CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761111Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124793

MEETING MINUTES

Hospira Inc., a Pfizer Company
Attention: Navayath Shobana, PhD
Senior Manager, Global Regulatory Lead
275 North Field Drive, Bldg. H1
Lake Forest, IL 60045-5046

Dear Dr. Shobana:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HSP-130 (also referred to as PF-06881894).

We also refer to the meeting between representatives of your firm and the FDA on March 11, 2019. The purpose of the meeting was to discuss with the Agency the overall content and format of the future 351(k) BLA for HSP-130 (PF-06881894), a proposed biosimilar to US-licensed Neulasta (pegfilgrastim).

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 Michael Gwathmey, Regulatory Project Manager, at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, 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:	March 11, 2019, 3:00 PM – 4:00 PM ET
Meeting Location:	White Oak Building 22, Conference Room: 1309
Application Number:	IND 124793
Product Name:	HSP-130
Indication:	HSP-130 is being developed for the same indications as approved for US-licensed Neulasta
Sponsor/Applicant Name:	Hospira, Inc.
Meeting Chair:	Tanya Wroblewski, MD
Meeting Recorder:	Michael Gwathmey,RN

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Clinical Team Leader
Patricia Oneal, MD, Clinical Reviewer
Michael Gwathmey, RN, Regulatory Project Manager

Office of Product Quality, Division of Biotechnology Review and Research II
Patrick Lynch, PhD, Team Leader
William Hallett, PhD, Team Leader
Anjali Shukla, PhD, Product Quality Reviewer
Emanuela Lacana, PhD, Associate Director Biosimilar and Biologics Policy

Office of Product Quality, Division of Microbiology Assessment
Patricia Hughes, PhD, Branch Chief
Monica Commerford, PhD, Team Leader

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Salaheldin Hamed, PhD, Team Leader

Office of Biostatistics (OB), Division of Biometrics V
Yeh-Fong Chen, PhD, Team Leader
Lola Luo, PhD, Mathematical Statistician

OB, Division of Biometrics VI
Yu-Ting Weng, PhD, Mathematical Statistician

Office of New Drugs, Therapeutic Biologics and Biosimilars Staff
Stacey Ricci, MEng, ScD, Acting Director Scientific Review Staff
Cristina Ausin, PhD, Reviewer

Center for Devices and Radiological Health, Office of Device Evaluation, General Hospital Devices Branch
David Wolloscheck, PhD, Reviewer

Office of Regulatory Policy, Division of Regulatory Policy IV
Daniel Gottlieb, JD, Regulatory Counsel

Eastern Research Group
Hannah Busey

SPONSOR ATTENDEES

Hospira, Inc.
Nathaniel Asamere, MS, RAC, US Regulatory Lead
Reginald Ewesuedo, MD, Global Clinical Development Lead
Natalia Isaeva, RAC, PMP, Comb. Prod./Diff. Drug Delivery, Global Reg. Affairs
Shahrzad Moosavi, MD, Safety Risk Lead
Navayath Shobana, PhD, Global Regulatory Lead
Martin Summers, DPhil, Asset Team Lead
Jeffery Thomas, Clinical Assay Lead
Love-Grace Thompson, PMP, Co-Development Team Lead
Hsuan-Ming Yao, PhD, Clinical Pharmacology Lead
Jeffery Zhang, MS, Biostatistics Lead
Edel Shannon, MSc, CMC Regulatory Lead
Amy Freyman, PhD, Clinician
Bilal Aslam, PharmD, Regulatory Affairs
Jennifer Hefele Wald, PhD, Director, Global Reg Affairs, Devices and Combo Prod.

1.0 BACKGROUND

The Sponsor is planning to submit a Biologics License Application (BLA) under section 351(k) of the Public Health Service (PHS) Act in June 2019 for PF-06881894, a proposed biosimilar to US-licensed Neulasta. The Sponsor requested for a BPD Type 4 meeting to discuss and obtain the Agency's concurrence regarding the overall content and format of the planned 351(k) BLA submission for PF-06881894, including Chemistry, Manufacturing, and Controls (CMC)/quality, combination product, nonclinical and clinical sections, as well as the concept for labeling development.

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).

2.0 DISCUSSION

Question 1: *Does the Agency have any feedback regarding the proposed content and format of the 351(k) BLA for PF-06881894 as presented in Appendix 1 - Table of Contents such that it meets the Agency's expectations for electronic common technical document (eCTD) submission?*

FDA Response to Question 1: Overall the proposed content appears acceptable. However, the decision on the adequacy of your clinical package supporting filing will be made during the review of your BLA submission.

From a technical standpoint (not content related), the structure and eCTD format for the planned BLA is generally acceptable. However, Applicants should not create additional nodes beyond what is in the specifications, because it is likely that the information will not display properly.

Also, please see additional comments below:

- 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. For more information on submitting pdf files, please refer to the PDF Specifications located here: 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 5 literature references should reside in Module 5.4 only
- Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in Module 5 with the exception of Module 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. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

In addition, refer to the Additional Product Quality Microbiology comments below.

Discussion: **No Discussion.**

Question 2: *In Section 1.12.11 of the BLA, the Sponsor will provide a user-friendly navigation tool to the data presented in the BLA. The document maps each regulatory requirement for the 351(k) licensure pathway of the PHS Act to the data package presented in the BLA. Does the Agency have any feedback regarding the approach of providing the "351(k) roadmap" as a mapping tool to data within the BLA to demonstrate compliance with 351(k) statutory requirements?*

FDA Response to Question 2: Your proposal to include a "351(k)" roadmap or navigation tool appears reasonable.

Discussion: **No Discussion.**

Question 3: *Does the Agency have additional comments on the adequacy of the proposed content and format of the BLA to support the review?*

FDA Response to Question 3: See response to Question 1.

Discussion: **No Discussion.**

Question 4: *Does the Agency have any feedback regarding the proposed content and location of information pertaining to the PF-06881894 PFS combination product within the BLA?*

FDA Response to Question 4: The proposed roadmap and reviewer guide for a future BLA application are acceptable. Please ensure that sections that discuss device performance (i.e., 3.2.P.8.3 Stability Data and 3.2.R.2.3 Device – Design Validation) address the essential performance requirements of the device constituent parts of the proposed product. For a prefilled syringe, we recommend that the essential performance requirements include, break loose/glide force and dose accuracy. In addition, please ensure that real time or accelerated aging stability studies are representative of the entire shelf-life of the device.

Discussion: **The preliminary comments to Question 4 stated that the essential performance requirements (EPRs) of the device constituent parts should be discussed in 3.2.R.2.3 Device – Design Validation. CDRH intended to state that the EPRs should be addressed as part of 3.2.R.2.3 Device – Design Verification and 3.2.P.8.3 Stability Data.**

Question 5: *The Sponsor plans to submit clinical study datasets in the Clinical Data Interchange Standards Consortium (CDISC) format following:*

- *The Study Data Tabulation Model (SDTM) Version 1.4 implemented using guidance from Version 3.2*

- *The Analysis of Data Model (ADaM) Version 2.1 implemented using guidance from Version 1.1*
- *Study data definitions for both SDTM and ADaM Version 2.0 Does the Agency agree with this approach?*

Does the Agency agree with this approach?

FDA Response to Question 5: We have a few comments for the data submission:

- FDA requests that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the BLA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document," available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf.
- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.
- Provide executable SAS program(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets

Discussion: The Sponsor stated ADRG and SDRG will be provided as part of the BLA. Comments, bookmarks, and hyperlinks will be included in the define files(s) as part of the BLA. In addition, the sponsor clarified that they intend to include the SAS programs for the analysis of the primary endpoint in the immunogenicity study. However, they do not plan to include the SAS programs for the analysis datasets derived from the raw data because the procedures are simple, straight forward and require minimal data manipulation. The Agency conveyed to the Sponsor that their proposal is acceptable.

Question 6: *Study C1221001 is a single dose comparative PD/PK study in healthy subjects conducted to show PK/PD similarity between PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU. This study was conducted in Australia outside of the IND and therefore subject to requirements of 21 CFR 312.120(b). In the "Notes for Reviewer" document that will be placed in Module 1 of the BLA, the Sponsor will provide a table that lists documents intended to demonstrate compliance with 21 CFR 312.120(b). Please refer to Appendix 6 – Non-IND Foreign Study GCP Documentation. Additionally, the table will provide hyperlinks to the location of each document within the eCTD.*

Does the Agency agree with our approach for delineating in the planned BLA the location of all information required by 21 CFR 312.120(b)?

FDA Response to Question 6: The proposal to provide a table in Module 1 that lists the documents intended to demonstrate compliance with 21 CFR 312.120(b) appears reasonable. The clinical study report for this study should be located in Module 2 and the clinical summary should also include hyperlinks to the documents intended to demonstrate compliance with 21 CFR 312.120(b).

Discussion: **The Sponsor's proposal to place the CSR for Study C1221001 in Module 5, Section 5.3.4.1 along with other documents supporting compliance with 21 CFR 312.120 is acceptable. The Agency clarified that Module 1 should include a summary or list of studies subject to 21 CFR 312.20 with hyperlinks to the CSRs or location in CSR where the documents supporting compliance with 21 CFR 312.120 can be found.**

Question 7: *Does the Agency have any feedback on the proposed labeling concept for PF-06881894 to support the BLA submission?*

FDA Response to Question 7: Yes, we have the following comments:

- The Initial U.S. Approval date in Highlights should be proposed as '20XX' as this date will be the year of approval of your product. [Source: FDA guidance for industry: *Labeling for Biosimilar Products* (July 2018); https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf.
- The biosimilarity statement beneath the initial U.S. approval in Highlights should read: TRADENAME (pegfilgrastim-xxxx) is biosimilar* to NEULASTA (pegfilgrastim). [Note there is no "a" before the word "biosimilar"]. [FDA guidance for industry: *Labeling for Biosimilar Products* (July 2018)].
- Section 16: The preferred statement for products that contain no latex is "Not made with natural rubber latex". You may use the same text for patient labeling.

Discussion: **No Discussion**

Question 8: *The Hematopoietic Subsyndrome of Acute Radiation Syndrome is protected by orphan exclusivity that last until November 2022.* (b) (4) [redacted] *Does the Agency agree with our proposal?*

FDA Response to Question 8: No. We do not agree with your statement, (b) (4) [redacted] Per the Labeling for Biosimilar Products Guidance, section VI(B), "The biosimilar product applicant may seek licensure for an additional condition(s) of use of the reference product in these scenarios by submitting a *prior approval supplement(s)* to the 351(k) application that contains the necessary data and information, including draft labeling revised to include the additional condition(s) of use sought."

Otherwise, your proposal appears acceptable.

Discussion: (b) (4) **Regarding the Sponsor's question about review timeframe and user fee, the Agency explained that this type of supplement would have a 10-month review goal (according to BsUFA II Performance Goals and Procedures) and there are no users fees for supplements.** (b) (4) **The Agency indicated that sufficient information needs to be available to evaluate the justification for extrapolation and can include data and information included in the original BLA.**

Question 9: *Does the Agency have any feedback on the proposed locations, method use, and validation/verification/qualification information for the analytical methods as proposed in Appendix 8- Analytical Methods Table?*

FDA Response to Question 9: Your proposal appears reasonable. However, we recommend removal of bioburden and endotoxin testing from filgrastim intermediate (FI) and drug substance (DS) stability samples. The adequacy of the information provided to support the analytical methods in your BLA will be a review issue.

Discussion: **No Discussion.**

Question 10: *The Sponsor is seeking a mechanism to facilitate the Agency's 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 at the Sponsor's site in Zagreb, Croatia. Does the Agency have any feedback on this proposal?*

FDA Response to Question 10: Your proposal to host the review of raw analytical similarity data at the Zagreb site could be acceptable. However, FDA reserves the option to conduct pre-approval inspection(s) (PAI) of analytical similarity results at sites where raw analytical data were generated to support similarity between PF-06881894 and the reference product. Provide a listing of all sites where analytical similarity assessments were conducted and identify the testing sites for each method. Report this information in the 3.2.R, Regional section of your 351(k) BLA.

Discussion: **The Sponsor stated that a list of sites (Lake Forest and Zagreb) where analytical similarity testing was conducted will be provided in the BLA. The Sponsor also stated that analytical lab books, raw data, equipment records, equipment qualification documentation, and alarm books will be available and fully accessible. Lake Forest Laboratories, where a part of the analytical similarity testing was performed, are now decommissioned and not accessible for inspection. The Sponsor stated that subject matter experts will be made available to provide information regarding the analytical testing; however, the equipment and operators that performed the analytical similarity testing at Lake Forest will likely not be accessible. The Agency acknowledged this information.**

Question 11: *The Sponsor plans to submit in the BLA, specific manufacturing schedule options to support preapproval inspections (PAIs), 3-6 months after the BLA submission. The manufacturing schedule for PF-06881894 FI, at Hospira Adelaide and DS and DP at Hospira Zagreb, will be aligned to support the Agency's PAI. Does the Agency agree that this schedule will meet the needs of the Agency for PAI?*

FDA Response to Question 11: Your pre-licensing inspections proposal for the FI, DS, and drug product (DP) appear acceptable and will be reviewed upon BLA submission. Refer to the additional Product Quality Microbiology comments below.

Discussion: No Discussion.

Question 12: *Does the Agency concur with the placement of the nonclinical data generated from both the original 351(a) and the 351(k) licensure pathways across the modules proposed for inclusion in the PF-06881894 351(k) BLA?*

FDA Response to Question 12: We agree with your proposal for placement of the nonclinical material in the 351(k) BLA eCTD.

Discussion: No Discussion.

Question 13: *The proposed narrative plan will include narratives as defined below. Individual subject profiles and case report forms will be provided only for those requiring narratives. Does the Agency concur with the proposed narrative, subject profile and subject case report form plan to support the PF-06881894 BLA submission?*

FDA Response to Question 13: Include complete and detailed narratives for all deaths, serious adverse events and dropouts or discontinuations due to adverse events.

Discussion: The Sponsor's proposal to provide only CRFs for those subjects whose narratives are provided is acceptable. The Agency clarified that including narratives for discontinuations or drop-outs due to adverse events is acceptable. The Agency stated that during the review, additional narratives or CRFs may be requested.

Question 14: *The PF-06881894 proposed biosimilar clinical program consist of 2 clinical studies: comparative single-dose, crossover design, PD/PK study in healthy subjects (PF-06881894 vs pegfilgrastim-US and pegfilgrastim-EU, Study C1221001) and comparative multiple-dose immunogenicity study in healthy subjects (PF-06881894 vs pegfilgrastim-US, Study C1221005). The results for Study C1221001 were shared at the BPD Type 2 meeting in May 2017 and is also provided in Appendix 3 –Comparative PD/PK Study Summary (C1221001). Study C1221005 is complete and the top line results are provided in Appendix 4 Summary of Study C1221005 Results. The CSRs for these 2 studies will be provided in the BLA including discussion and interpretation of the immunogenicity results. Does the Agency agree that the clinical package as indicated, to be provided in the BLA, is complete and adequate for review?*

FDA Response to Question 14: Your proposed clinical package, including immunogenicity information, appears reasonable to support a BLA submission. However, the decision on the adequacy of your clinical package supporting filing will be made during the review of your BLA submission.

Discussion: No Discussion.

Additional Product Quality Microbiology Comments

1. The FI, DS, and DP endotoxin in-process and release specifications should be reported in units of EU/mL in your BLA submission because the FI, DS, and DP are liquid formulations.

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

   All facilities should be registered with the 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 the intermediate, the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

   Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

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

   - Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
   - Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
   - Microbial data from 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).

- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples 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"* at 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 type of fill line (e.g., open, RABS, isolator), including area classifications.
- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and plunger placement for the pre-filled syringes.
- A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- 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 protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.

- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Isolator decontamination summary data and information, 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.
- Information and summary results from shipping validation studies. For prefilled syringes, 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.

  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 should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe and autoinjector should be included. 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 every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished 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. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. Low endotoxin recovery studies may not be necessary for products that do not contain polysorbate.

Additional Clinical Pharmacology Comments

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:

a. Include the rationale for the selected dose used in the PK study in the BLA (e.g., Module 2 Summary of Clinical Pharmacology document).
b. Include an evaluation of the impact of immunogenicity on the activity, safety, and pharmacokinetics, as is applicable, for the studies included in the application.
c. Submit all the PK bioanalytical method validation reports and bioanalytical study reports; also see Comment #3 below.
d. Present the PK 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 studies. The subjects' unique ID number in the PK datasets should be consistent with the numbers used in the clinical datasets.
f. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

2. 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.

3. Please complete and include the tables (**Table 1 (**bioanalytical method life cycle information) and **Tables 2a-b** (summary method performance of each bioanalytical method)) in your 351(k) BLA submission to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in pivotal clinical pharmacology studies and it's life-cycle information pertaining to the submission. Do not delete any rows from the tables. We recommend that these tables be included as an Appendix in the Summary of Biopharmaceutics located in eCTD 2.7.1. In addition to including in the Appendix, we request you also submit both tables in docx format. Finally, include any other additional bioanalytical information that might be relevant for review in your BLA submission.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived 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.16 in FDA's draft guidance for industry *New and Revised Draft Q&As on Biosimilars Development and the BPCI Act (Revision 2)* (December 2018)). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and

FDA's Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

In addition, you should review the draft FDA Guidance for Industry, "*Labeling for Biosimilar Products*," March 2016 at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf.

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

NONPROPRIETARY NAME

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

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

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

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

MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the cGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to

facilitate planning of pre-license inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA II.

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

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

Consider using a table like 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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None identified during the meeting.

5.0 ACTION ITEMS

None identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's slides from the meeting are attached.

17 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
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