CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761082Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115333

MEETING MINUTES

Adello Biologics, LLC
Attention: Joel M Brittain
Senior Associate, Global Regulatory Affairs
3440 S. Dearborn Street, Suite 300
Chicago, IL 60616

Dear Mr. Brittain:

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

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2017. The purpose of the meeting was to discuss the content and format of the Biologics Licensing Application (BLA) to be submitted in support of licensure of Theragrastim as a biosimilar to US-licensed Neupogen (filgrastim) under section 351(k) of the Public Health Service (PHS) Act.

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

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	Biosimilar Biological Product (BPD) Type 4
Meeting Date and Time:	February 7, 2017; 2:00 PM – 3:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	IND 115333
Product Name:	"Theragrastim"
Indication:	Theragrastim is being developed for the same indications as approved for US-licensed Neupogen
Sponsor/Applicant Name:	Adello Biologics, LLC
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Kris Kolibab, PhD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP):
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Kelly Norsworthy, MD, Clinical Reviewer
Ashley LucciVaughn, MS, Regulatory Project Manager
Kris Kolibab, PhD, Senior Regulatory Health Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT):
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:
Sarah Schrieber, PharmD, Team Leader

Office of Biostatistics, Division of Biometrics V (DBV):
Kyung Y Lee, PhD, Statistics Reviewer

Office of Biostatistics, Division of Biometrics VI (DBVI):
Meiyu Shen, PhD, Statistics Team Leader
Zhuang Miao, PhD, Statistics Reviewer

Office of Biotechnology Products (OBP), Division of Biotechnology Research and Review (DBRR III):
Howard Anderson, PhD, Product Quality Team Leader
Richard Ledwidge, PhD, Product Quality Reviewer

Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS):
Sue Lim, MD, Team Leader
Carla Lankford, MD, PhD, Science Policy Analyst
Tyree Newman, BS, Senior Regulatory Project Manager

Office of Pharmaceutical Quality (OPQ), Division of Microbiology Assessment (DMA):
Patricia Hughes, PhD, Chief
Kathleen Jones, PhD, Microbiology Reviewer

Center for Devices and Radiological Health (CDRH), General Hospital Devices Branch (GHDB):
Sapana Patel, PharmD, Lead Reviewer

Office of Regulatory Policy (ORP):
Janice Weiner, JD, MPH, Senior Regulatory Counsel

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA):
Hina Mehta, PharmD, Team Leader
Nicole Garrison, PharmD, BCPS, Safety Evaluator

SPONSOR ATTENDEES
Peter Moesta, PhD, CEO, Adello
Michael Washabaugh, PhD, Chief Scientific Officer, Adello
Susan Lewis, PhD, Head of Global Regulatory Affairs, Adello
Joel Brittain, PhD, Senior Associate, Global Regulatory Affairs, Adello
Sunitha Lakshminarayanan, PhD, Project Team Lead, Adello
Michelle Zheng, PhD, Head of Analytical Research and Development, Adello
(b) (4) Device Design Consultant

1.0 BACKGROUND

Adello Biologics, LLC, is developing Theragrastim as a proposed biosimilar to US-licensed Neupogen (filgrastim). The Sponsor received advice from the Agency on 11/5/2012 in a Type B PIND meeting, and BPD Type 2 meetings were held on 10/28/2013 and 11/4/2014, and a BPD Type 3 meeting was held on 6/9/2016.

The Sponsor requested a BPD Type 4 meeting with FDA on December 6, 2016. On December 16, 2016, FDA sent Adello Biologics, LLC the meeting request granted letter. The purpose of this BPD Type 4 meeting is to discuss the content and format of the Biologics Licensing Application (BLA), to be submitted in support of approval of Theragrastim under section 351(k) of the PHS Act.

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

FDA sent Preliminary Comments to Adello Biologics, LLC on February 6, 2017.

2. DISCUSSION

2.1. Questions

Question 1:

In many source documents that will be provided in the Theragrastim BLA, the Drug Substance (DS) and intermediate product (IP) have been referred to by the non-proprietary name, filgrastim.

Does the Agency agree that it is acceptable to use Filgrastim DS and Filgrastim IP, when referring to Theragrastim DS and IP, in some documents?

FDA Response to Question 1:

We do not agree that it would be appropriate to refer to your proposed product as Filgrastim DS and Filgrastim IP in your BLA. For certain documents that have already been created, we recommend that you either change the terminology within the document or include an explanatory cover note for each document clarifying that "Filgrastim DS" and "Filgrastim IP" in such document refer to "Theragrastim DS" and "Theragrastim IP," respectively. We remind you that FDA has not yet made a determination regarding the nonproprietary name for your proposed biosimilar product. For more information about on the nonproprietary naming of biological products, see FDA's guidance for industry: Nonproprietary Naming of Biological Products at http://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf.

Discussion:

No discussion occurred.

Question 2: Annotated table of contents

In the briefing package submitted together with this meeting request, a comprehensive table of contents of the BLA package is provided as Appendices 1, 2, 3, 4, and 5 where each appendix represents the module of the same number. The applicant seeks the Agency's feedback in the case that additional documents should be included in the eCTD BLA package pursuant to section 351(k) of the Public Health Service Act.

Does the Agency agree that the proposed documents as described in the appendices are considered adequate and sufficient?

FDA Response to Question 2:

No. Whether the content of your application is complete and acceptable for review will be determined at filing. We have the following general observations regarding the information you provided in the Appendices:

a) Your plan for Module 1 is incomplete, especially with regard to Section 1.3. For additional information regarding sectioning of Module 1, please see the current Comprehensive Table of Contents Heading and Hierarchy at: http://www.fda.gov/downloads/drugs/ucm163175.pdf

b) Please note that Module 2.2 is an introduction rather than a summary. In general, it should not exceed one page. Information about the submission from the Reviewer's Guide need not be repeated in Module 2.2.

c) Module 2.5 is generally a short document (< 30 pages) that provides a very high-level summary of results, the conclusions, and the implications. This section may also include your justification for extrapolation.

d) Study TPI-CL-110 is a safety study. It should be submitted in Section 5.3.5.4 Other Study Reports and Related Information.

e) We note that you have not listed an analysis (ADaM) data set for any of the protocols in Module 5.3.5. If you do submit an ADaM data set, it should be placed in a folder separate from the data listing data set and have its own define file.

f) Regarding the information for the device constituent (syringe component with needle guard) located in Sections 3.2.P.7, if the letters of authorization for the purchased components (DMFs and 510(k)) are, as stated, found in Module 1 Section 1.4.1, then this information does not need to be resubmitted in Section 3.2.P.7.

g) Please note the following additional information is expected in Section 3.2.P.7 for the prefilled syringe device constituent:

i. **A comprehensive description of the device constituent, including the final product presentation, engineering drawings, device specifications, labeling and packaging in its final form.**

ii. **We expect that your Design Traceability matrix will include the essential performance requirements of your device and traceability to the test reports verifying that the device passed all established criteria associated with the performance requirement. We expect that you include full test reports for each test performed, along with a summary that explains the objective, acceptance criteria, sample size, method results, discussion, and discussions of deviations.**

iii. **A risk analysis should be provided to characterize and evaluate risks to the user or patient. The analysis should describe system hazards, mitigations implemented to reduce the risks and acceptability of system risks in the final finished device.**

iv. **Biocompatibility testing for the final finished device constituent parts should be included in your application. Testing should include cytotoxicity, sensitivity, and irritation testing. Please note additional testing may be required based on the evaluation of the biological evaluation of the device. Please include the full test reports for all tests performed. We recommend that if you intend to reference testing completed by the supplier you provide a right of reference from the supplier.**

v. **We expect that your Safety Feature will conform to ISO 23908 and that you refer to ISO 11040-4 for performance standards applicable to your prefilled syringe.**

vi. **Please be reminded that if you choose to leverage the DMF or 510(k) for specific components of your device constituent, please provide the locations within the referenced files for the requested information. Please note the Agency expects that all essential performance requirements and device risk analysis of the combination product be held under your marketing application.**

Discussion:

No discussion occurred.

Question 3: Scanned PDFs – OCR

Adello intends to submit supporting documentation as searchable PDF documents. However, some documents such as literature references or CRFs are not available in a searchable format (i.e. not created from a readable source or OCR).

Does the Agency agree that it is acceptable to include these documents in the BLA dossier as "non-searchable" PDF documents?

FDA Response to Question 3:

We agree to accept for this BLA submission your CRFs and copies of published literature that are not searchable. However, the CRFs will need to be bookmarked so that they can be navigated.

Discussion:

No discussion occurred.

2.2. Chemistry and Manufacturing Controls

Question 4:

Adello Biologics qualified one lot of in-house reference standard from a batch representing the proposed commercial manufacturing process against USP Filgrastim reference standard using a battery of comprehensive characterization methods. This reference standard lot will be named and used as our Primary Reference Standard for all future commercial testing. All of the data to be presented in the BLA were generated using USP Filgrastim reference standard.

Does the Agency agree with this practice?

FDA Response to Question 4:

It is appropriate to establish an in-house primary reference standard that has been characterized by a battery of comprehensive characterization methods and calibrated for potency against the available USP Filgrastim reference standard. As explained in FDA's guidance for industry on Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product, we note that studies with USP Filgrastim reference standard would not be adequate to demonstrate the biosimilarity of your proposed product to the U.S.-licensed reference product.

The in-house reference standard should be representative of clinical materials and the commercial manufacturing process. The adequacy of the testing strategy will be determined with the BLA review. We recommend you generate a secondary in-house reference standard that is calibrated against the primary in-house reference standard for routine testing of product lots, as recommended by ICH Q6B.

Discussion:

No discussion occurred.

Question 5:

Does the Agency agree that the CMC data package as outlined in Appendix 3 is sufficient to permit review of the BLA application?

FDA Response to Question 5:

Yes, the proposed documents for module 3 appear adequate to permit review of the BLA application. However, a filing determination will be made when the BLA is submitted. See comments (f) and (g) in FDA's response to Question 2 and product quality microbiology comments at the end of this document.

Discussion:

No discussion occurred.

Question 6:

Adello has responded in Appendix 6 to the Agency's comments made during the Type 3 meeting held on June 9, 2016 (see Type 3 meeting minutes).

Does the Agency agree with these responses and the approaches therein?

FDA Response to Question 6:

The approaches described in your responses to Agency comments for the June 9, 2016 meeting appear reasonable; however, a final determination on the adequacy of the responses will be made during BLA review.

Discussion:

No discussion occurred.

Question 7: Commercial Manufacturing Suite

Approximately 15 Drug Substance lots manufactured at Adello in Suite (b) (4) will support the Theragrastim BLA. Adello will provide a Process Performance Qualification (PPQ) report for manufacturing of Theragrastim DS in Suite (b) (4)

(b) (4)

Does the Agency agree that a DS process validation protocol and proposed commercial batch record, to support the commercial manufacturing suite, along with the opportunity for FDA inspection, will support BLA approval of the new manufacturing area?

FDA Response to Question 7:

No, your proposed approach is not acceptable to support BLA approval for production in Suite (b) (4) The proposed change of moving the entire process to a new suite has a high risk to impact product quality. If you intend to seek licensure of Suite (b) (4) then the BLA should contain the following results of all process validation studies for te (b) (4)

a. Full process validation information for at least three PPQ batches of drug substance manufactured in Suite (b) (4)

b. An analytical similarity exercise that includes data from Suite (b) (4) material.

c. Full comparability assessment between DS batches produced in Suites (b) (4) including:

i. Release, characterization and stability data from the PPQ DS lots manufactured in Suite (b) (4) and at least three DS lots manufactured in Suite (b) (4)

ii. Release and stability data under accelerated conditions for at least one DP lot derived from DS manufactur Suite (b) (4) and three DP lots derived from DS manufactured in Suite (b) (4)

d. A production schedule for DS manufactured in Suite (b) (4)

In this question, you note that Suite (b) (4) will be available for Pre-approval inspection. However, it is not clear if you will be manufacturing drug substance in Suite (b) (4) during the inspection. Suite (b) (4) should be available for inspection during all phases of manufacture during the Pre-approval inspection. If you decide to not include Suite (b) (4) in the original BLA then Suite (b) (4) should be available for inspection during all phases of manufacture and a production schedule for Suit (b) (4) should be provided in the original BLA.

Discussion:

Adello stated they seek licensure solely for Suite (b) (4) Adello proposed to perform comparability studies with three DS process qualification lots produced in suite (b) (4) to 3 lots manufactured in Suite (b) (4) in addition to other information, see Table 1 of the document provided by Adello. Adello also proposed to provide comparability results (characterization and formal stability data) and release results from drug product manufactured at (b) (4) from Suite (b) (4) in an amendment to the BLA.

The FDA indicated that the application must be complete when submitted and reiterated that FDA would accept simple stability updates amendments during the BLA review. The FDA stated that the acceptability of the proposed studies and rationales for process validation in Suite (b) (4) provided in Table 5 of the meeting addendum, are a review issue.

Adello indicated in meeting addendum item 7b1 that they did not have a plan to conduct analytical similarity on material manufactured in Suite (b) (4) The FDA disagreed, and indicated that analytical similarity data provided in the BLA needs to include data from Suite (b) (4) DS material. Adello sought guidance on the similarity assessment to be conducted using one lot (vial) of DP made from Suite (b) (4) DS material. FDA stated they would discuss the issue internally and provide additional guidance as post-meeting note in the meeting minutes. See "Post Meeting Note" below.

Adello confirmed that Suite (b) (4) would be operational and manufacturing during the BLA submission cycle and would be ready for inspection (2-6 months into the cycle).

The Agency agreed from product quality microbiology perspective with the microbiological controls listed in Table 5: Studies Proposed for Process Validation in Suite (b) (4) Additionally, Adello confirmed that all extended hold times are in (b) (4), and that the (b) (4) will be monitored microbiologically.

Post Meeting Note:
FDA recommends the following:

1. Regarding the use of Suite (b) (4) material: Three Suite (b) (4) DS lots should be included in the analytical similarity exercise to support Suite (b) (4) for commercial DS production. Certain drug product specific attributes relevant to the DP presentation, such as protein content could be excluded from the analytical similarity exercise. The comparative similarity data between 3 Suite (b) (4) DS lots and the reference product should be included in the original BLA submission.
2. Regarding your clarification (point 7c3 in the addendum material) for the 1 DP lot manufactured from Suite (b) (4) DS, we disagree with the proposal to submit 3 months of stability data as an amendment to the BLA. We recommend at least 6 months of stability results at normal and accelerated conditions from one lot of DP manufactured from suite (b) (4) DS. This information can be provided as an amendment to the BLA. The BLA should contain a commitment to place at least 3 DP lots manufactured from Suite (b) (4) DS material under stability surveillance.

Question 8: Stability Strategy

At the time of the planned BLA filing, Adello will have stability data on six (6) representative DS and fourteen (14) Drug Product (DP) lots, as identified in Appendix 7 Table 1 and Table 2, respectively. (b) (4) .

Does the Agency concur that the number of lots and time points provided in the stability data package as summarized in Appendix 7 Table 1 and Table 2 is sufficient to support the 351(k)-BLA stability data requirement? Does the Agency agree with the proposed shelf life (b) (4)

FDA Response to Question 8:

The determination of the expiry dating will be based upon the real-time stability data submitted from at least 3 batches in the final container closure system, representative of the commercial manufacturing scale. However, additional stability updates can be submitted through month seven of the BLA review process to support expiry dating as recommended by ICH Q5C guidelines.

If you decide to include Suite (b) (4) n your submission then you should also provide release data and stability data under accelerated conditions for at least one DP lot derived from DS manufactured in Suite (b) (4) and a commitment to place additional DP manufactured with DS from Suite (b) (4) on stability.

Discussion:

No discussion occurred.

Question 9: PPQ Strategy

(b) (4)

(b) (4)

Does the Agency find the described PPQ strategy and deliverables acceptable for 351(k) BLA submission?

FDA Response to Question 9:

Yes. The proposed strategy appears to be adequate; however, the acceptability of this approach will be a review issue. The BLA should contain a detailed summary of the underfilled lots, the investigation, and the corrective actions. However, we note that the proposed overfill volumes appear higher than the excess volume recommendations described in USP General Chapter <1151> and FDA Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, June 2015. In the BLA submission, provide a justification with recoverable volume data to support exceeding the recommended excess volumes and address whether this approach impacts the comparative assessment of protein content and concentration for your proposed biosimilar product and US-licensed Neupogen.

Discussion:

No discussion occurred.

Question 10:

Adello intends to propose the following specifications as provided in Appendix 8 to control the quality of Theragrastim at commercial stage including Intermediate product (IP), DS release and stability, as well as DP release and stability. The establishment of these routine testing and acceptance criteria are based on the principle of ensuring the product's identity, strength, purity and safety.

Does Agency agree with the proposed specifications?

FDA Response to Question 10:

No. Polysorbate 80 and product charge variants should be include as part of the release and stability testing program to adequately control product quality.

In addition, the BLA should include the following information:

- **Your Stability Data in Section 3.2.P.8 should include the following testing at the end of your proposed shelf life: activation of the safety feature, glide force and break loose force, container closure integrity, and expellable volume. If you do not believe the tests are necessary as part of your end of shelf life testing, we recommend you include a justification to why the shelf life will not impact the performance requirements of the device.**
- **In the BLA, clearly identify the location of all requirements of your DP shipping validation study. We recommend that container closure integrity testing and activation of the safety feature be included in your shipping process validation study.**
- **We also request that lot release testing be provided for all essential performance requirements to ensure that they are maintained after manufacturing of the combination products. If any of the essential performance requirements are not tested, we recommend you provide a justification to why the testing was not necessary. This information should be provided in Section 3.2.P.7.**

Discussion:

The Agency expects that stability data in Section 3.2.P.8 will include testing using real time studies or accelerated aging studies. If you are proposing a 24-month shelf life, then your device constituent should support the 24-month shelf life with recommended test points. The testing time points can be determined by you; however, we recommend you provide either accelerated aging or real time stability data for your proposed shelf life in the application. Accelerated aging reports are acceptable with real time reports being submitted as Post Market Commitments.

Container Closure Integrity (CCI) will be included in the shipping validation plan and protocol and Safety Device activation will be part of design verification testing. The Safety Device is a 510(k) cleared device and including the information in the design verification testing is considered acceptable if the cleared device has met the performance requirements of the safety device of the combination product.

Essential performance requirements are expected to be part of lot release testing to ensure that the final finished combination product meets the device requirements. Providing the Device Design Verification and Validation plan alone is not considered acceptable. For performance requirements that are not tested, it is expected you provide a justification to why testing was not necessary.

The Agency requested confirmation regarding testing for CCI in the shipping validation study (i.e., bullet two of FDA response to Question 10). Adello confirmed that the shipping validation would contain the appropriate CCI data to ensure continued maintenance of sterility.

Adello agreed to add Polysorbate 80 and product charge variant assays to their release and stability control strategy.

Question 11:

In the BLA, for Sections of Analytical Procedures (3.2.S.4.2 and 3.2.P.5.2) and Validation of Analytical Procedures (3.2.S.4.3 and 3.2.P.5.3), Adello Biologics intends to provide brief descriptions of analytical methods and summary of validation parameters and results, and then provide links to the approved methods and validation reports.

Does the Agency agree with this approach?

FDA Response to Question 11:

Yes, it is acceptable to provide brief descriptions of an analytical methods and summary validation results with links to detailed method and validation reports. However, the analytical procedure information in sections 3.2.S.4.2 and 3.2.P.5.2 should include information on critical reagents, data analysis, and system suitability criteria.

Discussion:

No discussion occurred.

Question 12:

During analytical similarity analysis a two-sided comparison (as per Tier 2) will be used for commonly observed impurities, some impurity comparisons may not meet the lower end of the acceptance criteria. In this case, Adello Biologics will justify the acceptance of the results

based on the fact that lower amounts of impurities in the Theragrastim profile have no impact on safety, efficacy and immunogenicity, and thus are not clinically meaningful.

Does the Agency agree with this approach?

FDA Response to Question 12:

Yes, it is appropriate to provide a justification for impurities that do not meet the lower end of the two-sided acceptance criteria.

Discussion:

No discussion occurred.

2.3. Nonclinical

Question 13:

Does the Agency agree that the pharmacology and toxicology package summarized in Appendix 4 is sufficient to support the review of the nonclinical development for the proposed BLA package?

FDA Response to Question 13:

The pharmacology and toxicology package appears sufficient; but whether the package is sufficient for review will be determined at filing.

Discussion:

No discussion occurred.

Question 14:

Does the Agency agree that for licensure of Theragrastim as a biosimilar product to Neupogen under 351(k) of the Public Health Service Act, the pharmacology and toxicology information can be submitted as study reports in PDF format, without providing electronic, individual animal data listings?

FDA Response to Question 14:

Your proposal to not include individual electronic animal data listings (e.g., in SEND format) is acceptable as long as individual animal data is included in the animal toxicology study (.PDF) reports.

Discussion:

No discussion occurred.

2.4. Clinical

Question 15:

Adello has completed 2 PK/PD trials that will be provided in Module 5 (see Appendix 5). In addition, an ongoing immunogenicity and safety trial (TPI-CL-110) will also be provided. An approved study report will be provided for all three studies in Appendix 5.

Does the Agency agree that the clinical data package summarized in Appendix 5 is sufficient for review of the clinical sections of the proposed BLA package?

FDA Response to Question 15:

Your clinical program development appears reasonable, but whether the package is sufficient for review will be determined at filing.

Discussion:

No discussion occurred.

2.5. Labeling

Question 16:

The draft labeling utilizes (b) (4) *, the Proprietary Name submitted for review with CDER under IND 115333, SN0038 on October 7, 2016. Adello considers the data and results presented in the BLA will justify the requirements for the licensure of* (b) (4) *as a biosimilar. Based on FDA guidance, extrapolation of indications is justifiable if the applicant provides, "sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use . . ." Adello confirms the proposed BLA demonstrates:*

- *Analytical and functional similarity between NEUPOGEN and* (b) (4) *are established.*
- *The approved NEUPOGEN indications sought by* (b) (4) *similarly facilitate binding specifically to the G-CSF receptor.*
- *The clinical data demonstrate PK and PD bioequivalence of* (b) (4) *and NEUPOGEN in healthy volunteers.*
- *Based on the achievement of similarity and the shared mechanism of action,* (b) (4) *is likely expected to act the same way in patient populations. Adello, seek approval for* (b) (4) *for the following indications based on the totality of the data demonstrating "sameness" to the Reference Product, NEUPOGEN, which has already proven safety and efficacy in the following indications:*

Adello, seek approval for (b) (4) *for the following indications based on the totality of the data demonstrating "sameness" to the Reference Product, NEUPOGEN, which has*

already proven safety and efficacy in the following indications:

- *Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.*
- *Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).*
- *Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).*
- *Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, Infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.*

NOTE: *Per FDA guidance on the BPCI Act, Adello will originally seek BLA licensure for fewer than all the conditions of use, for which NEUPOGEN is licensed. Based on the current requirements for additional clinical support and CD34+ evaluation, at this time Adello does not seek the following indications:*

- *Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis*
- *Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)*

Does the agency concur with the approach taken for the selected indications outlined in the draft labeling?

FDA Response to Question 16:

Your approach in general is reasonable, but whether the proposed labeling that you submit is acceptable will be a review issue. We remind you that FDA has not yet made a determination regarding the nonproprietary name for your proposed biosimilar product. For more information about on the nonproprietary naming of biological products, see FDA's guidance for industry: Nonproprietary Naming of Biological Products at http://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf

Discussion:

No discussion occurred.

2.6. Additional Question submitted on 1/25/2017

Question 17:

Adello is proposing a specific activity range as the potency acceptance criteria, rather than relative potency (%), due to USP filgrastim and Adello's qualified in-house reference standard having a slightly different specific activity which results in a different relative

potency (%). This acceptance criteria takes into account the label of the proposed reference product Neupogen, which has a stated specific activity of "1.0 ± 0.6 x 10^8 U/mg".

Does the agency agree that the proposed specification for potency is appropriate?

FDA Response to Question 17:

The agency agrees as a scientific matter that it appears acceptable to calibrate the potency of the primary in-house reference standard (RS) relative to the USP Filgrastim RS and establish the potency acceptance criteria in U/mg for control and manufacture of your own product. The acceptability of this approach will be a review issue. However, the assessment of potency for the analytical similarity study of your proposed biosimilar product and US-licensed Neupogen should be conducted in relative potency units.

Discussion:

The Agency stated that the following statements provided in response to Question 17 in the document submitted by Adello in support of the meeting would be review issues:

1. The Theragrastim label will claim a specific activity of (b) (4) U/mg
2. This label claim will be controlled by a potency specification of (b) (4) U/mg

Additional Clinical Pharmacology Comments:

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the BLA:
    a. Include the rationale for the selected dose used in the PK/PD studies in the BLA (e.g., Module 2 Summary of Clinical Pharmacology document).
    b. Include an evaluation of the impact of immunogenicity on the safety, and pharmacokinetics, as is applicable, for the studies included in the application.
    c. Submit all the PK and PD (ANC) bioanalytical methods and validation reports.
    d. Present the PK and PD (ANC) parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range, as appropriate.
    e. Include complete datasets for the PK/PD studies. The subjects' unique ID number in the PK and PD datasets should be consistent with the numbers used in the clinical datasets.
    f. Provide all concentration-time and derived PK and PD 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.

Additional Clinical Comments:

You have not identified the adverse events of interest that you will use for the comparison of safety. We recommend that you include in your safety analyses an evaluation for clinically meaningful differences in key class adverse reactions using grouped terms, such as Musculoskeletal and connective tissue disorders (MedDRA SOC) for musculoskeletal pain, Injection site reactions (MedDRA HLT) for injection site reactions, and Hypersensitivity (MedDRA SMQN) as well as Anaphylactic reaction (MedDRA SMQN) for hypersensitivity reactions.

Additional Product Quality Microbiology Comments:

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

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). 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 to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

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:

- Endotoxin removal steps should be clearly identified. WFI should be used (rather than purified water) for unit operations downstream of the endotoxin removal steps (3.2.S.2.2).
- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- A description of the in-process 0.2 µm filtration steps, process intermediate hold conditions, and bioburden and endotoxin monitoring at critical manufacturing steps (3.2.S.2.2). Bioburden sampling should occur prior to any 0.2 µm filtration step. Pre-established bioburden and endotoxin limits should be in place at critical manufacturing steps (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).
- Endotoxin removal validation data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).

- Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Hold time studies may not be required if closed single-use gamma-irradiated systems with in-line filter are used.

- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples to demonstrate adequate microbial control at scale. In addition, provide the bioburden and endotoxin acceptance criteria for resin and membrane storage. Bioburden and endotoxin samples for the storage validation study should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. 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 aseptic processing 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.

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

- Identification of the manufacturing areas and fill line, including area classifications.
- Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.).
- Sterilizing filtration parameters, as validated by the microbial retention study.
- The wetting agent used for post-use integrity testing of the sterilizing filter and the acceptance criterion for passing post-use integrity testing.
- Parameters for filling and plunger placement for the pre-filled syringe presentation
- Parameters for filling, stoppering, and capping for the vial presentation.

- Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
- Processing and hold time limits, including the time limit for sterilizing filtration.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

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

- Bacterial filter retention study for the sterilizing filter. In addition, provide the bacterial retention study report.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination, if applicable.
- Three successful consecutive media fill runs, 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.
- 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.
- Capping validation demonstrating maintenance of container closure integrity.

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

  - Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and

during stability for both presentations (vials and pre-filled syringe). Data demonstrating the maintenance of container closure integrity after the assembly of the PFS should be included. Container closure integrity test methods should be validated.

- Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns).
- Container closure integrity testing should be performed in lieu of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility and in-process 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.
- Summary report and results for the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- 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 (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time.

Discussion:

No discussion occurred.

2.0 OTHER MEETING INFORMATION

PREA REQUIREMENTS

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

Section 505B(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable

with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

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

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and FDA's Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidaces/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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

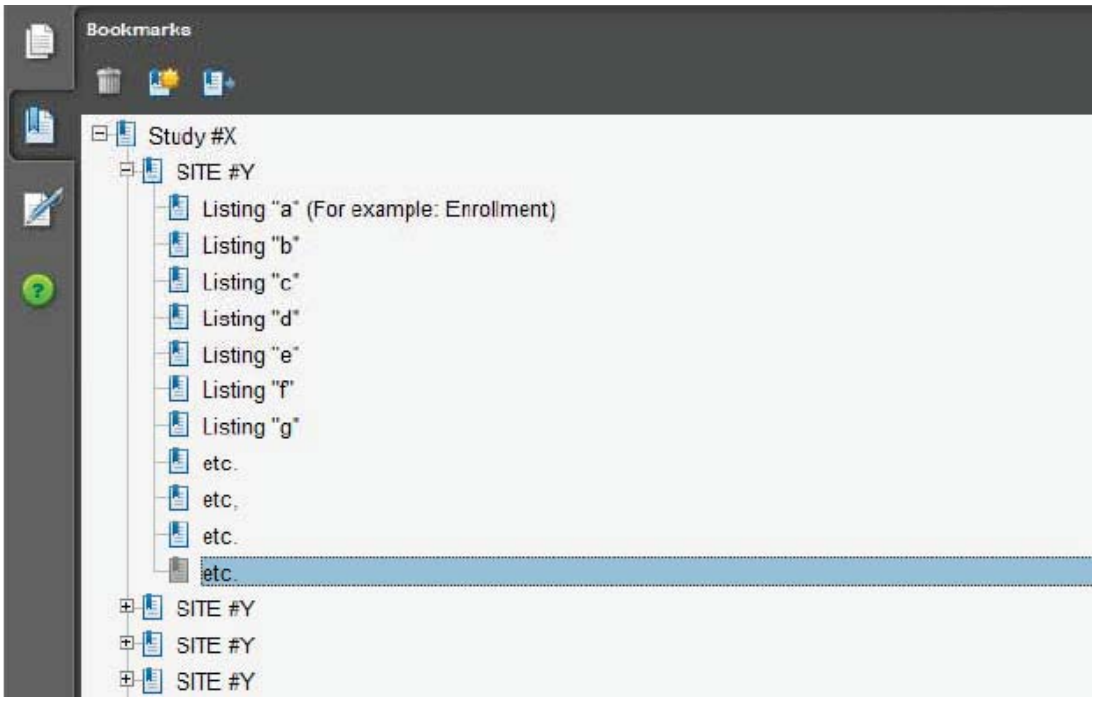
maintained. As above, this is the actual physical site where documents would be available for inspection.

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

The Sponsor provided the attached response document for the meeting.

11 Page(s) has 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/

DONNA PRZEPIORKA
03/09/2017