APPLICATION NUMBER:

761075Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Dear Ms. Militzer:

Please refer to your Pre-Investigational New Drug Application (PIND) file for MYL-1401H.

We also refer to the meeting between representatives of your firm and the FDA on June 1, 2016. The BPD Type 2 meeting was requested to discuss the adequacy of the proposed analytical techniques, the approaches used to establish analytical similarity and the criticality risk ranking of the quality attributes, and the proposal for establishing shelf life. The BPD Type 4 was requested to discuss the proposed data to be included in the 351(k) Biologics Licensing Application (BLA) and the 120-Day Safety Update Report.

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, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

[See appended electronic signature page]

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

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: Biosimilar Biological Product Development (BPD) Type 2 and 4

Meeting Date and Time: June 1, 2016; 1:00 PM – 2:30 PM (EDT)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: PIND 123389
Product Name: MYL-1401H
Indication: MYL-1401H is being developed for the same indication as approved for US-licensed Neulasta (pegfilgrastim)

Sponsor/Applicant Name: Mylan GmbH

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, Clinical Team Leader
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Rosanna Setse, MD, PhD, Clinical Reviewer
Kris Kolibab, PhD, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:
Bahru Habtemariam, PharmD, Team Leader
Vicky Hsu, PhD, Pharmacologist

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

Office of Biostatistics, Division of Biometrics VI (DBVI):
Yi Tsong, PhD, Statistics Team Leader
Xiaoyu Dong, PhD, Statistics Reviewer
**Office of Biotechnology Products (OBP), Division of Biotechnology Research and Review (DBRR III):**
Susan Kirshner, PhD, Review Chief
Maria-Teresa Gutierrez-Lugo, PhD, Team Leader
J. Paul Kirwan, PhD, Product Quality Reviewer

**Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS):**
Sue Lim, MD, Medical Officer
Carla Lankford, MD, PhD, Science Policy Analyst

**Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA):**
QuynhNhu Nguyen, MS, Acting Associate Director for Human Factors
Yelena Maslov, PharmD, Lead Pharmacist
Ebony Whaley, PharmD, BCPS, Safety Evaluator
Sarah Harris, PharmD, Safety Regulatory Project Manager
Hina Mehta, PharmD, Lead Pharmacist (Acting)

**Office of Pharmaceutical Quality (OPQ), Division of Microbiology Assessment (DMA):**
Colleen Thomas, PhD, Product Quality Microbiology Team Leader (Acting)
Monica Markovski, PhD, Product Quality Microbiology Reviewer

**SPONSOR ATTENDEES**

**Mylan:**
John Pakulski, Head, Regulatory Science, Biologics
Barbara Militzer, Director, Regulatory Science, Biologics
Abhijit Barve, Head, Global Clinical Research
Arnd Annweiler, Head, Global Pharmaceutical Sciences
Rajesh Ullanat, Head, Biologics Research and Development
Clair Newcomb, Director, Device Development

**Biocon Limited:**
Raja Sekhar Vanga, General Manager, Regulatory Sciences
Laxmi Adhikary, Chief Scientific Manager, Research and Development
Paul Thomas, Vice President and Head, Biosimilars Business Unit
Naren Chirmule, Senior VP, Head of Reasearch & Development

**1.0 BACKGROUND**

Mylan GmbH requested Biosimilar Biological Product (BPD) Type 2 and Type 4 meetings with FDA on March 4 and 7, 2016, respectively. The BPD Type 2 meeting was requested to discuss the adequacy of the proposed analytical techniques, the approaches used to establish analytical similarity and the criticality risk ranking of the quality attributes, and the proposal for establishing shelf life. The BPD Type 4 meeting was requested to discuss the proposed data to be included in the 351(k) Biologics Licensing Application (BLA) and the 120-Day Safety Update Report.
MYL-1401H is a pegylated form of recombinant human granulocyte colony-stimulating factor (rh-G-CSF), thereby providing a longer half-life in comparison to the nonpegylated molecule, G-CSF. Pegylated G-CSF, like G-CSF, is a growth factor that stimulates production of neutrophils and neutrophil precursors by binding to the granulocyte colony-stimulating factor receptor.

MYL-1401H is being developed as a proposed biosimilar product to US-licensed Neulasta (pegfilgrastim). The proposed and sought indication is the same as approved for US-licensed Neulasta, which is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

FDA sent Preliminary Comments to Mylan GmbH on May 27, 2016.

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

2. DISCUSSION

At the start of the meeting, FDA explained that there was not sufficient time for review and internal discussion of the new material received by email from the Sponsor on the morning of the meeting, so firm agreement might not be reached at the meeting for all of the Sponsor’s new proposals, but FDA would offer advice where possible and use post-meeting notes to provide comments on issues that would require internal discussion.

2.1. BPD Type 2 - CMC

Question 1:

Mylan proposes to establish analytical similarity of MYL-1401H (pegfilgrastim) with US-licensed NEULASTA. Pairwise comparisons of MYL-1401H, US-licensed NEULASTA, and EU-approved NEULASTA will be used to support and establish the validity of the analytical bridge among MYL-1401H, US-licensed NEULASTA, and EU-approved NEULASTA.

Mylan has used state-of-the-art analytical techniques to characterize the physicochemical and biological properties of MYL-1401H and the reference product, US-licensed NEULASTA, and supportive data for EU-approved NEULASTA. A stepwise approach has been used to demonstrate analytical similarity of MYL-1401H with US licensed NEULASTA and EU-approved NEULASTA, in accordance with Agency’s feedback received in the pre-IND meeting (PIND 123389). In this approach based on criticality risk ranking, quality attributes have been organized into 4 categories: very high, high, moderate, and low.

a) Does the Agency agree that the proposed analytical techniques are adequate to establish analytical similarity of MYL-1401H in comparison with US-licensed NEULASTA?
**FDA Response to Question 1a:**

The proposed analytical techniques appear reasonable for assessing analytical similarity of the quality attributes listed in Table 5 of your meeting package. However, the final determination of acceptability of the proposed analytical techniques will be based on the review of the assay qualification and validation data submitted in your 351(k) BLA. Please also refer to the FDA response to Question 1c.

b) Does the Agency concur with the approach followed for establishing the criticality risk ranking of the quality attributes?

**FDA Response to Question 1b:**

The approach followed for establishing the criticality risk ranking of the quality attributes described in your criticality risk ranking document appears reasonable. However, a complete review of the criticality risk ranking assessment will be performed at the time of the 351(k) BLA review.

c) Does the Agency concur with the adequacy of the overall approach taken to demonstrate analytical similarity between MYL-1401H and the reference product US-licensed NEULASTA?

**FDA Response to Question 1c:**

No, we do not concur with your overall approach to establish analytical similarity between MYL-1401H and the reference product, US-licensed Neulasta. Any observed differences in quality attributes between the MYL-1401H and the reference product US-licensed Neulasta should be assessed for their potential impact on clinical performance.

In your 351(k) BLA, you should revise your analytical similarity plan to address the following:

1. Additional data and information are needed to establish analytical similarity of the PEG moiety between MYL-1401H and US-licensed Neulasta. The PEG analytical similarity assessment should include:

   a. An assessment of the average molecular mass and polydispersity of the PEG moiety in MYL-1401H and US-licensed Neulasta. Characterization of the PEG moiety may be performed after removal of PEG from the G-CSF moiety (to the extent possible) using enzymatic or alkaline treatment of PEG-G-CSF followed by mass spectrometry analysis of the PEG moiety. Several mass spectrometric techniques have been described for the rigorous characterization of PEGs and conjugates (e.g. Bagal et al. Analytical Chemistry 2008, 80:2408-2418).

   b. Physicochemical evidence of similarity of the chemical linkage between PEG and the G-CSF molecule. Approaches to consider include an evaluation of the ability,
or lack thereof, for acid, base, or carboxypeptidase treatment to hydrolyze the linkage or NMR analysis of a pegylated N-terminal peptide derived from PEG-G-CSF after peptidase treatment.

c. The levels of unconjugated PEG in MYL-1401H and US-licensed Neulasta, including both unreacted PEGylation reagent and free PEG, if any, produced upon cleavage of PEG from G-CSF. An evaluation of free PEG levels under forced degradation conditions should also be performed to support a demonstration of similar degradation rates.

2. You propose to use clinical and commercial lots of MYL-1401H in your analytical similarity assessment. If the clinical and commercial lots were manufactured by a different process, comparability between clinical and commercial lots should be demonstrated. The adequacy of these results will be a review issue.

3. The analytical similarity approach described in the meeting package does not appear to include comparative stability studies between MYL-1401H and US-licensed Neulasta. As we communicated in a meeting held on 2/17/2015, these studies are part of the analytical similarity exercise. You should provide a scientific justification for the conditions used in the comparative stability studies (e.g. high temperature, freeze thaw, light exposure, and agitation) and the product quality attributes selected for the analysis. You should select stability conditions that are relevant to your product. Please refer to ICH Q1A and ICH Q5C for additional guidance.

4. In Table 5 for the quality attribute “related protein variants”, you propose to assess total pre-peaks and total post-peaks. In addition to this analysis, you should characterize and determine the levels of the individual species (e.g. dimers, oxidation, N-terminal truncation, etc.) monitored by the different separation methods and assess their impact on biological activity.

Discussion:

The Sponsor reviewed their overall approach for the characterization of product variants (slides 20-25). They described the variants identified to date in MYL-1401H and US-licensed Neulasta using their assays. FDA recommended that they provide in the BLA the justification for the overall approach to characterize product variants, and that they also consider the age of their proposed biosimilar and the reference product lots used in their characterization of product variants. The Sponsor agreed to these recommendations.

For the assessment of the biological activity of the product variants, the Sponsor proposed a risk-based approach. FDA indicated this would be a review issue.

The Sponsor further described the plan for PEG characterization (Slides 26-28). The FDA identified no issues with the plan as described except to emphasize that the same
analytical approach should be used for both MYL-1401H and the reference product lots in order to allow for an assessment of analytical similarity of the PEG moiety.

5. Consider including orthogonal methods for assessment of intact molecular mass and purity (e.g. SDS-PAGE).

6. For your Tier 1 equivalence test, all reference product lots can be used to compute the confidence interval and to estimate the equivalence margin. In general, we recommend using a similar number of lots of the proposed biosimilar and the reference products. When the number of reference product lots is much larger than the number of proposed biosimilar lots (e.g., more than 50%), we recommend the following equation for sample size imbalance adjustment to calculate the confidence interval of the mean difference:

\[
(\bar{X}_B - \bar{X}_R) \pm t_{1-\alpha, df^*} \times \sqrt{\frac{S^2_B}{n_B} + \frac{S^2_R}{n_R^*}}
\]

where \( n^*_R = \min(1.5 \times n_B, n_R) \), \( n_B \) and \( n_R \) are respectively the number of the proposed biosimilar lots and the number of the reference product lots; \( \bar{X}_B \) and \( \bar{X}_R \) are respectively the sample mean of the proposed biosimilar lots and the sample mean of the reference product lots; \( S^2_B \) and \( S^2_R \) are respectively the sample variance estimated by all the biosimilar lots and the sample variance estimated by all the reference lots; \( t_{1-\alpha, df^*} \) is \( 1-\alpha \) quantile of the \( t \)-distribution with degrees of freedom \( df^* \) where \( df^* \) can be approximated by the Satterthwaite method. If the number of the proposed biosimilar lots, \( n_B \), is 50% more than the number of reference product lots, \( n_R \), a similar approach can be applied with \( n_B^* = \min(1.5 \times n_R, n_B) \) for the confidence interval calculation.

**Question 2:**

Does the Agency agree with the proposal of establishing shelf life based on

**FDA Response to Question 2:**

No, we do not agree that the shelf life of MYL-1401H can be established from

You indicate your intention to establish a DP shelf life of 24 months. In your 351 (k) BLA, a minimum of 6 months of stability data should be provided on at least three process validation lots (ICH Q5C). Stability data from clinical and development lots may be used to support shelf life of your product provided you submit data to demonstrate comparability between process validation and clinical and development lots, and the products were stored in a
container closure system which properly represent the final commercial container closure system and the products were stored under the same conditions. The actual shelf-life of your product will be determined at the time of licensure.

Please be aware that you may provide updated stability data during review of your 351 (k) application, however, the last stability data update should be provided 4 months prior to the BsUFA action date.

Discussion (Slides 29-30):

The Sponsor clarified that FDA indicated that the information in their meeting package was unclear with respect to manufacturing changes between development, clinical and process validation batches and reiterated that if manufacturing changes were made, comparability data will need to be submitted.

FDA reiterated that Mylan should provide at least 6 months of stability data on at least three batches of final container product representative of commercial manufacture, including container closure system and storage conditions. Mylan should provide justification in the BLA supporting that the batches used to support the shelf life of the product (e.g. development and clinical batches) are representative of commercial manufacture. Final determination of the shelf life of MYL-1401H will be a review issue.

2.2. BPD Type 4 - CMC

Question 1:

Mylan is planning to complete MYL-1401H’s drug substance and drug product manufacturing process validation and data from the initial analysis (T0) will be submitted in the BLA. Stability studies for the same will be initiated and continued as per the stability program. Stability data from representative clinical and development lots at 24 months (24M) will be submitted in the BLA. Mylan proposes to update the stability data of both process validation and development lots during the review of the BLA. Does the Agency agree with this approach?

FDA Response to Question 1:

See our response to Question 2 of the BPD Type 2 meeting package.

Discussion:

No discussion occurred.

2.3. BPD Type 4 - Clinical
**Question 2:**

Does FDA agree with Mylan’s planned approach for the data to be included in the BLA and in the 120-Day Safety Update Report?

**FDA Response to Question 2:**

We do not agree with your planned approach for data submission. Safety and immunogenicity data from cycles 1 – 6 of study MYL-1401H-3001 should be included in your initial submission to support your BLA application. The data from the day 168 additional time point may be submitted in a 120-day safety update report.

In a meeting held on October 22, 2015, the Agency communicated that the general study design of MYL-1401H-1002 (a two-dose parallel arm study in healthy subjects) for assessment of immunogenicity seemed reasonable. However, we did not agree with the approach for assessing immunogenicity which was based on a demonstration that no more than 13% of subjects will develop anti-drug antibodies (ADA) in either arm if no immunogenicity events were observed. We recommended that you revise your study to demonstrate that the rates of ADA are similar for MYL-1401H and US-licensed Neulasta and that you provide a revised protocol for review. We did not receive your revised protocol.

The data from study MYL-1401H-1002 which includes 25 patients per arm may be insufficient on its own to demonstrate that the rates of ADA are similar for MYL-1401H and US-licensed Neulasta to support a demonstration of no clinically meaningful differences. You may be able to leverage the immunogenicity data from study MYL-1401H-3001) with proper justification that these data support a demonstration that there are no clinically meaningful differences in the immunogenicity response between MYL-1401H and US-licensed Neulasta. The adequacy of the data would be a review issue.

Please refer to the meeting minutes from the BPD type 2 meetings held on Feb 17, 2015 and Oct 22, 2015 regarding the need to provide adequate data or information to scientifically justify the relevance of data from an animal study or a clinical study using EU-approved Neulasta to support a demonstration of biosimilarity to US-licensed Neulasta.

The Agency will consider the totality of the evidence submitted in your application, (including human PK and PD data, clinical immunogenicity data, and comparative clinical study data, safety and risk-benefit analyses) to make a determination if the submitted data support a demonstration of biosimilarity between your proposed biosimilar product and the reference product.
Discussion (Slides 6-17):

The Sponsor agreed to submit all safety and immunogenicity data for cycles 1-6 of protocol MYL-1401H-3001 as part of the original 351(k) BLA. They also described the ADA assays that they developed for assessment of ADAs, including screening, confirmatory, and neutralizing assays and assays to assess the PEG and GCSF components of the molecule. They further reviewed the results of the ADA assays available to date, and described the analyses of the data that will be presented in the BLA, including presenting the data on a per patient basis. The Agency agreed with the proposed approach for immunogenicity assessments and analyses plans as described by the Sponsor.

Question 3:

The clinical program for MYL-1401H includes 2 clinical studies in healthy subjects and 1 confirmatory efficacy and safety study in patients with breast cancer. Considering the differences in study designs, study populations, and dose regimens across these studies, Mylan proposes to present the efficacy and safety results in the form of clinical summaries within Module 2 (i.e., Modules 2.7.3 and 2.7.4) without formal integrated data analyses of efficacy and safety. Does the Agency agree with this proposal?

FDA Response to Question 3:

Yes, we agree with your proposal. However, please provide an integrated dataset, at least for demographics and adverse events, in your eCTD submission for FDA reviewer use.

Discussion:

No discussion occurred.

Additional Comments:

CMC:

You state that pairwise comparisons of MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta will be used to support the analytical portion of the scientific bridge to justify the relevance of comparative data generated using EU-approved Neulasta. Your BLA should clearly indicate the lots of MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta that you will use to establish the analytical bridge. All three pair-wise comparisons (US-licensed Neulasta to MYL-1401H, EU-approved Neulasta to MYL-1401H, and US-licensed Neulasta to EU-approved Neulasta) should meet the pre-defined analytical similarity acceptance criteria.
Additionally, we recommend you submit a comprehensive use-related risk analysis or provide your determination regarding the necessity of a human factors (HF) validation study. Please note that a comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

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

The risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency. Please note we will need 120 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.
The following items are needed to inform the review of your HF study protocol:

- Side-by-side graphical depiction of proposed presentation to corresponding presentation for the Reference Product (RP)
  - Include a discussion of similarities and differences between the physical external operating principles and design features for both presentations
- A summary of preliminary analyses and evaluations, including formative studies;
  - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product;
- Detailed HF validation study protocol to include the following elements:
  - Description of intended product users, uses, use environments, and training (if applicable) for commercial product
  - Graphical depiction and written description of product user interface
  - Summary of known use problems with previous models or similar products
  - User task selection, categorization (e.g., critical) and prioritization
  - Validation testing details
    - Objective(s)
    - Type of testing (simulated or actual use)
    - Test environment and conditions of use
    - Training provided to participants and rationale for how it corresponds to real-world training (if applicable)
    - Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations
    - User tasks and use scenarios that will be studied
    - Description of data to be collected and methods for documenting observations and interview responses
    - Methods for root cause analysis of all use errors, difficulties, close calls
    - Definition of performance success and performance failure
    - Moderator transcript
- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study
  - If an IFU is proposed, see next bullet.
- In general, your proposed IFU should incorporate relevant information from the IFU for US-licensed Neulasta and present the information in a similar manner. Your proposed IFU may differ from the IFU for US-licensed Neulasta where, for example, modified language or images are needed to accurately describe your proposed product. If you believe that other changes would be useful, we recommend that you discuss your proposed changes with the Agency and along with any additional data that might support such changes. Additionally, if you plan to conduct a Human Factors study to support your product, you should seek
FDA input on your proposed IFU when you submit your HF study protocol for FDA review. However, it should be noted that a full and final review of proposed product labeling, including the IFU, will occur in the context of your planned 351(k) BLA submission, and may be informed by the HF study findings you submit or other relevant data in the submission.”

- Five intend-to-market samples of product that will be tested in the HF validation study

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at:

Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:

Discussion (slide 18):

The Sponsor stated that they will be using the Ultra-Safe Plus Passive Needle® Guard which is already in use with numerous approved products. Therefore, they proposed to provide a use-related risk analysis and to provide a rationale to justify not performing a human factors study. FDA clarified that the proposal will need to cover administration across all age and weight groups that fall under the proposed indications. FDA could not comment further on the Sponsor’s proposal without reviewing the details of the plan and recommended that the Sponsor submit a comprehensive use-related risk analysis and justification to the IND for review prior to submission of the BLA. The
Sponsor stated they plan to request a deferral for the development of a pediatric presentation to post-approval as part of their PSP. FDA asked the Sponsor to include that information in the submission of the use-related risk analysis. FDA acknowledged the Sponsor’s proposed 351(k) BLA submission timeline and will work with the Sponsor to review and comment on the proposed use-related risk analysis in a timely manner.

**Product Quality Microbiology:**

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 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). Please 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 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. Microbial data from three successful product intermediate hold time validation runs at manufacturing scale should be provided. 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).

c. Data demonstrating microbial control after column resin and UF/DF membrane sanitization during reuse and storage (3.2.S.2.5).

d. Bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).

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

f. Drug substance bioburden and endotoxin release specifications (3.2.S.4).
g. Summary report and results from bioburden and endotoxin test methods qualification performed for in-process intermediates and the drug substance should be provided (3.2.S.4). In addition, the test methods should be described.

III. 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.

a. Provide the following information in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:
   • Description of the manufacturing areas and fill line, including air classifications.
   • Description of the environmental and personnel monitoring programs.
   • Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
   • Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), the pressure limit or flow rate limit for sterilizing filtration, and the acceptance criterion for post-use integrity testing.
   • Parameters for filling and stoppering.
   • Processing and hold time limits, including the time limit for sterilizing filtration.

b. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:
   • Bacterial filter retention study for the sterilizing filter.
   • Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.
   • Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
• Isolator decontamination, if applicable.
• Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
• 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 that demonstrate that the pre-filled syringe plunger movement during air transportation does not impact product sterility.

c. Provide the following information regarding drug product testing:
• Qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate. In addition, the test methods should be described.
• Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).
• Low endotoxin recovery studies. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin standard (CSE or RSE) into undiluted drug product and testing for recoverable endotoxin over time.
• Container closure integrity testing information and data. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).

Discussion (Slide 19):

The FDA indicated that the shipping validation protocol must be provided in the initial BLA submission and that internal Agency discussion regarding the acceptable timeframe for a delayed submission of the shipping validation study report would be needed. The Agency would provide further advice on this matter as a post-meeting note.

Post-meeting note:

The shipping validation data will be needed in order to complete the review of drug product sterility assurance data and information. Failure to demonstrate that the sterile barrier is maintained during worst-case shipping conditions (including air transportation) would be an approvability issue. Therefore, in order to allow sufficient time for the Agency to determine whether the application is fileable, the shipping
validation study data should be submitted no later than 45 days after submission of the BLA.

The shipping validation study should be performed with the commercial container closure system and should be designed to validate the entire in-process control range for plunger position. A developmental lot which meets these criteria may be used for the study instead of a process validation lot.

**CDRH Comment:**

Please note that due to the lack of information in the briefing document about the prefilled syringe, we will not be able to provide comments on the acceptability of the syringe that you propose to use in this combination product.

**Additional Meeting Discussion:**

FDA asked the Sponsor to identify the drug substance and drug product manufacturing sites. The Sponsor agreed to provide the list to the FDA by email.

### 3.0 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/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 PLLR 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.
DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide
feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

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.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
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<tr>
<td>2.</td>
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<td></td>
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</tr>
</tbody>
</table>
Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

**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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Line listings, by site)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
  ➕ [m5]
  ➕ datasets
  ➕ bimo
  ➕ site-level
```

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.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

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

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1 Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

1. The Sponsor will submit the comprehensive use-related risk analysis and justification to the IND for review prior to submission of the BLA. Additionally, the Sponsor will include information regarding their plan to defer the development of a pediatric presentation to post-approval in the submission of the use-related risk analysis.

2. The Sponsor will email the list of drug substance and drug product manufacturing sites to the RPM.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached slide deck for the meeting.
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
06/30/2016