# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761080Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109991

**MEETING MINUTES**

Hospira, Inc.
Attention: Neeti Arora, PhD, RAC
Manager, Global Regulatory Affairs - Biologics
275 N. Field Drive
Dept. 0389, Bldg. H2
Lake Forest, IL 60045-5046

Dear Dr. Arora:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Act for PF-06881893.

We also refer to the meeting between representatives of your firm and the FDA on February 8, 2017. The purpose of the meeting was to discuss and obtain concurrence from the Agency on the overall content, format and procedural considerations of a future 351(k) BLA for PF-06881893, a proposed biosimilar to US-licensed Neupogen (filgrastim).

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 Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

*{See appended electronic signature page}*

Donna Przepiorka, PhD, MD
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 Development (BPD) Type 4 |
| **Meeting Date and Time:** | Wednesday, February 8, 2017<br>9:00AM – 10:00AM (ET) |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1415<br>Silver Spring, Maryland 20903 |
| **Application Number:** | IND 109991 |
| **Product Name:** | PF-06881893 |
| **Indication:** | PF-06881893 is being developed (b) (4) |
| **Sponsor/Applicant Name:** | Hospira, Inc. |
| **Meeting Chair:** | Donna Przepiorka, PhD, MD |
| **Meeting Recorder:** | Kimberly Scott, RN, BSN, OCN® |

**FDA ATTENDEES**

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products:
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Patricia Dinndorf, MD, Clinical Reviewer
Kimberly Scott, RN, BSN, OCN®, Regulatory Project Manager

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

Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology V
Sarah Schrieber, PharmD, Team Leader
Sriram Subramaniam, PhD, Reviewer

Office of Biostatistics (OB)/Division of Biometrics V
Kyung Lee, PhD, Reviewer

OB/Division of Biometrics VI
Yi Tsong, PhD, Director
Meiyu Shen, PhD, Team Leader

Office of Biotechnology Products/Division of Biotechnology Review and Research II
Juhong Liu, PhD, Review Chief
Christopher Downey, PhD, Team Leader

Office of Regulatory Policy (ORP)/Division of Regulatory Policy I (DRPI)
Janice Weiner, JD, Regulatory Counsel

Office of Medication Error Prevention and Risk Management/Division of Medication Error Prevention and Analysis
Hina Mehta, PharmD, Acting Team Leader
Nicole Garrison, PharmD, BCPS, Reviewer

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

**SPONSOR ATTENDEES**
Craig Whitehead, Vice President Biosimilars, Global Regulatory Affairs
Neeti Arora, PhD, RAC, Senior Manager, Biosimilars Regulatory Affairs
Scott Tennyson, Regulatory Strategist, Biosimilars Regulatory Affairs
Bharat Damle, Senior Director, Clinical Pharmacology Head
Atulkumar Ramaiya, Manager, Clinical Pharmacology
Martin Summers, Biosimilars Development Asset Lead
Tom May, Associate Director, CMC Coordination and Planning
Faith Ottery, Global Medical Director, Biosimilars
Elaine Daniels, Vice President, Biosimilars Clinical Development
Jeffrey Zhang, Associate Director Biostatistics
Maureen Mullen, Technical Project Leader, Pfizer Global Supply
Xiaoyu Chen, Director, Analytical Development

## 1.0 BACKGROUND

Hospira Inc. is currently developing PF-06881893 as a proposed biosimilar to US-licensed Neupogen (filgrastim). Hospira received advice from the Agency on March 27, 2014, a BPD Type 2 meeting was held on February 25, 2015, and a BPD Type 3 meeting was held on August 30, 2016. The purpose of the meeting is to obtain feedback from the Agency on the overall content, format and procedural considerations of a future 351(k) BLA for PF-06881893. The Sponsor is currently planning for submission of its BLA under the 351(k) pathway in August 2017.

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 Hospira 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).

FDA sent Preliminary Comments to Hospira on January 3, 2017.

## 2.0 DISCUSSION

*Question 1:*
*Does the FDA have any feedback on the proposed structure and format of the PF-06881893 351(k) BLA as presented in Appendix 5 to ensure it meets the Agency's expectations for eCTD submission?*

**FDA Response to Question 1:**
We have the following comments:

- From a technical standpoint (not content related), the structure and eCTD format for the planned 351(k) BLA is generally acceptable. However, the additional nodes created beyond what is in the specification, specifically, within sections 3.2.R. For module 2.3, it is acceptable for nodes to contain only one more level of hierarchy (2.3.S, 2.3.P, etc.). Instead, use leaf titles to differentiate sections.

- For ease of review, all pdf documents more than 5 pages long should have a table of contents (TOC), proper and clear bookmarks, and hyperlinks (including the Briefing Package, which was not bookmarked). For more information on submitting pdf files, refer to the PDF Specifications
at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf.

- Make sure leaf titles of documents are clear and indicative of the content.

- All module 4 literature reference should reside in m4.3 only and Module 5 Literature References in m5.4 only.

- Note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References, and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including Case Report Forms (CRFs). Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form." Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008)
at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

**Discussion: The Sponsor accepted FDA's response.**

*Question 2:*
*Does FDA have any feedback on the approach for an overview of regulatory requirements from Section 351(k) of the PHS Act "351(k) Roadmap" as presented in Appendix 6 in CTD Section 1.12.11?*

**FDA Response to Question 2:**
This is a reasonable approach.

**Discussion: The Sponsor accepted FDA's response.**

*Question 3:*
*Does FDA have additional comments on the adequacy of the proposed structure of the BLA to support the review?*

**FDA Response to Question 3:**
This is a reasonable approach. Refer also to additional product quality microbiology comments below.

**Discussion: The Sponsor accepted FDA's response.**

*Question 4:*
*Does FDA concur with the proposed approach to extend the PF-06881893 DS and DP shelf-life via annual report to the 351(k) application based on completion of the stability protocols in Section 3.2.P.8.1 of the BLA, provided the real-time stability results for the long-term storage condition meet the proposed commercial specifications?*

**FDA Response to Question 4:**
Yes, we concur. The extension of shelf-life of DS and DP via annual report based on completion of stability protocols is acceptable.

**Discussion: The Sponsor accepted FDA's response.**

*Question 5:*
*Does FDA have any feedback on the proposed locations, method use, and validation/ verification/qualification information for the analytical methods as proposed in Appendix 7?*

**FDA Response to Question 5:**
Your proposed placement of analytical methods and method validation/verification/ qualification in Module 3 is acceptable.

**Discussion: The Sponsor accepted FDA's response.**

*Question 6:*
*Does FDA have any comments on the inclusion of the proposed representative executed batch records for PF-06881893 DS and DP to support the 351(k) BLA submission?*

**FDA Response to Question 6:**
Your approach to include representative batch records for one each of PF-06881893 DS stored at [redacted] (b) (4) °C, as well as one each for PF-06881893 DP in PFS and SDV at both 300 mcg and 480 mcg dose strengths, is acceptable.

**Discussion: The Sponsor accepted FDA's response.**

*Question 7:*
*The Sponsor is seeking a mechanism to facilitate FDA review of raw data from development sites supporting the demonstration of analytical similarity, if required, and proposes to host the review of this data package during PAI at the Sponsor's site in Zagreb, Croatia. Does FDA have any feedback on this proposal?*

**FDA Response to Question 7:**
In your 351(k) BLA submission, provide a table listing the testing site for each assay included in your analytical similarity analysis. While we agree with your plan to review analytical similarity assessment data package at the Zagreb site, we may also request separate inspections of the testing site for certain attributes.

**Discussion: The Sponsor accepted FDA's response.**

*Question 8:*
*The Sponsor plans to submit specific manufacturing schedule options to support PAIs, 3-6 months after the BLA submission. The manufacturing schedule for PF- 06881893 DS and DP in PFS at the Zagreb, Croatia and PF-06881893 DP in SDV at McPherson, KS, will be aligned to support FDA PAI. Does FDA agree that this schedule will meet the needs of the Agency for PAI?*

**FDA Response to Question 8:**
Yes, we agree with your approach to setting the manufacturing schedule such that the PAI inspections occur 3-6 months after BLA submission.

**Discussion: The Sponsor accepted FDA's response.**

*Question 9:*
*Does FDA concur with the placement of the nonclinical data across the modules proposed for inclusion in the PF-06881893 351(k) BLA?*

**FDA Response to Question 9:**
The proposal for placement of the nonclinical studies is acceptable.

**Discussion: The Sponsor accepted FDA's response.**

*Question 10:*

*The safety, and immunogenicity data, and when appropriate the PK/PD data, from each individual study will be summarized in Module 2.7. Individual CSRs will be included in Module 5. Does the Agency concur with this plan to present PK/PD, safety and immunogenicity data without integration in Module 2.7 and in Module 5.3.5.3? Does the Agency concur with the acceptability of Module 5.3.5.3 as a mapping document?*

**FDA Response to Question 10:**
No, we do not concur. Your submission will likely be able to follow Example 4 in Section V.D of "*Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*" available at:
http://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf.

As described in this example, the text will be in Module 2 Section 2.7.4. The Module 5 ISS folder should include a) a pdf document explaining that the text of the SCS in 2.7.4 is the text of the ISS (no mapping document is needed), b) any post-text tables or appendices to which the SCS refers, and c) any integrated safety data files used to generate the post-text tables or appendices. If your SCS has no additional integrated analysis, you may not have post-text tables, appendices or integrated safety data files. See the response to Question 11 regarding the narratives.

Please note, however, that the SCS should include a summary of all safety information about your product and any discussion regarding clinically meaningful differences in safety in comparison to the reference product. A hyperlink to your postmarketing reports (as you propose in Appendix 5) is not sufficient to serve as a summary.

You have not identified your adverse events of interest. 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.

**Discussion: The Sponsor described their approach to assessment of AESI. FDA clarified that the intent of the comment was to ensure that the safety analysis included AESI, but the Sponsor could choose AESI that they identified as most useful to support a demonstration of no clinically meaningful differences between PF-06881893 and US-licensed Neupogen. Whether FDA agreed that the results of the analysis were sufficient will be a review issue.**

**The Sponsor proposed a side-by-side comparison of safety rather than pooling data. FDA agreed with the approach.**

**The Sponsor clarified that Nivestim, their biosimilar to EU-Neupogen approved in the EU, was a different product than PF-06881893. The Sponsor proposed to present safety data for Nivestim only in Module 5.3.6 as supporting information. FDA agreed with this approach.**

*Question 11:*
*The proposed narrative plan will include narratives as defined above. Individual subject profiles and case report forms will be provided only for those requiring narratives. Does FDA concur with the proposed narrative, subject profile and subject case report form plan to support the PF-06881893 BLA submission?*

**FDA Response to Question 11:**
Yes, but please include in the SCS a tabulation of hyperlinks to the relevant individual narratives in the CSRs as the cases are summarized in the SCS text.

**Discussion: The Sponsor accepted FDA's response.**

*Question 12:*
*Does the Agency concur with the Sponsor's proposal to provide a simplified Module 2.5, Clinical Overview that is adjusted for biosimilar content and refers the reviewer to the content of Module 2.7 Summaries?*

**FDA Response to Question 12:**
No. Module 2.2 is an introduction rather than a summary. In general, it should not exceed one page, but we would have no objection to including the roadmap in this Module. 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. Please note that Module 2.5 can be submitted as a single document, since subsectioning of Module 2.5 is not a U.S. requirement. You should not submit a simplified mapping document in Module 2.5, since this will not be a sufficient Clinical Overview. For additional information, see "Guidance for Industry. *M4: Organization of the CTD*"
at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073257.pdf.

**Discussion: The Sponsor re-iterated their request to put the summary of the totality of evidence and justification for extrapolation in Module 2.2 and no summary in Module 2.5. FDA did not agree with this proposal and continued to recommend that the totality of the evidence be placed in Module 2.5.**

*Question 13:*
*Considering the PF-06881893 clinical program of 3 healthy volunteer Phase 1 studies, in a total of 2 clinical sites, does the Agency concur with the proposal to submit information as outlined in Table 4 above (i.e., Section I - General Study related information and comprehensive clinical investigator information) to satisfy the BIMO requirement?*

**FDA Response to Question 13:**

In addition to the information you are providing in Table 4 of the briefing package, FDA also requests that you provide the following (site-specific) individual subject data listings for each of the studies (ZIN-FIL-1502, ZIN-FIL-1501, C1121012):

a. each subject consented/enrolled; subjects not randomized to treatment or treated with study therapy should be listed and the reason for not randomizing or treating provided
b. subject listing for treatment assignment
c. list of subjects who discontinued from treatment and/or study with date and reason for discontinuation
d. subject listing of eligibility determination (for each inclusion, exclusion criteria)
e. subject listing of AEs, SAEs, and deaths (if applicable) along with dates of occurrence
f. subject listing of protocol violations and/or deviations reported in the 351(k) BLA
g. by subject listing of PK parameters
h. by subject listing of concomitant medications (unlikely in healthy subject study)
i. by subject listing of testing (e.g., laboratory, ECG) performed for safety monitoring

**Discussion: The Sponsor accepted FDA's response.**

*Question 14:*
*Does FDA concur with the proposed labeling concept for PF-06881893(Nivestym), based on the FDA Draft Guidance for Industry – Labeling for Biosimilar Products (March 2016), to support the 351(k) BLA submission? Distinct from US-licensed Neupogen and Zarxio, Nivestym does not have latex in the needle cap of the prefilled syringe. The Sponsor proposes to include a statement in Section 2.6 and 16 of the Package Insert of Nivestym to reflect the absence of latex in the prefilled syringe. Is this acceptable to the Agency?*

**FDA Response to Question 14:**
Your approach to the proposed labeling concept in general is reasonable, but whether the proposed labeling that you submit is acceptable will be a review issue. Regarding your proposal to include a statement in Sections 2.6 and 16 to reflect the absence of latex in the prefilled syringe, we refer you to the FDA guidance for industry: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex Guidance for Industry and Food and Drug Administration Staff*
at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm342872.pdf. The acceptability of the inclusion of statements regarding the absence of latex will be a review issue.

**Discussion: The Sponsor accepted FDA's response.**

*Question 15:*
*The Sponsor will like to get feedback from the Division of Medication Error Prevention and Analysis with regards to the timing for submission of the suffixes and what would be the maximum number of suffixes permitted for submission for review by the Agency?*

**FDA Response to Question 15:**

Subject to approval of the submission provisions under the Paperwork Reduction Act, the guidance on *Nonproprietary Naming of Biological Products* (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf) recommends that companies submit up to ten proposed suffixes. The guidance states that proposed suffixes should be devoid of meaning and follow the recommendations listed in Section VI of the guidance. The guidance also recommends that submissions be made during the investigational new drug application (IND) phase* or at the time of BLA submission. Submissions may include supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in the guidance.

* A request for FDA review of a proposed suffix submitted during the investigational new drug application (IND) phase should be submitted no earlier than at the request for a biosimilar biological product development (BPD) type 4 meeting for biological products to be submitted under section 351(k) of the PHS Act.

**Discussion: The Sponsor accepted FDA's response.**

*Question 16:*
*Does the Agency agree that based on the totality of evidence (analytical, preclinical and clinical) establishing biosimilarity between PF-06881893 and the US-licensed Neupogen reference product; labeling claims, as per the label of the US-licensed Neupogen reference product, with regards to efficacy and safety, can be used for promotion for PF-06881893 for the indications being sought? The Sponsor plans to request review of launch material by the Office of Prescription Drug Promotion, prior to dissemination.*

**FDA Response to Question 16:**
The appropriateness of your proposed labeling claims for PF-06881893 will be a review issue. We encourage you to request review of launch material by the Office of Prescription Drug Promotion prior to dissemination.

**Discussion: The Sponsor accepted FDA's response.**

*Question 17:*
*In view of the Agency's recent experience with proposed biosimilars for Filgrastim, and to assist in the Sponsor's planning for a potential Advisory Committee public hearing, the Sponsor requests that the Division comment on the potential need to hold an Advisory Committee meeting to review the 351(k) application for PF-06881893, assuming the application meets the statutory requirements for licensure as a biosimilar product?*

**FDA Response to Question 17:**
Whether your application will be discussed at an Advisory Committee is, in part, a review issue. The earliest formal notification regarding an Advisory Committee will be in the correspondence you receive at the time of filing the BLA.

**Discussion: The Sponsor accepted FDA's response.**

**Additional Clinical Pharmacology Comments:**

1. Apply the following advice when preparing the BLA:

    a. Include the rationale for the selected dose used in the PK, PD, and immunogenicity studies in the BLA (e.g., Module 2.7: Summary of Clinical Pharmacology).

    b. Include an evaluation of the impact of immunogenicity on the pharmacokinetics, pharmacodynamics, and safety, as is applicable, for the studies included in the application.

    c. Submit all the PK and PD (ANC and $CD34^+$) bioanalytical methods and validation reports.

    d. For Study ZIN-FIL-1502, in addition to $C_{max}$, include the following as coprimary PK and PD endpoints: AUC0-∞, AUC0-t, ANC AUC0-∞, and ANC $AUC_{0-t}$. The PK and PD similarity results for these endpoints should be also be calculated and presented.

    e. For Study ZIN-FIL-1501, $CD34^+$ $AUC_{0-\infty}$ should be included as a coprimary PD endpoint. The PD similarity results for this endpoint should be also be calculated and presented.

    f. Include a final study report for each PK, PD, and immunogenicity study. Present the PK and PD parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range, as appropriate.

    g. Include complete datasets for the PK, PD, and immunogenicity studies. The subjects' unique ID number in the PK and PD datasets should be consistent with the numbers used in the clinical datasets.

    h. 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.

**Discussion to (d): The Sponsor agreed to complete the PK/PD similarity analysis and present the results in the application for both AUC0-t and AUC0-∞.**

**The Agency re-iterated that the PD similarity results for both ANC AUC0-t and ANC AUC0-∞ be calculated and presented in the application. The Agency stated that in the Agency review of the application, ANCmax, ANC AUC0-t, and ANC AUC0-∞, would be considered as co-primary PD endpoints. The Sponsor agreed to complete the similarity analysis and present the results in the application for both ANC AUC0-t and ANC AUC0-∞. The Agency agreed to review justifications included in the application by the sponsor for parameters not meeting the pre-specified similarity criteria.**

**Discussion to (e): The Agency referred the Sponsor to the discussion held under the Additional Clinical Pharmacology Comment 1d. The Sponsor agreed to complete the similarity analysis and present the results in the application for both $CD34^+$ AUC0-t and $CD34^+$ AUC0-∞.**

**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.

I. 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). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the 351(k) BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the 351(k) BLA (3.2.A) as background information for the pre-license inspections. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

II. 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. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
   b. Provide bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).
   c. Provide microbial data from (b) (4) should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
   d. Provide (b) (4) lifetime study protocols and acceptance criteria. During the lifetime studies, bioburden and endotoxin samples should be taken (b) (4) (3.2.S.2.5).
   e. Provide information and summary results from the shipping validation studies (3.2.S.2.5).
   f. Provide drug substance bioburden and endotoxin release specifications (3.2.S.4).
   g. Provide summary reports and results from bioburden and endotoxin test method qualification studies performed for (b) (4) 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).

III. The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) 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.

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

- (b) (4)

b. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

- (b) (4)

- (b) (4)

c. Provide the following information regarding drug product testing:

- (b) (4)

## 3.0 OTHER IMPORTANT INFORMATION

**PREA REQUIREMENTS**

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

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

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

your comparative clinical study (see additional comments below regarding expected review timelines).

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

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

## 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 to applicants 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).

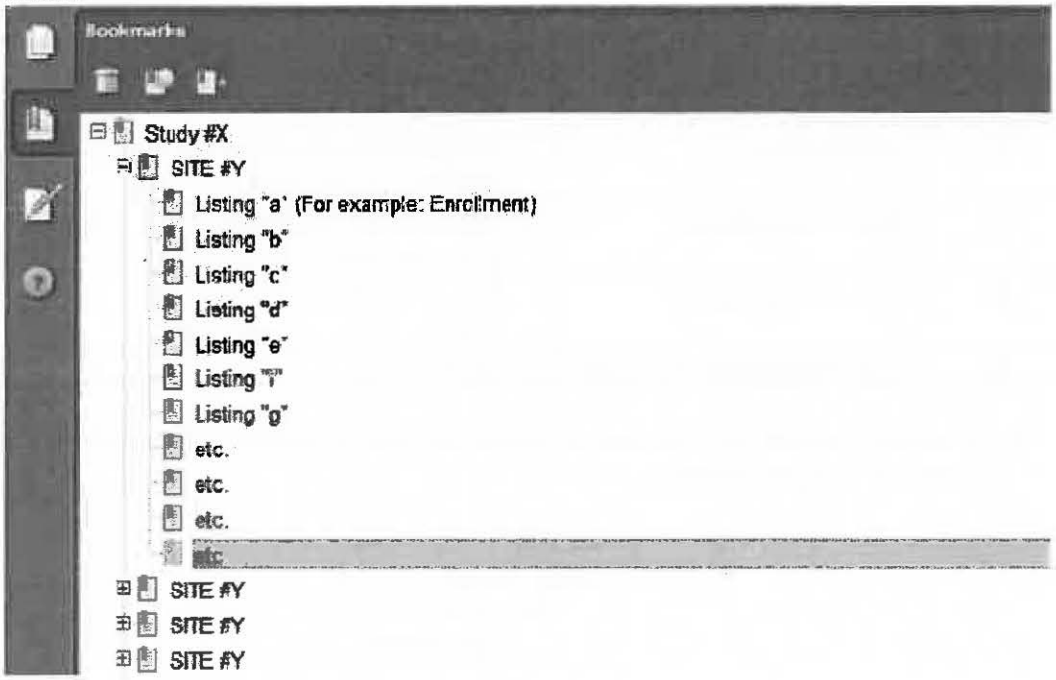
5. For each clinical study provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

**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."

| (b) (4) 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

No issues requiring further discussion.

## 5.0 ACTION ITEMS

No action items identified.

## 6.0 ATTACHMENTS AND HANDOUTS

Please see attached agenda and power point slide presentation, "PF-06881891; IND 109991 BPD Type 4 Meeting February 8, 2017," sent by the Sponsor on February 8, 2017.



23 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

**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
03/02/2017