CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761216Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 119540

MEETING MINUTES

Coherus Biosciences, Inc.
333 Twin Dolphin Drive
Suite 600
Redwood City, CA 94065

Attention: Nathalie Yanze, PhD
Executive Director, Regulatory Affairs

Dear Dr. Yanze:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CHS-1420.

We also refer to the telecon between representatives of your firm and the FDA on October 27, 2020. The purpose of the meeting was to provide feedback on the format and content of a complete application for a future 351(k) BLA submission as a proposed biosimilar biological product to U.S.-licensed Humira.

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

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Sincerely,
{See appended electronic signature page}
Sadaf Nabavian, PharmD
CDR, US Public Health Service
Sr. Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: October 27, 2020, from 8:00-9:00 a.m. EST
Meeting Location: Teleconference

Application Number: IND 119540
Product Name: CHS-1420

Indication: CHS-1420 is being developed for the same indications as those approved for U.S.-licensed Humira

Sponsor: Coherus Biosciences, Inc. (Coherus)

Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Nikolay Nikolov, MD
Meeting Recorder: Sadaf Nabavian, PharmD

FDA ATTENDEES

Nikolay Nikolov, MD, Director, Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII), Office of New Drugs (OND)
Raj Nair, MD, Clinical Team Leader, DRTM, OII, OND
Stefanie Freeman, MD, Clinical Reviewer, DRTM, OII, OND
Ping Ji, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Shalini Wickramaratne Senarath Yapa, PhD, Clinical Pharmacology Reviewer, DIIP, OCP, OTS
Yanming An, PhD, Product Quality Team Leader, Division of Biotechnology Review and Research II (DBRRII), Office of Biotechnology Products (OBP), Office of Pharmaceuticals Quality (OPQ)
Dong-Hyun Ahn, PhD, Product Quality Reviewer, DBRRII, OBP, OPQ
Maria Gutierrez-Hoffmann, PhD, Microbiology Team Leader, DBRRIIII, OBP, OPQ
Kathleen Fritsch, PhD, Mathematical Statistical Reviewer, Division of Biometrics III
Andrew Goodwin, PhD, Director (Acting), Division of Pharmacology-Toxicology for Immunology & Inflammation, Office of Immunology and Inflammation, Center for Drug Evaluation and Research
Marlene Schultz-Depalo, MS, MA, RAC, OBP-IO Biosimilar Program and Policy Analyst, OBP, OPQ

Chen Sun, PhD, Product Quality Reviewer, DBRRII, OBP, OPQ
Dupeh Palmer, PhD, Microbiologist Team Leader, Microbiologist Reviewer, Biotechnology Manufacturing Branch 2 (BMB2), Division of Biotechnology Manufacturing (DBM), Office of Pharmaceutical Manufacturing Assessment (OPMA)
Stacey Ricci, MEng, ScD, Director (Acting), Scientific Review Staff (SRS), Office of Therapeutic Biologics and Biosimilars (OTBB), OND
Nina N. Brahme, PhD, MPH, Clinical Analyst, SRS, OTBB, OND
Sarah Schrieber, PharmD, Reviewer, SRS, OTBB, OND
Jessica Greenbaum, JD, Regulatory Counsel, OTBB, OND
Xiao Chen, PhD, Nonclinical Reviewer, Division of Pharmacology Toxicology for Immunology and Inflammation (DPTII), Office of Immunology and Inflammation (OII), Office of New Drugs (OND)
Nichelle Rashid, Safety Regulatory Team Leader, Office of Surveillance and Epidemiology (OSE)
Sadaf Nabavian, PharmD, Sr. Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation (DROII), Office of Regulatory Operations (ORO), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)

SPONSOR ATTENDEES
Vince Anicetti, Chief Operating Officer
Benjamin Drucker, Senior Director, Regulatory Affairs
Barbara Finck, MD, Acting Chief Medical Officer
Helen Tang, MSc, Senior VP, Biostatistics
Nathalie Vandenkoornhuyse-Yanze, PhD, VP, RA
Lisa Miyasaki, VP, Drug Safety and Pharmacovigilance

1.0 BACKGROUND

The purpose of the meeting is to discuss and provide feedback on the content and format of a complete application to support a future 351(k) BLA submission of CHS-1420 as a proposed biosimilar to U.S.-licensed Humira. The FDA issued the Final Preliminary Comments to Coherus on October 25, 2020, and after review Coherus requested to further discuss and provide further clarification on the safety data to be included in the original 351 (k) BLA submission (and corresponding CSRs) and to also discuss and confirm FDA's recommendation in the way to present the % change in PASI at week 16.

Questions from the briefing document are listed below in ***bold italics*** and FDA responses are provided in normal italic. The Discussion that took place during the meeting is captured under the Discussion section in normal font.

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 Biosciences, Inc. and as the Agency's thinking evolves on certain

statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Question 1:
Does the Agency agree with the proposed CHS-1420 BLA CTD structure and content?

FDA Response to Question 1:
The proposed structure and content appear to be acceptable. We have also provided some general comments related to content in FDA responses to the other Questions below and the Additional Comments.

Discussion:
No further discussion was required.

Question 2:
Can the Agency comment on the feasibility of the proposed schedule for manufacturing activities presented in Table 3 to support the pre-approval inspection, assuming that the BLA is submitted end of November 2020?

FDA Response to Question 2:
The FDA must assess the ability of the manufacturing facilities to conduct the listed manufacturing operations in compliance with CGMP. Under normal circumstances, the proposed manufacturing schedule appears reasonable, assuming the BLA is submitted in November 2020. However, given the current public health situation, as well as travel restrictions, we are unable to determine whether inspection of the facilities can be conducted prior to the User Fee Date. For more information, please refer to FDA guidance related to COVID-19. Guidance can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

Discussion:
No further discussion was required.

Question 3:
Does the FDA agree with Coherus' proposal to provide responses to information requests by email, and following up shortly with the electronic submission?

FDA Response to Question 3:
You may provide the responses to the information requests via email correspondence to the Regulatory Project Manager followed by an official submission of identical content to the BLA within a reasonable timeframe. We encourage you to submit all responses to

the BLA on the same day the email is sent. For those requests that are time sensitive, responses may be sent via a courtesy email followed by official submission to the BLA.

Discussion:
No further discussion was required.

Question 4:
Coherus seeks the Agency agreement on facilities to be listed in Sections 3.2.S.2.1 and 3.2.P.3.1 Manufacturers and transposed to the FDA Form 356h, following the final October 2019 Guidance for Industry (GfI) entitled Identification of Manufacturing Establishments in Application Submitted to CBER and CDER Questions and Answers.

a. ***Does the Agency agree that DS raw material and DP excipient testing facilities can be excluded from 3.2.S.2.1 and 3.2.P.3.1, respectively?***

FDA Response to Question 4a:
We agree that DS raw material and DP excipient testing facilities can be excluded from 3.2.P.3.1. However, we expect the DP manufacturer to have adequate testing/controls in place to ensure that the raw materials and excipients meet their established acceptance criteria as per 21 CFR 211.84.

b. ***For single-use and product-contact equipment or components used in the DP manufacturing process (such as bioprocess containers and other pre-sterilized and disposable components), does the Agency agree that the facilities involved in sterilization of these equipment or components by or on behalf of the suppliers can be excluded from 3.2.P.3.1?***

FDA Response to Question 4b:
We agree that facilities involved in sterilization of single-use and product contact equipment or components (i.e. bioprocess containers and other pre-sterilized and disposable components) by or on behalf of suppliers can be excluded from 3.2.P.3.1. However, all product contact equipment or containers must be described in 3.2.P.3.3 and sterilization validation data must be provided in 3.2.P.3.5 of the BLA. 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.

c. ***Following recommendation provided in the GfI, the Company will provide list of facilities used solely for warehousing or storage purposes in 3.2.S.2.1 and 3.2.P.3.1. However, it is the Company's understanding that such facilities do not require registration (thereby FEI not necessary) since these facilities are not involved in the manufacture, preparation,***

propagation, compounding or processing of drugs that are commercially distributed in the U.S. or offered for import to the U.S (21 U.S.C. § 360). Does the Agency agree?

FDA Response to Question 4c:
We agree that facilities used solely for warehousing or storage purposes should be listed in 3.2.S.2.1 and 3.2.P.3.1. Furthermore, the Agency agrees that such facilities do not require registration. However, in accordance with the Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, Guidance for Industry, these facilities should be listed in Form FDA 356h. In addition, having a FEI number will facilitate the application process. The applicant may submit their application in the absence of a FEI number and request a FEI number without registering the facility.

d. ***Following the recommendation provided in the GfI, the company should list facilities that developed analytical method(s) in Module 3 of the application. However, it is the Company's understanding that such facilities do not require registration (thereby FEI not necessary) if they are not involved in the manufacture, preparation, propagation, compounding or processing of drugs that are commercially distributed in the U.S. or offered for import to the U.S (21 U.S.C. § 360). Does the Agency agree?***

FDA Response to Question 4d:
We agree that facilities that develop analytical method(s) should be listed in Module 3 of the application and that such facilities do not require registration.

e. ***Does the Agency agree that the facilities involved in analytical and functional similarity and comparability assessment, and the GMP testing facilities (release and stability) used during clinical development but not proposed for commercial use, be described in 3.2.S.2.1 and 3.2.P.3.1?***

FDA Response to Question 4e:
It is acceptable to provide information regarding the facilities involved in comparative analytical assessment in section 3.2.R.1 and GMP testing facilities used during clinical development but not proposed for commercial use in sections 3.2.S.2.1 and 3.2.P.3.1. The facilities involved in comparative analytical assessment should be ready for a pre-license inspection during BLA review.

f. ***Does the Agency agree that only those facilities with associated FEI are listed in the electronic form 356h?***

FDA Response to Question 4f:
No, we do not agree that only those facilities with associated FEI numbers should be listed in the electronic Form FDA 356h. You should list all facilities included in the application on Form FDA 356h and assign an arbitrary number (i.e. 000000) to the

facility(ies) not involved in the manufacture, preparation, propagation, compounding or processing of drugs that are commercially distributed in the U.S. or offered for import to the U.S, without an associated FEI number. You should request a FEI number for those facilities from us as soon as possible.

Discussion (a-f):
No further discussion was required.

Question 5:
Does the Agency agree that providing the design verification (DV) testing result summaries for the CHS-1420 drug-device combination product (prefilled syringe with finger flange) is sufficient and that the testing reports are not needed for the BLA?

FDA Response to Question 5:
We recommend that you include the completed design verification (DV) testing reports for the CHS-1420 prefilled syringe in your BLA submission for review.

Discussion:
No further discussion was required.

Question 6:
Coherus plans to seek approval for the use of the master cell bank (MCB) in the initial license application.

Does the Agency agree that a working cell bank (WCB) qualification protocol may be omitted from the initial BLA?

FDA Response to Question 6:
Per ICH Q5D, it is recommended that a two-tiered cell bank (i.e., MCB and WCB) be developed and qualified for commercial product manufacture. If a WCB is not available prior to your BLA submission, then include a protocol for qualification of future WCBs in your BLA submission for review. A WCB for commercial manufacture can be introduced in a future prior approval supplement (PAS).

Discussion:
No further discussion was required.

Question 7:
Does the Agency agree that the nonclinical dataset does not need to be submitted according to the Clinical Data Interchange Standards Consortium (CDISC) Standard Exchange for Nonclinical Data (SEND)?

FDA Response to Question 7:
Yes, we agree.

In the alternative, we note that you may wish to include in your application a justification for why animal studies are unnecessary (see section 351(k)(2)(A)(ii) of the PHS Act).

Discussion:
No further discussion was required.

Question 8:
Does the Agency concur with Coherus' approach in presenting clinical safety information in the BLA?

FDA Response to Question 8:
The proposed approach to presenting clinical safety data appears generally reasonable. However, (b) (4) *In your meeting materials it is unclear how you intend to present Study CHS-1420-01 in your BLA submission. Clarify if you intend to include the clinical study report from study CHS-1420-01 in Module 5 but do not plan to include the safety information from this study in the Summary of Clinical Safety (Module 2). Note, given that Study CHS-1420-01 was conducted using product manufactured by an early-development process using a different cell line, production process, and formulation, inclusion of this study is not necessary in your 351(k) BLA.*

Discussion:

Slides 5, 6, and 7

The Sponsor summarized the available clinical studies conducted and sought clarification that Studies CHS1420-04 and CHS1420-05, (b) (4) would not be required as part of the original 351(k) BLA.

The Sponsor provided their rationale regarding inclusion of the clinical safety data from those studies to the original 351(k) BLA.

The Sponsor noted that CHS-1420-02 study is a comparative efficacy study in chronic psoriasis and they also have a small study, CHS-1420-04, that includes use of the CHS-1420 AI in RA patients. As described by the Sponsor, the CHS-1420-04 study includes safety information from RA subjects. The Sponsor proposes to include this safety data in the original 351(k) BLA as it would provide important and relevant information to the FDA as it accounts for 141 RA patients receiving CHS-1420. In addition, the Sponsor added that the data would be cited as part of the justification for extrapolation to support licensure for the RA indication.

The Sponsor also discussed Study CHS-1420-03, a PK similarity study, as well as Studies CHS-1420-05 and CHS-1420-07, which account for hundreds of subjects receiving a single dose of CHS-1420. The Sponsor considers this is a significant number of healthy subjects receiving the study drug and is planning to include this information in the original 351(k) BLA submission.

The Sponsor stated that Study CHS-1420-01 uses a different formulation and process. The Sponsor however plans to include information from this study for completeness and will provide it in the ISS but does not plan to include it in Section 2.7.4. The Sponsor will provide analyses both with and without data from Study CHS-1420-01.

The Sponsor requested to include all of the safety data for completeness in their original 351(k) BLA submission including the safety data from -02 from the PsO subjects and -04 from RA subjects and the pooled safety data (from Studies -05, -03 and -07) from the single dose studies in HV. CSRs for each of the studies will also be submitted.

The Sponsor asked if the FDA was in agreement with the proposed presentation of safety data for the BLA as outlined in Slide 6. The Sponsor stated that the BLA is currently in publishing phase and is planning to submit the original 351(k) BLA by end of November with all the CSRs as presented during today's meeting. The FDA agreed to Sponsor's proposal to include this information as outlined in Slide 6 in the original 351(k) BLA, noting that it will be at the discretion of the Sponsor regarding what they include in the submission.

The Sponsor appreciated FDA's feedback in accommodating their request and in keeping them on schedule for the BLA submission and added that even though they acknowledge that FDA plans to focus on reviewing Studies -02 and -03, they strongly felt that the additional safety studies will show that there are no important safety issues with the proposed product.

As a last note, the FDA informed the Sponsor they would issue another round of iPSP comments to be conveyed soon and added that the Sponsor should have an Agreed iPSP prior to submitting the original 351 (k) BLA.

Question 9:
Does the Agency agree (b) (4) [redacted]

FDA Response to Question 9:
As noted above in response to Question 8, (b) (4) [redacted]

(b) (4)

Discussion:
Refer to the discussion section under Question 8.

Question 10:
Does the Agency concur with Coherus' proposal to submit Office of Scientific Investigations (OSI) line listings only for the two pivotal studies, CHS-1420-02 and CHS-1420-03?

FDA Response to Question 10:
Yes, we agree with your proposal.

Discussion:
No further discussion was required.

Additional Clinical Comments

The Clinical Study Reports section should include the study report, all versions of the protocol, the statistical analysis plan, and an annotated case report form. Submit tabulation datasets (SDTM format) and analysis datasets (ADaM format preferred) in *SAS transport format (.xpt). The analysis datasets should include all variables (including derived variables) needed for conducting the primary, secondary, and sensitivity analyses included in the study report. Include dataset documentation (define.xml and define.pdf files) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables. Submit statistical programs for all complex or non-standard analyses, such as the codes for calculating confidence intervals in Protocol CHS-1420-02.*

Note that our recommendations for the primary endpoint in a comparative clinical study in subjects with psoriasis have evolved since 2015. We now recommend evaluating the percent change in PASI at Week 16, evaluated using a 90% confidence interval with margins of ± 10. We recommend including the results of this analysis in your study report or in an addendum.

Discussion:

Slides 3, 4, and 7

The Sponsor sought clarification regarding FDA's recommendation to include the evaluation of the percent change in PASI at Week 16. The Sponsor stated that they have the data available even though it was not their primary analysis and they are able to include the evaluation of percent change in PASI at Week 16 using the 90% confidence interval with margins of ± 10 in an amended version of the Clinical Study Report (CSR) as well as update sections of Module 2 accordingly to include the requested data.

The Sponsor added that this will be a post-hoc analysis and they plan to keep the efficacy data that's already included in the CSR and add the requested data as an additional analysis.

The Sponsor described the efficacy data currently included in the CSR (bullets 1 and 2) (Slide 7) and noted they will add the analysis described in the third bullet based on the FDA's recommendation.

- Pre-specified primary endpoint: percentage of subjects achieving PASI-75 at Week 12
- Pre-specified key secondary endpoint: percent change in PASI from baseline at Week 12
- Another key endpoint using change in PASI at Week 16 and using the criteria suggested by the FDA

The Sponsor asked if this approach will meet FDA's expectation. The FDA replied that Sponsor's approach to keep the existing analyses and add the requested analyses of percent change in PASI from baseline at Week 16 to the CSR and Module 2 in the BLA package is acceptable.

Additional Comments

Nonclinical

Provide a safety assessment of extractables and leachables in the BLA for all primary container closure components that are in contact with the drug substance and drug product during storage as well as secondary container closure components where there is a potential for migration of leachables into the drug product. See USP Chapters for 1663 and 1664 for the design of extractables and leachables studies, respectively.

Chemistry, Manufacturing, and Controls

Refer to FDA Meeting Minutes from your BPD Type 2 Meeting on February 04, 2020, on reference materials used in the comparative analytical assessment. In regards to future marketing applications, we expect that you will provide adequate information to support the comparative analytical assessment between CHS-1420 and US-licensed Humira.

Clinical Pharmacology

You plan to submit data from Study CHS-1420-07 in the original BLA. Note that this study is considered not necessary to assess PK similarity between your proposed biosimilar product and US-Humira.

Discussion:
No additional discussion was required.

3.0 OTHER INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA II. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the BsUFA II agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on the Program is available at FDA.gov.[1]

[1] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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(l) 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, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

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 iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP 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.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act*. 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 iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study*

Plans and Amended Pediatric Study Plans[2]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov 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)[3] and 201.57[4] 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[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- 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.
- 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 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.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[5] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[6] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.[7]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

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

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

MANUFACTURING FACILITIES

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). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-approval inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA II.

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications 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 ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:
    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.
    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. 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.

3. Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports. In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document[10] to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slide deck

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

[10] https://www.fda.gov/media/131425/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SADAF NABAVIAN
11/19/2020 06:28:09 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119540

MEETING MINUTES

Coherus BioSciences, Inc.
333 Twin Dolphin Drive, Suite 600
Redwood City, CA 94065

Attentions: Elijah Tan
Director, Regulatory Affairs

Dear Elijah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CHS-1420.

We also refer to the meeting between representatives of your firm and the FDA on May 17, 2017. The purpose of the meeting was to discuss the format, content and overall acceptability of your proposed information package detailed in your briefing document for CHS-1420, a proposed biosimilar to US-licensed Humira.

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 me, at (301) 796-2777.

Sincerely,
{See appended electronic signature page}

Sadaf Nabavian, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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:	Biosimilar Biological Product Development (BPD) Type 4
Meeting Date and Time:	May 17, 2017; 1:00-2:00 p.m. EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1348
Application Number:	IND 119540
Product Name:	CHS-1420 (a proposed biosimilar to US-licensed Humira)
Indication:	CHS-1420 is being developed for the same indications as approved for US-licensed Humira
Sponsor:	Coherus BioSciences, Inc.
Meeting Chair:	Badrul A. Chowdhury, MD, Ph.D.
Meeting Recorder:	Sadaf Nabavian, Pharm.D.

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Janet Maynard, MD, MHS, Clinical Team Leader, DPARP
Raj Nair, MD, MPH, Clinical Team Leader, DPARP
Anshu Marathe, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology (OCP)
Lei He, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, OCP
Xianghong Jing, PhD, Product Team Leader, Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research II (DBRRII)
Brian Roelofs, PhD, Product Reviewer, OPQ/OBP/DBRRII
Yongmin Liu, PhD, Product Reviewer, OPQ/OBP/DBRRII
Yu-Ting Weng, PhD, Statistical Reviewer, OTS/OB/DBVI
Meiyu Shen, PhD, Statistical Team Leader, OTS/OB/DBVI
Sue Lim, MD, Medical Officer Team Leader, Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS)
Stacey Ricci, MEng, ScD, Senior Toxicologist, OND, TBBS
Tyree Newman, Regulatory Project Manager, OND, TBBS (via phone)
Leila Hann, Regulatory Project Manager, OND, TBBS (via phone)
Carlos Mena-Gillasca, PharmD, Safety Evaluator, OSE/DMEPA (via phone)
Denis Cook, MD, Clinical Reviewer, DDDP
Emanuela Lacana, PhD, Associate Director Biosimilar, Biologics, Policy, OBP/OPQ/CDER

Kathleen Fritsch, PhD, Biostatistical Reviewer, OB/DBIII
John McMichael, Biomedical Engineer, GHDB/ODE/CDRH
Alan Stevens, PhD, Branch Chief, GHDB/ODE/CDRH
Kathleen Fitzgerald, PhD, Reviewer, GHDB/ODE/CDRH
Dann Orr, JD, Regulatory Counsel, ORP
Patricia Hughes, PhD, Acting Branch Chief, OPF, DMA
Sadaf Nabavian, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Vince Anicetti, PhD, Senior VP, Quality and Compliance (via phone)
Lisa Bell, PhD, Executive VP, Global Regulatory Affairs
Constance Cullen, PhD, VP, Analytical and Pharmaceutical Sciences
Barbara Finck, MD, Chief Medical Officer (via phone)
Taruna Arora, Senior Director, Translational and Development Sciences (via phone)
Yijia Jiang, PhD, Director of Analytical R&D
Denny Lanfear, Chief Executive Officer
Michelle Frazier, PhD, VP, Regulatory Affairs
Helen Tang, MS, Executive Director for Biostatistics
Elijah Tan, MS, Director of Regulatory Affairs
Vladimir Vexler, PhD, Senior VP, Translational and Development Sciences
Peter Watler, PhD, Chief Technical Officer

1.0 BACKGROUND

Coherus BioSciences, Inc. submitted a BPD Type 4 Meeting Request to discuss the format, content and overall acceptability of the CHS-1420, a proposed biosimilar to US-licensed Humira.

The FDA's preliminary comments were sent to Coherus on May 16, 2017. After review of these comments, Coherus stated their intent to continue with the meeting as scheduled and requested to discuss the FDA's responses to Questions 7 (b) and the Additional Comment pertaining to a complete application. For the meeting, Coherus provided a slide presentation with their responses to our preliminary responses prior to the meeting which some of their responses have been incorporated before the discussion sections in ***bold italic***. The slides are included in section 6, Attachments and Handouts.

The original questions from Coherus are also in ***bold italic***, FDA's responses to the questions are in *italic*, and any discussion that took place with between Coherus and the FDA is in regular font.

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 Public Health Service Act (PHS Act).

2. DISCUSSION

Question 1:

Does the Agency agree with the proposed CHS-1420 BLA CTD structure, organization and content:

a. Administrative or region-specific information in CTD Module 1

FDA Response:

The proposed structure, organization and content for CTD module 1 appear reasonable.

b. CMC, including microbiological quality information in CTD Module 3

FDA Response:

The proposed structure, organization, and content for the CMC Module 3, including microbiological information appear to be acceptable. Refer to "Additional Product Quality Microbiology Comments" included at the end of the document.

In Module 3, provide a summary of the data and information contained in each study report, your evaluation and interpretation of the data, and your rationale supporting your final conclusion that the manufacturing process has the capability to produce CHS-1420 with the expected quality characteristics.

From the CMC statistics perspective, the proposed structure, organization, and content of the analytical similarity section for Tier 1 Quality Attributes (QAs) are reasonable.

c. Device aspects of drug-device combination product in CTD Module 3

FDA Response:

The proposed content for device related information in 3.2.P.2.4 appears acceptable from the product quality perspective. Refer to our response to Question 7b for additional details.

d. Clinical study information in CTD Modules 2 and 5

FDA Response:

The Clinical Study Reports section should include the study report, all versions of the protocol, the statistical analysis plan, and an annotated case report form. Submit tabulation datasets (SDTM format) and analysis datasets (ADaM format preferred) in SAS transport format (.xpt). The analysis datasets should include all variables

(including derived variables) needed for conducting the primary, secondary, and sensitivity analyses included in the study report. Include dataset documentation (define.xml and define.pdf files) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables. Submit statistical programs for all complex or non-standard analyses, such as the codes for calculating confidence intervals in Protocol CHS-1420-02.

From the clinical pharmacology perspective, summary of biopharmaceutic studies and associated analytical methods should be summarized in Module 2.7.1, whereas the summary of clinical pharmacology studies should be located in Module 2.7.2. The reports of bioanalytical and analytical methods for human studies should be in Module 5.3.1.4. The reports and analysis data of human pharmacokinetic studies and efficacy and safety studies should be placed in Modules 5.3.3 and 5.3.5, respectively.

Refer to Question 4 regarding content to include for extrapolation of data intended to support a demonstration of biosimilarity in one condition of use (e.g., indication) to other conditions of use.

e. Extrapolation of indication information in CTD Section 2.7.3 Summary of Clinical Efficacy

FDA Response:

Refer to Question 4 regarding content to support extrapolation.

Discussion:

The Sponsor noted that a reviewer's guide will be provided in the BLA to facilitate the review and no further discussion took place under Question 1.

Question 2: Pre-license inspection (PLI)

a. Can the Agency comment on the proposed schedule for manufacturing activities to support the PLI, assuming that the BLA is submitted toward the latter part of Q2 2017?

FDA Response:

The proposed manufacturing schedule appears appropriate to support an inspection of the drug substance site based on a submission date at the end of June, 2017. Submit an updated production schedule at the time of BLA submission. Refer to "Additional Product Quality Microbiology Comments" included at the end of the document for information regarding manufacturing site inspections.

b. As part of lifecycle management activities, Coherus is exploring (b) (4) [redacted]

FDA Response:

The proposed plan (b) (4) [redacted]

c. In the initial BLA, Coherus will seek licensure of the master cell bank (MCB) as the source for the commercial DS manufacturing process. A protocol will be included to support introduction of the initial working cell bank (WCB) post-licensure. Does the Agency agree that the WCB may be used for DS manufacture during the CHS-1420 DS PLI?

FDA Response:

Yes, we agree that WCB can be used for DS manufacture during the CHS-1420 DS PLI.

d. Does the Agency agree that the CHS-1420 PFS labeling, assembly with the plunger rod and finger flange, and secondary packaging at (b) (4) [redacted] ***do not require observation during the PLI? Coherus can simulate the processes if requested.***

FDA Response:

The following information should be provided in the BLA to demonstrate compliance with applicable medical device Quality System Regulations 21 CFR Part 820. The following applies to all manufacturers responsible for manufacturing, storing, labeling and packaging of the finished device constituent and/or finished combination product. We will review the following information provided in your future BLA and will inform you if an inspection is necessary based on the information provided.

1. ***Management Control, 21 CFR 820.20:*** *The Sponsor should specify which Sponsor has ultimate responsibility over the overall combination product. The Sponsor should describe the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements).*

2. ***Design Controls, General, 21 CFR 820.30:*** *The Sponsor should describe its design control system which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. The Sponsor should also provide a copy or a summary of the plan used to design the combination product. The Sponsor should explain how it implemented the plan for the combination product project.*

3. ***Purchasing Controls, 21 CFR 820.50:*** *The Sponsor(s) should summarize its procedure(s) for purchasing controls. The procedure(s) should describe Sponsor's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers. The procedure(s) should define how the Sponsor maintains records of acceptable suppliers and how it addresses the purchasing data approval process. The procedure(s) should explain how the Sponsor will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. The Sponsor should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product. The Sponsor should describe how it applied the purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e. supplier's agreement).*

4. ***Corrective and Preventive Action (CAPA), 21 CFR 820.100:*** *The Sponsor(s) should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions.*

5. ***Installation, 21 CFR 820.170:*** *The Sponsor should identify if installation is applicable to their combination product. The Sponsor should describe its plan to ensure adequate installation of the combination product so that it will perform as intended after installation.*

6. ***Servicing, 21 CFR 820.200:*** *The Sponsor(s) should identify if servicing is applicable to their combination product. The Sponsor should summarize its instructions and procedures for performing and verifying that the servicing meets the specified requirements. The servicing plan should include requirements to analyze service reports with appropriate statistical methodology in accordance with §820.100. Furthermore, the plan should require for service reports that represent an event which must be reported to FDA under §803 to be automatically considered complaints to be processed it in accordance with the requirements of §820.198.*

7. ***Production and Process Controls:*** *The Sponsor(s) should provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.*

8. ***Production Flow:*** *The Sponsor(s) should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.*

Acceptance Activities: *The Sponsor(s) should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The Sponsor should specify which Sponsor will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The Sponsor should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.*

Discussion:

The Sponsor noted that detailed information will be included on the activities conducted in each of the sites involved in the manufacture of CHS-1420 and no further discussion too place.

Question 3: Similarity/Comparability

a. Does the Agency agree that the studies (structural, functional and clinical) conducted to support a demonstration of biosimilarity between CHS-1420 and Humira (US) are sufficient to support a substantive review of the BLA?

FDA Response:

The attributes tested in your analytical similarity assessment appear sufficient for us to evaluate analytical similarity of CHS-1420 and US-licensed Humira. We acknowledge that you plan to include a cell-based ELISA to measure mTNFα binding of CHS-1420 as a Tier 1 attribute and include all other cell-based assays to assess reverse signaling in Tier 3. You will need to demonstrate as part of characterization that the results from the mTNFα binding assay correlate with cell-based reverse signaling functional test results. For all other product quality attributes, we will assess the analytical similarity data you submitted in accordance with the initial recommendation for tier ranking, including reverse signaling, provided in the BPD Type 2 meeting held on November 10, 2016.

In addition to the figures as provided in this meeting package for each attribute, also provide a table listing the numerical test value and the corresponding drug product lot number from which the value was derived for CHS-1420 Drug Product and US-licensed Humira. For the quantitative tests with chromatograms, such as reducing CE-SDS, non-reducing CE-SDS, and SE-HPLC, provide the original chromatograms from the representative lots including enlarged images to allow a comparison of minor peaks. Wherever applicable, label the identified peaks, and provide quantitative results for each peak when the result is greater than the limit of quantitation (LOQ).

In addition, submit a table detailing testing site(s) that performed assays included in your analytical similarity assessment. We may request separate inspection(s) of these sites during BLA review if these cannot be inspected during our inspection of the DS manufacturing facility.

We note that you included DP lot 3-FIN-2847 in your analytical similarity assessment. Since this lot is manufactured using DS produced from a WCB for which you are not seeking approval in your BLA, data generated from this lot cannot be used to support analytical similarity assessment or process validation.

From the clinical pharmacology perspective the proposed PK similarity study, Study CHS-1420-03, appears sufficient to support the BLA review. However, the adequacy of the data to demonstrate PK similarity between CHS-1420 and US-licensed Humira will be a review issue.

We also have these additional comments from the CMC Statistical perspective:

a. *To the extent possible, the same lots should be used for Tier 1, Tier 2, and Tier 3 analysis. The lots used for Tier 3 analysis may be a subset of the lots used in Tier 1 and Tier 2 testing.*
b. *For Tier 1 QAs:*

    I. *You did not include all available lots of US-licensed Humira for the apoptosis (TNF-α neutralization), sTNF-α binding, and mTNF binding assays, but selected 21, 12, and 11 lots of US-licensed Humira, respectively. Provide the justification for your lot selection of US-licensed Humira for these three assays.*

    II. *For TNF- α neutralization, the sponsor measured 12 lots of CHS-1420 and 21 lots of US-licensed Humira. However, only 11 lots of CHS-1420 and 18 lots of US-licensed Humira were included in equivalence testing analysis. Provide the justification for your lot selection of CHS-1420 and US-licensed Humira for the TNF-α neutralization equivalence test.*

    III. *Provide a summary table to show the value of each individual lot that was tested for each quality attribute.*

b. Does the Agency agree that the studies (structural and functional) conducted to support a demonstration of comparability between commercial process CHS-1420 and late-development process CHS-1420 are sufficient to support a substantive review of the BLA?

FDA Response:

The proposed comparability studies appear sufficient to assess analytical comparability between late-development and commercial process CHS-1420 DS lots. The sufficiency of the data for comparability will be evaluated during BLA review.

Discussion:

The Sponsor noted that they will address FDA's comments in the relevant CTD sections of the BLA.

Question 4:

The basis for extrapolation to all requested Humira indications will include the structural and functional similarity and comparability studies (presented in Appendix 2) as well as the clinical studies CHS-1420-02 in plaque psoriasis subjects and CHS-1420-03 in healthy subjects. Does the Agency agree that the proposed studies are sufficient to allow a substantive BLA review and that no other information is needed to support extrapolation of indications?

FDA Response:

We recommend that you provide a separate document with your justification of extrapolation which can be submitted under Module 2. If CHS-1420 meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, you may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed. However, you would need to provide sufficient scientific justification for extrapolating data to support a determination of biosimilarity for each condition of use for which licensure is sought. Such scientific justification for extrapolation should address, for example, the following issues for the testing and extrapolating conditions of use:

a. *The mechanism(s) of action in each condition of use which licensure is sought; this may include:*
    I. *The target/receptor(s) for each relevant activity/function of the product;*
    II. *The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;*
    III. *The relationships between product structure and target/receptor interactions;*
    IV. *The location and expression of the target/receptor(s)*
b. *The pharmacokinetics and biodistribution of the product in different patient populations; relevant PD measures also may provide important information on the mechanism of action*
c. *The immunogenicity of the product in different patient populations*
d. *Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to "off-target" activities)*
e. *Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population from which licensure is sought*

The validity of your scientific justification based on the mechanism(s) of action of adalimumab and these additional factors listed above for extrapolating data intended to support a

demonstration of biosimilarity, including clinical data using CHS-1420 to treat patients with psoriasis, to other conditions of use will be a review issue. In addition, the reference product has orphan drug exclusivity for some indications which would preclude approval of a biosimilar to US-licensed Humira for the protected indication until the expiration of orphan drug exclusivity. You can submit data and information intended to provide sufficient scientific justification for extrapolating data to support a demonstration of biosimilarity for a condition of use for which the reference product has unexpired orphan exclusivity in the original 351(k) BLA. However, we will not be able to approve CHS-1420 for the protected indication(s) until the reference product orphan exclusivity expires.

Discussion:

The Sponsor noted that they will address FDA's comments in the justification for extrapolation. No further discussion took place under Question 4.

Question 5:

Does the Agency agree that the executed process performance qualification strategy for CHS-1420 DS and DP is sufficient to support a substantive review of the BLA?

FDA Response:

The PPQ strategy described appears to be appropriate, except that you cannot include DP lot 3-FIN-2847 in your DP process validation report because you do not intend to seek approval of the WCB in the initial BLA filing. Final determination of adequacy will be made during the BLA review. Refer to "Additional Product Quality Microbiology Comments" included at the end of the document for expectations regarding microbial control of PPQ batches.

Discussion:

The Sponsor noted they will follow FDA's recommendations to remove DP lot 3-FIN-2847 from the DP PPQ. No further discussion took place.

Question 6:

Coherus intends to request at least (b)(4)-month of shelf life for the CHS-1420 PFS when stored under the recommended long-term storage condition of 2 to 8°C. Does the Agency agree that the proposed stability data package for the CHS-1420 DP in primary syringe container and assembled prefilled syringe at time of BLA submission constitutes a fileable application?

FDA Response:

We agree that the proposed stability data package supports a fileable application. Whether your stability data support the requested (b)(4)-month shelf life is a review issue.

Discussion:

No further discussion took place.

Question 7:

Commercial specifications (DS and PFS)

a. Does the Agency agree with Coherus' approach for setting the commercial specifications for CHS-1420 DS and CHS-1420 PFS?

Discussion:

No further discussion took place.

FDA Response:

Your approach for setting the commercial specifications appears appropriate. However, you should also take the results of your analytical assessment into consideration in setting commercial release and stability specifications for CHS-1420 DS and DP. Determination of the adequacy of the commercial specifications will be a review issue.

b. Does the Agency agree that the methods selected for DS and DP specifications are sufficient?

FDA Response:

The proposed DS and DP methods chosen for specifications are acceptable. However, we may request for additional release and stability specifications to be included if differences between CHS-1420 and US-licensed Humira are identified in your analytical similarity assessment. A final determination will be conducted during the BLA review.

With regard to specifications for the prefilled syringe, the proposed tests and acceptance criteria appear adequate. However, additional tests are required to assess the functionality performance of the proposed PFS. The additional tests include:

1) *Dose Accuracy*
2) *Needle functional performance tests*
3) *Vibration and Free Fall/Drop testing*

Additionally, refer to the CDRH/ODE post meeting comments from your November 10, 2016, meeting on device combination product information. In regards to future marketing applications, we expect that you will provide all necessary information to support the safety and functionality of the device constituent parts.

Discussion:

(Slides 8 and 9)

The Sponsor sought clarification on FDA's request for additional tests required to confirm the functionality performance of the PFS and proposed to address FDA's concern by listing the following:

-For the dose accuracy, design verification testing of CHS-1420 PFS will include measurement of the volume of the drug solution expelled as either the volume in the container or the delivered dose; these measurements are also part of the release testing for every batch of CHS-1420 PFS.

-For the Needle Functional Performance Test the Sponsor will confirm that the 'Customer Quality Specifications of the [redacted] (b) (4) Syringe Barrel with needle' will include quality criteria for the needle. The Sponsor added that the syringe is available commercially and the PFS components are manufactured by [redacted] (b) (4) The Sponsor will include the cross reference to the [redacted] (b) (4) master file and the LoA in the BLA.

-The Vibration and Free Fall/Drop Testing will be met by using shipping validations studies.

The FDA was in agreement with the Sponsor's proposal and stated that dose accuracy is typically used for the PFS. The FDA also stated that the quality specification for the needles appear acceptable. The Sponsor will reference the device master file for needle and syringe information and provide the additional test report data requested by FDA.

Question 8:

Does the Agency agree with the proposed content of the 120-day safety update? Coherus intends to submit clinical safety data from on-going clinical studies (CHS-1420-02 Treatment Period 3, CHS-1420-05, and CHS-1420-07) in the safety update.

FDA Response:

The application should be complete at the time of submission. Our understanding is that you [redacted] (b) (4) *Thus, we agree with the proposed content of the 120-day safety update.*

Discussion:

No further discussion took place.

Question 9:

Office of Scientific Investigations (OSI) Clinical Site Information Request

a. Does the Agency agree that the specific OSI-recommended line listings need to be provided only for clinical studies CHS-1420-02 and CHS-1420-03, since these studies will provide the basis for demonstration of no clinically meaningful differences between the proposed biosimilar CHS-1420 and the reference product Humira (US)?

FDA Response:

Your proposal is reasonable.

Discussion:

No further discussion took place.

b. Does the Agency agree that Coherus may omit the submission of site-level datasets (III. Request for Site Level Dataset) for CHS-1420-02 and CHS-1420-03 studies?

FDA Response:

Submission of site level datasets for CHS-1420-02 and CHS-1420-03 is optional, but not required.

Discussion:

No further discussion took place.

Question 10:

For the Summary of Clinical Safety (CTD Section 2.7.4 Summary of Clinical Safety) of the CHS-1420 BLA, Coherus intends to present safety data (including ADA results) from each CHS-1420 clinical study individually or side-by-side. Similarly, for CTD Section 5.3.5.3 Reports of Analyses of Data from More than One Study of the BLA, safety data tables will be provided for each study. Coherus does not plan to conduct an integrated analysis of safety data from pooled results of any of the studies that will be used to support the BLA. Does the Agency agree that a pooled analysis is unnecessary?

FDA Response:

Your proposal to present data side by side and not pooled appears reasonable for your proposed BLA submission.

Discussion:

No further discussion took place.

Question 11: Clinical Immunogenicity

a. Does the Agency agree with the proposed plan to characterize and compare ADA of CHS-1420 and Humira (US) in study CHS-1420-02?

FDA Response:

The proposed plan to characterize ADA of CHS-1420 and US-licensed Humira is acceptable.

b. Does the Agency agree with the proposed competitive ligand-binding NAb assay to characterize and compare CHS-1420 and Humira (US)?

FDA Response:

Yes, we agree.

c. Does the Agency agree that the following timepoints are sufficient to characterize and compare the ADA and NAb of CHS-1420 and Humira (US) in the safety and efficacy study CHS-1420-02: predose, Weeks 4, 12, and 16 in Period 1; Week 24 in Period 2 (8 weeks after the first group of subjects switch from Humira (US)); and Week 55 (EOS - 8 weeks after last dose) in Period 3?

FDA Response:

Consider including unscheduled blood sampling as triggered by suspected immunogenicity related adverse event in addition to the prespecified sampling schedule in order to establish the clinical relevance of antidrug antibodies. The adequacy of the data will be a review issue.

Discussion:

The Sponsor will take FDA's recommendation and will provide justification to the BLA.

Additional Comments:

Product Quality: CMC

We refer you to the minutes of the November 10, 2016, BPD Type 2 meeting for additional agreements that were reached.

Product Quality: Microbiology

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 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 the Module 1 of the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited to the following:

a. *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur* (b) (4) *step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*

b. *Bioburden and endotoxin data obtained* (b) (4) *(3.2.S.2.5).*

c. *Microbial data from* (b) (4) *Bioburden and endotoxin levels* (b) (4) *should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*

d. (b) (4) *study protocols and acceptance criteria for bioburden and endotoxin samples to demonstrate adequate microbial control* (b) (4) *In addition, provide the bioburden and endotoxin acceptance criteria for* (b) (4) *Bioburden and endotoxin samples for the storage validation study should* (b) (4) *(3.2.S.2.5).*

e. *Information and summary results from the shipping validation studies (3.2.S.2.5).*

f. *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*

g. *Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process* (b) (4) *. If*

compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the [redacted] *operations. 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"*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

a. *The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.*

   I. *Identification of the manufacturing areas and fill line, including area classifications.*

   II. *Description of the* [redacted]

   III. *Parameters for filling and plunger placement.*

   IV. *Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.*

   V. *Processing and hold time limits, including the* [redacted].

   VI. *Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken* [redacted] *bioburden limits should not exceed* [redacted] *mL.*

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

   I. [redacted]

   II. *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the* [redacted] *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.*

III. In-process microbial controls and hold times. [redacted] (b) (4) *Bioburden and endotoxin levels* [redacted] (b) (4) *should be monitored and bioburden and endotoxin limits provided.*

IV. [redacted] (b) (4) *if applicable.*

V. [redacted] (b) (4) *including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*

VI. Information and summary results from shipping validation studies. The effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.

c. The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

VII. Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress [redacted] (b) (4) *microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.*

VIII. 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. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.

IX. Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

X. Certain formulations 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 (RSE or CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

Discussion:

The Sponsor asked whether BsUFA II would apply to their future 351(k) BLA submission as they plan to submit it in the next few months before BsUFA II is in effect. The Sponsor specifically asked if there will be a transition period if the BLA gets submitted close to and before October 1, 2017, such that more frequent communications will take place during the BLA review phase per BsUFA II agreements. The FDA stated that the BLA will not be subject to BsUFA II agreements if the BLA is submitted prior to October 1, 2017.

Post-meeting note:

FDA reiterates that a 351(k) BLA submitted before October 1, 2017 will be managed to the goals that existed at the time of submission, and will not be subject to agreements authorized under BsUFA II.

In closing, the FDA reminded the Sponsor to submit an Agreed iPSP as follow-up to FDA's iPSP Written Responses communicated on February 21, 2017 in order to ensure that an agreed iPSP has been established between the FDA and the Sponsor prior to submitting their BLA.

3.0

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

If the original 351(k) application is submitted on or after October 1, 2017, it may be subject to "the Program" under BsUFA II (subject to the reauthorization of BsUFA). Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), as applicable. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the BsUFA II proposals and the Program is available at http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/ucm461774.htm.

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 *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- 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.
- 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 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry entitled *Nonproprietary Naming of Biological Products*, available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm459987.pdf, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a

"collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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.

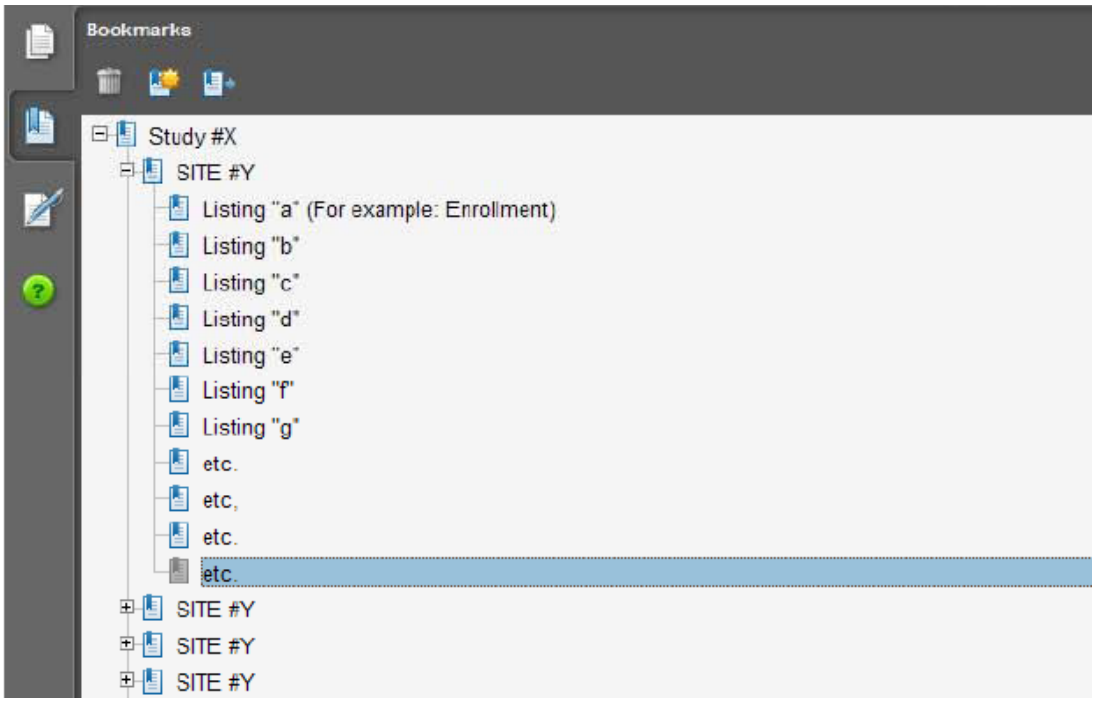
4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

4.0 ISSUES REQUIRING FURTHER DISCUSSION
None

5.0 ACTION ITEMS
None

6.0 ATTACHMENTS AND HANDOUTS
Coherus BioSciences, Inc. Slide Deck

10 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/

SADAF NABAVIAN
06/16/2017