of the PHS Act.

FDA may provide further clarifications of, or refinements and/or changes to, the responses and the advice provided at the meeting based on further information provided by Coherus and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the PHS Act.

FDA sent Preliminary Comments to Coherus Biosciences, Inc. on August 4, 2016.

2. DISCUSSION

Question 1: Coherus intends to provide Chemistry, Manufacturing and Controls details for the proposed biosimilar product, CHS-1701, in the body of data sections of Module 3, with minimal comparison data to the US sourced reference product (US Neulasta) in section 3.2.S.1 (e.g. certain physicochemical properties such as density). All other Sections in 3.2.S and 3.2.P will focus on the proposed biosimilar product, CHS-1701.

a) Data to support the demonstration of analytical similarity of the proposed biosimilar product CHS-1701 to the US sourced reference product (US Neulasta) will be provided in the Regional Section (3.2.R) and summarised in the QoS of the BLA. Does the Agency agree?

FDA Response to Question 1: *Yes, we agree.*

Discussion: No discussion pertaining to this question.

Question 2: In accordance with FDA Guidance for Industry *Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)* a description sufficient in detail to allow a competent analyst to reproduce the necessary conditions and obtain results within the proposed acceptance criteria of the analytical procedure for each non compendial method will be provided in Section 3.2.S.4.2, *Analytical Procedures*.

a) As such, Coherus is seeking confirmation that copies of the controlled SOPs are not required to be submitted with the BLA, but can be made available during PAI. Does the Agency agree with this proposal?

FDA Response to Question 2: *The copies of the controlled SOPs are not required to be submitted with the BLA. The SOPs could be requested if the summary is not sufficient for review of the assay validation.*

In addition, please provide a detailed description of bioburden, endotoxin, and sterility methods for release and all in-process pools of drug substance (DS) and drug product (DP) as applicable.

Discussion: Refer to Sponsor's slide 8, attached. The Agency agreed with the Sponsor's response.

Question 3: In accordance with FDA Guidance for Industry *Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)* details of the Analytical method validation studies including a demonstration of conformance to the predetermined and

established acceptance criteria for each non compendial method will be provided in Section 3.2.S.4.2, *Validation of Analytical Procedures*. To further facilitate the review of the BLA, validation reports for the validated analytical methods will be submitted with the BLA. Does the Agency agree?

FDA Response to Question 3: *Provide details of the analytical method validation studies for each non-compendial method in Section 3.2.S.4.3, Validation of Analytical Procedures. Provide the qualification reports for all other compendial methods used for release and stability testing of DS and DP. Additionally, since you have multiple DS and DP release and stability testing sites, include methods transfer reports for all methods that have been transferred to alternate test sites then where the validation was performed. In addition, please provide the summary and qualification report for bioburden, endotoxin, and sterility methods for release and all in-process pools of drug substance and drug product as applicable.*

Discussion: Refer to Sponsor's slides 9-10, attached. The Agency agreed with the Sponsor's proposed layout of the content. The Sponsor indicated that validation data for the container closure integrity test used on stability samples would be in section 8.1.

Refer to Sponsor's slide 11, attached. The Agency agreed with the Sponsor's response.

Question 4: At the time of the BLA submission, 12 months of real time stability data at the recommended storage condition of 2-8°C for the Drug Substance will be provided on the four primary registration batches. Results for the 24 month time-point will be available during review (Jan through March 2017). Does the Agency concur that the 24 month stability data can be provided during the review period?

FDA Response to Question 4: *To support the proposed expiry period for your product, FDA may request submission of a "simple stability update." "Simple stability updates" are defined as stability data and analyses performed under the same conditions and for the same drug substance batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the "simple stability update" will use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. A"simple stability update" can be requested through month seven of the standard BLA review clock to support the proposed expiry period.*

Discussion: No discussion pertaining to this question.

Question 5: At the time of the BLA submission, Coherus intends to request an expiry of (b) (4) months for the drug product (DP), UDENYCA. 12 months of real time stability data at the recommended storage condition of 2-8°C for the Drug Product will be provided on the four primary registration batches. Results for the 24 month time-point will be available during

review (March –May 2017) and can be provided to the BLA upon Agency request. Does the Agency concur that the DP 24 month stability data can be provided during the review period?

a) These stability studies will continue per protocol (will be presented in Section 3.2.P.8.1, *Stability Summary and Conclusion* of the BLA) and the subsequent stability data to support shelf life extension will be provided in Annual Reports to the BLA. Assuming the ongoing stability results conform to the pre-specified acceptance criteria as defined in the protocol, with no adverse trends, does the Agency agree that the commercial shelf life for UDENYCA can be extended post approval via the Annual Report?

FDA Response to Question 5: *Regarding stability data to support the proposed DP expiry, See FDA response to question 4. The commercial shelf life for UDENYCA can be extended post-approval via Annual Report provided that the stability protocol submitted in the BLA application is approved.*

Discussion: No discussion pertaining to this question.

Question 6: Per ICH M4Q(R1), *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality,* Coherus intends to provide all required information related to batch production for the drug substance and drug product in the applicable sections of the 3.2.S and 3.2.P, respectively. Reports for all process performance qualification studies will also be submitted. Batch production records for three representative drug substance batches and the subsequent manufactured drug product batches will be provided in the 3.2.R, *Regional* section with the BLA submission. Does the Agency agree?

FDA Response to Question 6: *Yes, we agree. However, submitting executed batch records for one batch of drug substance and drug product is acceptable.*

Discussion: No discussion pertaining to this question.

Question 7: [redacted] (b) (4) . Does the Agency agree?

FDA Response to Question 7: *No, we don't agree. Per the ICH Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality: M4Q(R1) guidance, the BLA should contain a sufficient description, narrative, diagrammatic, or both, of the manufacturing process and include relevant information regarding critical steps, process controls, equipment, and operating conditions. The ability to minimize reporting of*

process parameters and in-process controls will be dependent in part on the overall control strategy, assessment of criticality, and process understanding and robustness as based on data provided in the BLA.

Discussion: Refer to Sponsor's slides 12-13, attached. The Sponsor provided an overview of the manufacturing process lifecycle. The Sponsor indicated that the process ensures product quality and process control. The Agency asked the Sponsor if they would include information on where the DS filtration steps will occur and the Sponsor stated that they would.

Refer to Sponsor's slides 14, attached. The Agency agreed with the Sponsor's content proposal.

Question 8: To facilitate the scheduling of the Pre Approval Inspection (PAI), Coherus has provided the current planned commercial campaign schedules for the drug substance. Can the Agency confirm that the anticipated timing of the PAI at the drug substance manufacturing site can be coordinated with the manufacturing schedule (1.6.2.6.1.6.1) as outlined in this briefing document?

FDA Response to Question 8: *We acknowledge your manufacturing schedule for DS ((b) (4)) and DP ((b) (4)). The inspections will be conducted during the review cycle after the filing decision and we will plan the inspection to meet the proposed campaign schedules.*

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). During the inspection, the DS manufacturing facility should be in operations manufacturing CHS-1701 and the DP manufacturing facility should be in operations manufacturing CHS-1701 or a similar product on the same filling line.

Discussion: No discussion pertaining to this question.

Question 9: (b) (4) the intended commercial drug product manufacturing site for UDENYCA, is an approved commercial sterile drug product manufacturer. The annual GMP inspection of (b) (4) is due to occur any time after (b) (4). Assuming this inspection aligns with previous determinations and does not reveal any significant GMP deficiencies in areas related to the process as applicable to the UDENYCA BLA or other systemic problems, Coherus would like to request a waiver of the Pre Approval Inspection (PAI) for UDENYCA. Does the Agency agree?

a) Should the Agency determine that a PAI of (b) (4) is necessary to support the review of the BLA, to facilitate the scheduling of the Pre Approval Inspection (PAI), Coherus has provided the current planned commercial campaign schedule for the

drug product. Can the Agency confirm that the anticipated timing of the PAI at the drug product manufacturing site can be coordinated with the manufacturing schedule (1.6.2.6.1.6.2) as outlined in this briefing document?

FDA Response to Question 9: *As indicated in the response to Question 8, all manufacturing facilities should be should be ready for inspection during the review cycle. Waiving of the inspection of the DP site will be assessed during the application review.*

Discussion: No discussion pertaining to this question.

Question 10: The analytical similarity assessment was conducted under a pre specified protocol with extensive, robust comparative physicochemical and functional studies, as well as biological and binding assays. All methods used were characterized, shown to be fit for their intended purpose and to yield reproducible results, in adherence with FDA Guidance for Industry, *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015).* With the exception of Potency by Proliferative bioassay and certain Tier 3 assays, all testing was executed at the Coherus Analytical laboratory, a non GMP site. Can the Agency comment as to the whether a Pre-approval Inspection of this site is to be anticipated?

a) If so, for Coherus resource planning purposes, can the Agency advise as to the scope and anticipated timing of this inspection?

FDA Response to Question 10: *Provide a listing of all sites where the analytical similarity assessment was conducted and identify the site(s) where each method was used to support analytical similarity between CHS-1701 and US-licensed Neulasta. Report this information in the 3.2.R, Regional section of your BLA application. The Agency may decide to inspect sites where analytical similarity assessments were conducted.*

Discussion: No discussion pertaining to this question.

Question 11: The Clinical Study report for the supportive CHS-1701-01 PK/PD study will be provided in Module 5 and relevant aspects of the study will be summarized in the clinical overview and clinical summary sections of Module 2. Given that this study was executed with CHS-1701 drug product at a higher than target labelled dose of the reference product and manufactured using an early development process at a site other than the current commercial manufacturer and did not demonstrate PK bioequivalence, Coherus proposes:

a) Safety data, with respect to Adverse Events will be integrated with the CHS-1701-03, CHS-1701-04 and CHS-1701-05 studies by treatment at onset; by period and treatment at onset, and presented in Section 2.7.4, *Summary of Clinical Safety* and 5.3.5.3, *Integrated Safety Summary* (tables and datasets). Does the Agency agree?
b) Safety data with respect to immunogenicity (ADA) will be integrated with the CHS-1701-03 (a cross-over design study), CHS-1701-04 (a 2 sequential dose, parallel

group design study) and CHS-1701-05 (a three sequence, three period design study) studies, summarized by period and treatment at onset and by treatment using only Period 1 results. Results will be presented in section 2.7.2.4, *Special Studies* and 5.3.5.3, *Integrated Safety Summary* (tables and datasets). Does the Agency agree?

c) Pharmacokinetic and Pharmacodynamic results from CHS-1701-01 will be summarized as standalone and presented in Section 2.7.2, *Summary of Clinical Pharmacology studies* and Section 2.7.3, *Summary of Clinical Efficacy*, respectively. Does the Agency agree?

FDA Response to Question 11: *Yes. Your proposal for submission of safety related data and PK/PD data appears acceptable.*

Discussion: **No discussion pertaining to this question.**

Question 12: The Clinical Study report for the supportive CHS-1701-03 PK/PD BE study will be provided in Module 5 and results of the study will be summarized in the clinical overview and clinical summary sections of Module 2. Given that this study is not supportive in demonstrating PK bioequivalence, Coherus proposes:

a) Safety data, with respect to Adverse Events will be integrated with the CHS-1701-01, CHS-1701-04 and CHS-1701-05 studies, summarized by treatment at onset and by period and treatment at onset. The results will be presented in Section 2.7.4, *Summary of Clinical Safety* and 5.3.5.3, *Integrated Safety Summary (tables and datasets)*. Does the Agency agree?
b) Safety data with respect to immunogenicity (ADA) will be integrated with the CHS-1701-01 (a cross-over design study), CHS-1701-04 (a 2 sequential dose, parallel group design study) and CHS-1701-05 (a three sequence, three period design study) studies, summarized by period and treatment at onset and by treatment using only Period 1 results. Results will be presented in section 2.7.2.4, *Special Studies* and 5.3.5.3, *Integrated Safety Summary* (tables and datasets). Does the Agency agree?
c) Pharmacodynamic results by way of the surrogate biomarker, ANC, will be integrated with the CHS-1701-05 study by treatment sequence and period and presented in Section 2.7.3, *Summary of Clinical Efficacy* and 5.3.5.3, *Integrated Summary of Efficacy.* Does the Agency Agree?
d) Pharmacokinetic results from CHS-1701-03 will be summarized as standalone and presented in Section 2.7.2, *Summary of Clinical Pharmacology studies*. Does the Agency agree?

FDA Response to Question 12: *Yes. Your proposal for submission of safety related data and PK/PD data appears acceptable***.**

Discussion: **No discussion pertaining to this question.**

Question 13: The Clinical Study report for the pivotal CHS-1701-04 Immunogenicity study will be provided in Module 5 and results of the study will be summarized in the clinical overview and clinical summary sections of Module 2. Given that this study is a two dose parallel design intended to discern clinically meaningful differences in immunogenicity rates between the proposed biosimilar product, CHS-1701 and the Reference product, US Licensed Neulasta, Coherus proposes:

a) Safety related data, with respect to Adverse Events will be integrated with the CHS-1701-01, CHS-1701-03 and CHS-1701-05 studies per treatment and by period and presented in Section 2.7.4, *Summary of Clinical Safety* and 5.3.5.3, *Integrated Safety Summary (tables and datasets)*. Does the Agency agree?
b) b. Safety data with respect to immunogenicity (ADA) will be integrated with the CHS-1701-01 (a cross-over design study), CHS-1701-03 (a cross over design) and CHS-1701-05 (a three sequence, three period design study) studies, summarized by period and treatment at onset and by treatment using only Period 1 results. Results will be presented in section 2.7.2.4, *Special Studies* and 5.3.5.3, *Integrated Safety Summary* (tables and datasets). Does the Agency agree?
c) Additionally, given this study had sparse sampling for Pharmacodynamic and Pharmacokinetic analysis, these results will be summarized as standalone and presented in Section 2.7.2, *Summary of Clinical Pharmacology studies* and Section 2.7.3, *Summary of Clinical Efficacy*, respectively. Does the agency agree?

FDA Response to Question 13: *Yes. Your proposal for submission of safety related data and PK/PD data appears acceptable.*

Discussion: **No discussion pertaining to this question.**

Question 14: The Clinical Study report for the BLA enabling CHS-1701-05 PK/PD BE study will be provided in Module 5 and results of the study will be summarized in the clinical overview and clinical summary sections of Module 2. Coherus proposes:

a) Safety data, with respect to Adverse Events will be integrated with the CHS-1701-01, CHS-1701-03 and CHS-1701-04 studies, summarized by treatment at onset and by period and treatment at onset. The results will be presented in Section 2.7.4, *Summary of Clinical Safety* and 5.3.5.3, *Integrated Safety Summary (tables and datasets)*. Does the Agency agree?
b) Safety data with respect to immunogenicity (ADA) will be integrated with the CHS-1701-01 (a cross-over design study), CHS-1701-03 (a cross over design) and CHS-1701-04 (a 2 sequential dose, parallel group design study) studies, summarized by period and treatment at onset and by treatment using only Period 1 results. Results will be presented in section 2.7.2.4, *Special Studies* and 5.3.5.3, *Integrated Safety Summary* (tables and datasets). Does the Agency agree?
c) Pharmacodynamic results by way of the surrogate biomarker, ANC, will be integrated with the CHS-1701-03 study by treatment sequence and period and presented in

Section 2.7.3, *Summary of Clinical Efficacy* and 5.3.5.3, *Integrated Summary of Efficacy*. Does the Agency agree?

d) Pharmacokinetic results from CHS-1701-05 will be summarized as standalone and presented in Section 2.7.2, *Summary of Clinical Pharmacology studies*. Does the Agency agree?

FDA Response to Question 14: *Yes. Your proposal for submission of safety related data and PK/PD data appears acceptable.*

Discussion: **No discussion pertaining to this question.**

Question 15: To demonstrate clinical similarity, all clinical studies in the CHS-1701 program were conducted at clinical pharmacology units (CPU) as listed in Table 40. Can the Agency advise as to the likelihood and timing of the anticipated Pre-approval inspections at the Coherus Corporate site and/or the CPUs?

FDA Response to Question 15: *No.*

Discussion: **No discussion pertaining to this question.**

Question 16: Per the FDA Guidance for Industry, Envi*ronmental Assessment of Human Drug and Biologics applications (July 1998),* an environmental assessment is required if the approval of the application results in an increased use of the active moiety. Attachment A of this same guidance outlines types of actions that are not considered to result in increased use of the active moiety and of those lists abbreviated applications. It is Coherus' understanding that this exemption also applies to a BLA under the 351(k) pathway. Can the Agency please confirm this understanding is accurate?

FDA Response to Question 16: *Yes, we agree.*

Discussion: **No discussion pertaining to this question.**

Question 17: As a follow up to the CHS-1701 BPD Type 3 meeting held on 01 December 2015, Coherus submitted a Request for Written Responses (Serial #0058) to the Agency to address the FDA's Additional Comments to provide a comprehensive use-related risk analysis to inform the determination regarding the necessity of a human factors (HF) validation study. Can the Agency comment on the following:

a. Based on this assessment, Coherus concluded that a summative human factors study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and correct use of the product is not necessary to assess the adequacy of the combination product user interface design to eliminate or mitigate potential use-related hazards. Does the Agency agree?

FDA Response to Question 17: *We disagree. The FMEA submitted on April 7, 2016 lists* (b) (4) *as the intended users of CHS-1701. However, the labeling for the reference product, US-licensed Neulasta, includes healthcare providers, patients and caregivers as intender users. Based on the information provided to date, we expect that CHS-1701 will have the same intended user population. Therefore, we find your FMEA to be incomplete. The FMEA should be revised to include all intended users.*

Based on this risk analysis, you will need to determine whether you need to perform a human factors (HF) validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that an HF validation study is not needed for your product, submit your updated risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

Discussion: Refer to Sponsor's slide 15, attached. The Agency agreed with the Sponsor's response.

Question 18: In accordance with FDA Guidance for Industry, *Integrated Summaries of Effectiveness (ISE) and Safety: Location within the Common Technical Document,* and given the projected size of the integrated summary of safety and integrated summary of efficacy are expected to be fairly small and will consist of a few small studies, with less than 100 pages of text (with incorporated tables and figures), about 1,000 pages of appendices of supporting table and figures and about 1 GB of data sets used in the integrated safety analysis or integrated efficacy analysis, respectively, Coherus proposes to split the ISS and ISE as follows :

a. Provide the narrative portion in Module 2, Section 2.7.4, with a cross reference to Section 5.3.5.3 for the appendices and datasets

b. Provide the appendices and datasets in Module 5, Section 5.3.5.3, , with a cross reference to Section 2.7.4 for the narrative portion of the ISS

Does the Agency agree?

a. Provide the narrative portion in Module 2, Section 2.7.3, with a cross reference to Section 5.3.5.3 for the appendices and datasets

b. Provide the appendices and datasets in Module 5, Section 5.3.5.3, , with a cross reference to Section 2.7.3 for the narrative portion of the ISE

Does the Agency agree?

FDA Response to Question 18: *Yes. Your proposal appears acceptable.*

Discussion: No discussion pertaining to this question.

Question 19: In accordance with FDA Guidance for Industry, *Structure and Content of Clinical Study Reports and in alignment with ICH E3,* Subject Narratives related to a death, other serious adverse event and other significant adverse event that is judged to be of special interest due to clinical importance should be provided. As such, narratives for each subject with a serious adverse event, discontinued or an adverse event of special interest as pre-defined in the safety management plan will be provided for each clinical study. The narrative will be placed in section 14.3.3, *Narrative of Deaths, Other Serious and Certain Other Significant Adverse Events,* of each clinical study report. Does the Agency agree?

FDA Response to Question 19: *Narratives for each subject who died, experienced a serious adverse event, adverse events of special interest as pre-defined in the study management plan, discontinued due to adverse event should be provided for each clinical study.*

Discussion: **No discussion pertaining to this question.**

Question 20: In compliance with 21 CFR 314.50, *Content and Format of an Application,* individual subject's Case Report Forms (CRF) are required for each subject associated with a death, discontinued from the study due to an adverse event (AE) or experienced a serious adverse event during the study. In accordance with FDA Guidance for Industry, *Providing Regulatory Submission in Electronic Format- Submission General Considerations (Draft, October 2003)* and Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005),* for each clinical study, Coherus proposes to provide the following with the BLA submission:

a. A single PDF file of the annotated case book reflecting each unique CRF

b. The completed subject case book as a single PDF file for each subject associated with a death, discontinued due to study drug, serious adverse events due to study drug or an adverse event of special interest as pre-defined in the safety management

Does the Agency agree?

FDA Response to Question 20: *Yes. Your proposal appears acceptable. Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form."*

Discussion: **No discussion pertaining to this question.**

Question 21: In accordance with FDA Guidance for Industry, *Providing Regulatory Submission in Electronic Format- Submission under Section 745(A) of the Federal Food, Drug, and Cosmetic Act (December 2014),* all Clinical Study data will be submitted

electronically. For each clinical study, CHS-1701-01, CHS-1701-03, CHS-1701-04 and CHS-1701-05, the following will be submitted:

a. SDTM datasets

b. SDTM define.xml

c. ADaM datasets

d. Adam define.xml

Furthermore, as outline in the FDA Guidance for Industry, *Providing Regulatory Submission in Electronic Format- Standardized Study Data (draft February 2012)*, the raw pharmacokinetic and pharmacodynamics datasets for each applicable clinical study will be submitted as a single sas transport file.

Does the Agency agree with the approach as defined above?

FDA Response to Question 21: *We agree with the approach for clinical study data. Besides the above datasets and define files, you should provide the SAS programs for analysis datasets and primary and key secondary analyses. In addition, study data reviewer's guide and analysis data reviewer's guide should be submitted too. Please refer to http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf*

In addition, your submission approach for the raw PK and PD datasets is acceptable.

Discussion: No discussion pertaining to this question.

Question 22: Section 505B(n) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. As such, an agreed initial Paediatric Study Plan (Agreed iPSP, provided with this briefing document for ease of reference) requesting a deferral was granted by the Agency.

(b) (4)

FDA Response to Question 22a: *No, we do not agree. Since you intend to seek licensure for the "neutropenia" indication in adults for which US-licensed Neulasta was previously licensed, you must address PREA. You may fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating pediatric information from the reference product to CHS-1701. See Q.I.16 in the guidance for industry: Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf*

Discussion: Refer to Sponsor's slide 16, attached. The Agency agreed that the Sponsor's plan to amend the pediatric plan and provide justification to support biosimilar extrapolation within the first 30 days of the BLA review will not constitute a refuse-to-file issue. The Agency informed the Sponsor that the amended pediatric plan and justification should be provided within 30 days of the BLA submission. The Agency and Sponsor agreed that the content can be placed in section 2.5 of the BLA.

FDA Response to Question 22b: *No, we do not agree. As stated above, CHS-1701 is subject to PREA. Therefore, your application must include a pediatric assessment, which includes the development of an appropriate pediatric presentation. The proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. The proposed pediatric presentation(s) can be developed prior to approval, or you can request a deferral of the pediatric assessment pending development of an appropriate pediatric presentation. If you choose the latter approach, the development of an appropriate pediatric presentation will be required as a post marketing requirement (PMR).*

Discussion: Refer to Sponsor's slide 17, attached. The Agency agreed with the Sponsor's response.

Question 23: Can the Agency comment as to the probability that an Oncologic Drug Advisory Committee Meeting will be held for the proposed biosimilar product, CHS-1701?

FDA Response to Question 23: *This will be a review issue.*

Discussion: No discussion pertaining to this question.

Question 24: In compliance with 21 CFR 314.50 (vi)(b), *Content and Format of an Application*, the applicant shall, under section 505(i) of the act, update its pending application with new safety information 4 months after the initial submission. With the exception of subjects in the CHS-1701-04 study, all safety data for each subject in the clinical studies (CHS-1701-01, CHS-1701-03 and CHS-1701-05) will be available and provided in the initial BLA submission.

Subjects in the CHS-1701-04 study who were confirmed positive for antidrug antibodies (ADA) at their last visit were followed every 3 months for a duration of up to 12 months until their ADA returned to baseline (e.g. pre dose level). Coherus proposes to provide the following data at the 120 days post submission:

- 1 visit for twelve subjects, 8 of whom reverted to baseline;
- 2 visits for one additional subject who reverted to baseline, .and
- 3 to 4 visits for three additional subjects who have not yet reverted to baseline.

At the day 120 safety update, one subject may still be in follow up and will not be included in the dataset. Does the Agency agree?

FDA Response to Question 24: *Please provide further details on the data you intend to provide 120 days after the initial submission, e.g., safety data only, or will there be data on the ADA assay.*

Discussion: **Refer to Sponsor's slide 18, attached. The Agency agreed to the Sponsor's proposal. The Sponsor indicated they plan to submit both the ADA and all related safety data available for all patients to the BLA. Additionally, the Sponsor noted that one patient is currently still being monitored and follow up ADA and safety data regarding this patient will be submitted once available.**

Question 25: Given that there are no discernible differences in immunogenicity between CHS-1701 and Neulasta® (US) as shown in Study CHS-1701-04, and analytical similarity has been demonstrated in the definitive analytical similarity data set per the attributes outlined in Table 27, and assuming that clinical similarity between CHS-1701 and Neulasta®(US) is demonstrated in terms of PK/PD bioequivalence in the pivotal Study CHS-1701-05,

a. Does the Agency agree that no additional Analytical Similarity or Clinical Similarity studies will be required to demonstrate biosimilarity between the proposed biosimilar biologic product, CHS-1701, and the reference product, Neulasta® (US), for the purpose of obtaining licensure under the PHS 351(k) path?

FDA Response to Question 25: *Whether the data provided is sufficient to support a demonstration that CHS-1701 is biosimilar to US-licensed Neulasta will be determined upon comprehensive review of all data submitted in your 351(k) BLA and whether residual uncertainty remains to be addressed. However, on the surface, your overall developmental approach appears reasonable with respect to the tests and studies conducted.*

Discussion: **No discussion pertaining to this question.**

Additional Comments

Product Quality comments to be addressed in the 351(k) BLA:

Provide a complete genealogy of the drug product registration and PPQ lots.

To support BLA approval, provide an evaluation of extractables and leachables, including a risk assessment, for both drug substance (DS) and drug product (DP). The BLA should include information that addresses the risk from potential leachables from the DS and DP Container Closure System (CCS) over the shelf-life of your product. The leachables studies may be performed as part of your stability protocol to support DS and DP expiry. Analysis of leachables should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS), and metals (e.g., ICP-MS) species including their chemical identification and quantitation. Additional information regarding extractables and leachables should be provided per FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999).

The presence of (b) (4) in syringes can impact product quality and stability. We recommend that you evaluate and control the amounts of (b) (4) in your pre-filled syringes and provide a risk assessment of the impact (b) (4) may have on the quality, stability and safety of your DP.

(b) (4) can lead to protein aggregation and the formation of subvisible particles. Provide information on your strategy to control the amounts of (b) (4) that may leach from the container closure system into your product.

Clarify your approach to establish DS and DP release and stability specifications. It appears that the variability of validated assays is used to justify your proposed DS and DP acceptance criteria. Note that this approach is not appropriate given that the release and stability test results have already captured the variability of each analytical test method.

It is unclear as to whether the analytical similarity data collected from the reference product were used to develop your DP release and stability specifications.

(b) (4)'. Use calendar year intervals when adding DS and DP lots to the stability monitoring program.

Discussion: Refer to Sponsor's slides 20-21, attached. The Agency agreed with the Sponsor's approach.

Microbiology

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(k) BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Include a complete list of the manufacturing and testing sites with their corresponding establishment registration number (FEI) number.

The Chemistry/Manufacturing/Controls (CMC) Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to, the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Information and summary results data demonstrating microbial control after column resin and UF/DF membrane sanitization during reuse and storage (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of at least three conformance lots (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance (DS) bioburden and endotoxin release specifications (3.2.S.4).
- Summary report and results from bioburden and endotoxin test methods qualification performed for in-process intermediates and the drug substance (3.2.S.4). In addition, the test methods should be described.
- If the formulation contains polysorbate, the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated (3.4.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

Provide the following information in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

- Description of the manufacturing areas and fill line, including air classifications.

- Description of the environmental and personnel monitoring programs.
- Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
- Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), the pressure limit or flow rate limit for sterilizing filtration, and the acceptance criterion for post-use integrity testing.
- Parameters for filling and stoppering.
- Processing and hold time limits, including the time limit for sterilizing filtration.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- Bacterial filter retention study for the sterilizing filter.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Pre-sterile filtration bioburden limits should be monitored and should be less than 10 CFU/100 mL.
- Isolator decontamination, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
- A description of the routine environmental monitoring program.
- Shipping validation studies, including container closure integrity data. The effects of varying air pressure on syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data that demonstrate that the syringe plunger movement during air transportation does not impact product sterility.
- Assembly validation studies, including container closure integrity data. The study should demonstrate that the assembly processes for the pre-filled syringe and autoinjector do not impact product sterility.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe should be included. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow

microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).

- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. In addition, the test methods should be described.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13 (b).
- Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (CSE or RSE) into undiluted in-process samples (if applicable) and the drug product and then testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.

eSub

From a technical standpoint (not content related), the proposed BLA format is acceptable. However, please see general comments below:

- The Briefing package was not bookmarked. All pdf files more than 5 pages long should contain bookmarks, Table of Content (TOC) and hyperlinks. Please refer to the PDF Specifications located here:- http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf
- Do not create additional nodes in the eCTD structure beyond what is in the specifications. Please make sure the LOAs are submitted under m1.4.1 (not m1.4.2). Section m1.4.2 is designated for "Statement of right of reference".
- If word versions of draft labeling are provided, please submit a pdf version, for archival purposes. Also, if word documents are submitted, the leaf title should include "word", so reviewers could quickly identify the word version of the document.
- All Literature References for m3 should reside in m3.3. (Literature References). Do not provide Literature References in m3.2.p.2.1 and m3.2.p.2.2.
- All individual files should be placed under their respective sections without creating a duplicate section numbering (e.g. 3.2.s.2.5, 3.2.s.2.6, etc.,).
- Providing Table of Contents in m4.1 is not necessary in the eCTD structure. Instead, a linked reviewer's aid/reviewer's guide can be provided in module m1.2, (as a separate document from the cover letter), to briefly describe where information can be found throughout the application.
- Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including Case Report Forms (crfs). Case Report Forms (if any), need to be

referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf

Clinical Pharmacology

Provide a table summarizing the impact of ADA response on PK and safety for subjects who test positive for ADA and include this information in the Immunogenicity Summary Report.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to initiating your comparative clinical study (see additional comments below regarding expected review timelines).

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each

indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and FDA's Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Discussion: Refer to Sponsor's slide 22, attached. The Agency informed the Sponsor that their labeling should still comply with the PLLR content and format requirements. The Agency agreed to provide further guidance. Refer to the Post-Meeting Note below.

Post-Meeting Note: The Division of Pediatric and Maternal Health will provide guidance for addressing PLLR labeling in an information request.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all clinical studies used to support a demonstration of no clinically meaningful differences between the proposed biosimilar biological product and the reference product in the application. Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the 351(k) BLA for each of the completed clinical studies:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

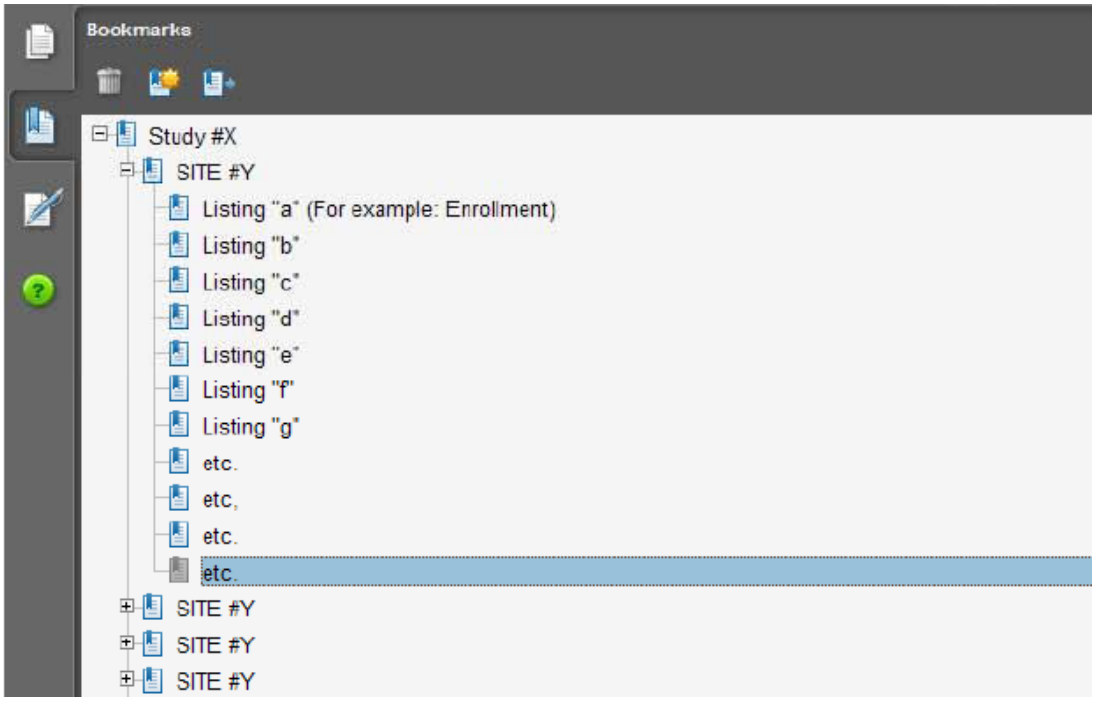
3. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each clinical study: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the 351(k) BLA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the clinical studies)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each clinical study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Discussion: Refer to Sponsor's slide 24, attached. The Agency informed the Sponsor that the information presented in the slide should be provided with the BLA submission or as early as possible within the first 30 days of the BLA submission.

Refer to Sponsor's slide 25, attached. The Agency agreed to the Sponsor's proposed format for the one requested PDF file for each clinical study with respect to the OSI requests.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified.

5.0 ACTION ITEMS

No actions identified.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's PowerPoint presentation.

29 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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.

/s/

NICOLE J GORMLEY
08/25/2016