# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761045Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND109743

**MEETING MINUTES**

Sandoz Inc.
Attention: John M. Pakulski, RPh
Head Regulatory Affairs
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LA-EP2006.

We also refer to the meeting between representatives of your firm and the FDA on October 15, 2014. The purpose of the meeting was to discuss the planned submission of LA-EP2006 as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim) under Section 351(k) of the Public Health Service Act (PHS Act).

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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574).

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Biosimilar |
| **Meeting Category:** | Biosimilar Biological Product Development (BPD) Type 3 |
| **Meeting Date and Time:** | Wednesday, October 15, 2014; 2:00-3:30 PM Eastern |
| **Meeting Location:** | FDA |
| **Application Number:** | 109743 |
| **Product Name:** | LA-EP2006 |
| **Indication:** | LA-EP2006 is being developed for the same indication as approved for US-licensed Neulasta |
| **Sponsor/Applicant Name:** | Sandoz, Inc. |
| **Meeting Chair:** | Albert Deisseroth, MD, PhD; Clinical Team Leader |
| **Meeting Recorder:** | Rachel McMullen, MPH, Regulatory Project Manager |

## FDA ATTENDEES

**Division of Hematology Products**:
Edvardas Kaminskas, MD, Deputy Director
Albert Deisseroth, MD, PhD, Clinical Team Leader
Nicole Gormley, MD, Medical Officer
Rachel McMullen, MPH, Regulatory Project Manager
Beatrice Kallungal, BS, Senior Regulatory Project Manager

**Division of Hematology Oncology Toxicology:**
Christopher Sheth, PhD, Acting Team Leader
Pedro DelValle, PhD, Pharmacologist/Toxicologist

**Office of Biotechnology Products:**
Juhong Liu, PhD, Lead Biologist
Cristina Ausin, PhD, Senior Staff Fellow
Cecilia Tami, PhD, Biologist
Susan Kirshner, Ph.D., Associate Chief, Laboratory of Immunology
Joao Pedras-Vasconcelos, PhD, Visiting Associate
Emanuela Lacana, PhD, Associate Chief, Laboratory of Chemistry

**Office of Clinical Pharmacology:**
Nam Atiqur Rahman, PhD, Director, Office of Clinical Pharmacology, DCP5
Sarah Schrieber, Pharm D, Pharmacologist

**Office of Manufacturing and Product Quality:**
Patricia Hughes, PhD, CMC Microbiology Lead
Bo Chi, PhD, CMC Microbiology Reviewer

**Office of Biostatistics:**
Lei Nie, PhD, Lead Statistician
Chia Wen Ko, PhD, Statistical Reviewer

**Office of New Drugs Therapeutic Biologics and Biosimilars Team:**
Leah Christl, PhD, Associate Director for Therapeutic Biologics
Sue Lim, MD, Senior Staff Fellow

**Office of Surveillance and Epidemiology:**
Yelena Maslov, Pharm D, Team Leader

**Office of Device Evaluation:**
Keith Marin, Senior Regulatory Research Officer

**Office of Regulatory Policy:**
Janice Weiner, JD, MPH, Senior Regulatory Counsel

**SPONSOR ATTENDEES**
John Pakulski, Head Regulatory Affairs, US Biopharmaceuticals
Zhengyu Liu, Team Leader Regulatory Affairs, US Biopharmaceuticals
Mark McCamish, Global Head Biopharmaceuticals & Oncology Injectables Development
Ingrid Schwarzenberger, Head Global Regulatory Affairs Biopharmaceuticals
Catherine Cornu-Artis, Head Global Clinical Development Biopharmaceuticals
Sigrid Balser, Global Head Biostatistics and Clinical Submission Management
Wolfgang Fischer, Head Global Project Management
Pritibha Singh, Biostatistician
Andrej Skerjanec; PK/PD Senior Expert
Ulrich Kronthaler, Global Preclinical Development Manager
Stefan Kramer, Global Program Leader
Tobias Kessler, Regulatory CMC Manager
Claudia Sailer, Team Leader Regulatory Affairs
Gregor Schaffar, Lab Head Bioanalytics
Michael Gschwandtner, Head Global Device Development
Wolfgang Wieder, Head Analytical Laboratories 4
Simona Jevsevar, Department Head Technical Development

## 1.0 BACKGROUND:

Sandoz requested a Biological Product Development (BPD) Type 3 meeting on June 16, 2014 to discuss the planned submission of LA-EP2006 as a proposed biosimilar to US-licensed Neulasta under Section 351(k) of the Public Health Service Act (PHS Act).

On October 14, 2014, FDA provided Sandoz with preliminary responses to the questions contained in the meeting information package.

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 Sandoz 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).

Discussion during the meeting and additional post-meeting responses from FDA are shown in regular font.

## 2.0 SPONSOR QUESTIONS AND FDA RESPONSES:

***Question 1 – CMC: Assessment of similarity on the analytical level***

*Does the Agency agree that the results of the comparative analytical similarity study indicate high analytical similarity between the proposed biosimilar LA-EP2006 and the US-reference product Neulasta?*

***FDA Response:***

**No, we do not agree. You have not provided sufficient information to support a demonstration that LA-EP2006 and US-licensed Neulasta are highly similar.**

**Based on the CMC information you provided, we identified the following issues:**

**a. You proposed to conduct analytical similarity studies that include testing side-by-side five batches of LA-EP2006 drug product used in nonclinical and clinical studies, two batches of the reference product (US-licensed Neulasta) and three batches of the comparator product EU-approved pegfilgrastim. However, FDA notes from page 64 of the meeting package that a total of 23 batches of both US-licensed Neulasta and EU-approved pegfilgrastim have been analyzed. You should provide a scientific justification for the number of lots of LA-EP2006, US-licensed Neulasta, and EU-approved pegfilgrastim used for the analytical similarity assessment performed to support licensure. The submission should include the basis for the selection of the specific lots being studied for those assays where only a subset of the total lots will be assessed, and provide the approximate ages of the lots being compared in each assay. The US-licensed Neulasta and EU-approved pegfilgrastim lots should ideally be selected across the shelf-life of the product. Your analytical similarity report includes five LA-**

**EP2006 drug product lots. However, you manufactured, at least three additional LA-EP2006 drug product lots (0834 (b) (4) 134, 0834 (b) (4) 142, and 0834 (b) (4) 146). You should include all available LA-EP2006 lots as part of the analytical similarity assessment or provide a justification for not including all available LA-EP2006 lots.**

**b. You did not provide information regarding the capability of the analytical assays used in your similarity assessment. Sensitivity, specificity and precision of the assays can affect the amount and type of additional data needed for the analytical similarity assessment. For example, we noted significant variability in the in vitro bioassay results. Because you did not provide any information regarding the precision of this assay, it is not possible to evaluate if the differences in results are due to assay variability or due to differences between the products. It may be necessary to improve your in vitro bioassay if we determine that its precision is not adequate to monitor the potency of LA-EP2006.**

**c. You cited potential interference of PEG in the detection of product variants as part of the determination of analytical similarity between LA-EP2006, US-licensed Neulasta, and EU-approved pegfilgrastim. Your marketing application should include sufficient data to demonstrate that the analytical assays are adequate and the presence of PEG does not interfere with the detection of any potential impurities and product variants.**

**d. As recommended in draft guidance: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf ), in addition to product-related impurities and product-related substances, process-related impurities such as host cell proteins should be part of the similarity assessment because of the potential impact on the safety, purity, and potency of the product. We do not expect the process-related impurities present in LA-EP2006 to "match" those observed in the reference product (US-licensed Neulasta). However, process-related impurities in LA-EP2006 should be assessed side-by-side with the reference product. We recommend that you perform a risk-based assessment regarding any differences in process-related impurities identified between LA-EP2006 and the reference product. If the manufacturing process used to produce LA-EP2006 introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary to evaluate the potential risk of any differences, and any differences should be justified. The adequacy of the risk-based assessment will be a review issue**

**Discussion (Refer to slides 22-23):**
Sandoz indicated that the side-by-side comparison of LA-EP2006 and US-licensed Neulasta using the HCP assay developed for LA-EP2006 was not possible and is not

relevant. Sandoz used a different cell line from US-licensed Neulasta for development of LA-EP2006. As the assay for HCP was developed specifically for their product, Sandoz questioned the relevance of this assay to test for HCP in US-licensed Neulasta.

The Agency acknowledged the limitations of the assay but stated the information could still be helpful as part of the overall evaluation of similarity. FDA will evaluate the results of this side-by-side comparison as supportive information in the analytical similarity assessment.

**e. Regarding the host cell protein assay, provide a summary description of the source (in-house or commercial) of the antiserum used for detection of host cell protein impurities (HCPs). FDA recommends developing a cell-line specific HCP detection reagent. For licensure, the anti-HCP antiserum needs to be qualified for its ability to detect potential HCP impurities. The data need to include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis (or another similarly sensitive assay) using the antiserum employed in the assay. It is FDA's experience that analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently sensitive for this purpose**

**f. You should revise your analytical similarity assessment and your stability protocols to include quantification of free PEG as part of the evaluation of the purity of LA-EP2006.**

**Discussion: (Refer to slides 20-21):**

Sandoz indicated that free PEG is efficiently removed (b) (4) In addition, as part of its stability program, Sandoz monitors hydrolysis of the PEG moiety at the intended storage conditions by measuring the levels of unpegylated filgrastim. Sandoz stated that no increase in unpegylated filgrastim has been observed in their stability studies.

The Agency stated that adequate information to confirm that the manufacturing process is able to remove free PEG efficiently should be submitted. This includes assay validation data on the SE-HPLC with laser light scattering detection (SEC-MALLS). The Agency asked whether Sandoz evaluated the capability of the process to remove amounts of free PEG larger than those removed under normal manufacturing conditions. Sandoz responded that the amount of PEG in the reaction is (b) (4) the amount of G-CSF and therefore in large excess, and that data supporting the validation of PEG removal will be included in the BLA.

**g. As part of the analytical similarity assessment, you should include an evaluation of the critical quality attributes of the PEG moiety, including average molecular weight and polydispersity, in LA-EP2006, US-licensed Neulasta, and EU-approved pegfilgrastim.**

**h. In addition to the data included in the analytical similarity report (BP94913), your meeting package included additional characterization data comparing LA-EP2006 and US-licensed Neulasta (report BP100213, titled Elucidation of structure and other characteristics) and additional stability data for EU-approved pegfilgrastim and US-licensed Neulasta lots (report BP07011, titled Comparability report: Comparison of batches of EU-approved pegfilgrastim and US-licensed Neulasta). You should integrate all comparative analytical data generated during development as part of the analytical similarity assessment if the corresponding analytical assays are adequate.**

**i. The analytical similarity assessment between EU-approved pegfilgrastim and US-licensed Neulasta demonstrated that you are able to quantify the different RP-HPLC pre- and post-peaks. However, in the analytical similarity report (BP94913) you provided the RP-HPLC results as grouped pre-peaks and post-peaks. Because the different species detected by RP-HPLC may have different effects in terms of safety and efficacy, you should establish individual acceptance criteria for each pre- and each post-peak, both as part of release and stability testing and as part of analytical similarity assessments, and comparability studies conducted after introducing changes in the manufacturing process.**

**Discussion (Refer to slides 24-27):**

Sandoz proposed to separate the reverse phase chromatography (RPC) acceptance criteria for impurities into the sum of pre- and sum of post-peaks. Sandoz presented information to support that there is only one product variant eluting in the pre-peak area. Two of the three product variants eluting in the post-peak area are not stability indicating and are controlled (b) (4)

The Agency agreed with Sandoz's proposal to establish separate RPC acceptance criteria for impurities as the sum of pre- and sum of post-peaks if Sandoz provides adequate information to demonstrate that the control (b) (4) . If, upon review of the data, the Agency does not agree with the proposed control strategy, Sandoz will be required to establish separate acceptance criteria for the three product variants eluting in the post-peaks.

**j. Regarding the evaluation of the analytical similarity of LA-EP2006 and US-licensed Neulasta in terms of size, you used SEC to separate the main product from high molecular weight (HMW) variants, low molecular weight (LMW) variants, and aggregates. You confirmed the size of the different products using orthogonal methods such as multiple angle laser light scattering (MALLS), asymmetric flow field-flow-fractionation (AF4), and dynamic light scattering (DLS). However, you should also use orthogonal methods to confirm that SEC is able to accurately measure the amount of HMW variants and aggregates in LA-EP2006 and in US-licensed Neulasta.**

**k. You used mechanical stress to induce degradation and compared the effect of this stress on LA-EP2006 and EU-approved pegfilgrastim in terms of aggregates and particle formation and potency. Because you did not include US-licensed Neulasta in the mechanical stress study, we were not able to evaluate if mechanical stress has different effects on LA-EP2006 compared to US-licensed Neulasta. Therefore, to support the analytical similarity assessment between LA-EP2006 and US-licensed Neulasta, you should conduct the mechanical stress study using LA-EP2006 and US-licensed Neulasta.**

**l. You should consider evaluating additional stress conditions such as oxidation, light exposure, and freeze-thaw as part of the analytical similarity assessment. Ideally, you should choose stress conditions your product is likely to be subjected to. Please refer to ICH Q1A and ICH Q5C for additional guidance.**

**m. Regarding the physicochemical characterization comparing EU-approved pegfilgrastim and US-licensed Neulasta, you should include the following additional information:**

**i. Physicochemical and biological characterization results, including stability data, for all EU-approved pegfilgrastim lots used in nonclinical and clinical studies LA-EP06-012, LA-EP06-013, LA-EP06-301, and LA-EP06-302.**

**ii. A justification for the differences in circular dichroism and mass spectrometry results for any EU-approved pegfilgrastim and US-licensed Neulasta lots included in reports BP94913 and BP07011.**

**iii. Quantitative chromatographic results (including percentage of peak areas and peptide masses) for EU-approved pegfilgrastim and US-licensed Neulasta lots analyzed by peptide mapping as part of the demonstration of analytical similarity between EU-approved pegfilgrastim and US-licensed Neulasta.**

**Discussion (Refer to slides 28-29):**

Sandoz indicated that peptide mapping is less powerful than other direct methods for detection and quantification of individual product variants. Sandoz proposed to use other direct methods.

The Agency agreed with Sandoz's proposal to use peptide mapping as an identity assay and not as a purity test.

**Regarding your statistical approach to support the analytical similarity assessment and the similarity acceptance criteria, we have the following comments:**

**n. There is insufficient information regarding your proposed statistical method to support a demonstration that LA-EP2006 is highly similar to US-licensed Neulasta and to support your bridging data to scientifically justify the relevance to comparative data with EU-approved pegfilgrastim (see response to question 3).**

**o. We do not agree with your proposal to use the combined data of US-licensed Neulasta and EU-approved pegfilgrastim to establish or justify the similarity acceptance criteria for your proposed biosimilar product. Information to demonstrate analytical similarity should be based on a direct comparison of LA-EP2006 to the US-licensed reference product. Use of similarity acceptance criteria that are derived from the range of combined data from analysis of US-licensed Neulasta and EU-approved pegfilgrastim cannot, by itself, support a determination that LA-EP2006 is highly similar to US-licensed Neulasta. An assessment against criteria based on the US-licensed reference product should be performed.**

**If the data generated by analysis of US-licensed Neulasta and EU-approved pegfilgrastim were combined, intra-product variability in addition to inter-product variability would be introduced into the statistical testing and may make the test unable to discriminate any important analytical differences between LA-EP2006 and US-licensed Neulasta. In addition, combining data may inappropriately allow for a wider range of quality attributes than observed for US-licensed Neulasta lots.**

**p. We do not agree with your proposed approach of comparing the "values" of the tested product with acceptance criteria derived from "several originator batches" as described in your meeting package. It is unclear what the terms in quotation marks mean. Furthermore, you didn't provide information on how the acceptance criteria will be determined, but instead cited several references in Table 7-1 , for example SOP 83.554 and SOP 83.557. In many cases you did not conduct an appropriate statistical analysis to support your proposed analytical similarity assessment. See FDA's comment q.**

**q. We currently recommend that you use a statistical approach to evaluate quality attributes of your proposed biosimilar product that is consistent with the risk assessment principles set forth in the International Conference on Harmonization Quality Guidelines Q8, Q9, Q10, and Q11. Consistent with the principles set forth in these guidelines, your program should implement an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used. One approach to determining the tier to which a particular quality attribute would be assigned would depend upon a criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity with quality attributes being assigned to tiers commensurate with their risk.**

**For your program, equivalency testing would be recommended for quality attributes with the highest risk ranking (Tier 1) and generally would include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought. We recommend that you consider the use of quality ranges (mean +/- X σ, where X should be appropriately justified) for assessing quality attributes with lower risk ranking (Tier 2), and an approach that uses raw data/graphical comparisons for quality attributes with the lowest risk ranking (Tier 3).**

**In addition to criticality, other factors should be considered in assigning quality attributes and assays to a particular tier using this approach. This approach includes, but it is not limited to, the levels of the attribute in both the reference product and proposed biosimilar product (as determined by your testing), the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute.**
**FDA also recommends that you carefully assess your analytical similarity plan to identify and address any other factors that could potentially impact the ability to demonstrate that LA-EP2006 is highly similar to the reference product. This could include, for example, considering the ages of the LA-EP2006 and reference product lots tested, optimizing assays and pre-specifying the criteria under which wider similarity acceptance criteria for a particular assay would be considered appropriate.**

**We think it would be appropriate for you to consider a statistical approach, such as the one set forth below based on FDA's current thinking on the topic, to evaluate certain quality attributes of your proposed biosimilar product and the reference product. You may propose alternative statistical approach(es) to evaluate quality attributes and support a demonstration that LA-EP2006 is highly similar to US-licensed Neulasta (the reference product).**

**Further, we note that while a statistical approach to evaluate quality attributes of a proposed biosimilar product may be considered in support of a demonstration that the proposed biosimilar product is highly similar to the reference product, FDA's determination that a proposed biosimilar product is highly similar to the reference product will be based upon the totality of the evidence relevant to the assessment.**

**A potential approach for the different statistical tiers is described below:**

i. **Tier 1 (Equivalence Test): One needs to test against the following null hypothesis.**
**$H_0 : \mu_B - \mu_R \leq -\delta \quad or \quad \mu_B - \mu_R \geq \delta$, where $\mu_B$ and $\mu_R$ are the mean responses of the proposed biosimilar and reference product lots, respectively, and $\delta > 0$ is the equivalence margin.**

**ii. Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if the (1-2$\alpha$)100% two-sided confidence interval of the mean difference is within (– $\delta$, $\delta$). In this context, the equivalence margin, $\delta$, would be a function of the variability of the reference product as identified in studies by the biosimilar applicant ($\sigma_R$).**

**iii. Tier 2 (Quality Range Approach): The quality range of the reference product for a specific quality attribute is defined as $(\hat{\mu}_R - X\hat{\sigma}_R, \hat{\mu}_R + X\hat{\sigma}_R)$, where the standard deviation multiplier (X) should be appropriately justified.**

**iv. Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if a sufficient percentage of test lot values (e.g. 90 percent) fall within the quality range.**

**v. Please note that each lot contributes one value for each attribute being assessed. Thus, $\sigma_R$ refers to the standard deviation of those lot values of the reference product.**

**vi. Ideally, the reference variability, $\sigma_R$, should be estimated from testing different lots than those used in statistical equivalence test. This may be a challenge when there are a limited number of lots. The sponsor should provide a plan for how the reference variability, $\sigma_R$, will be estimated with a justification for the approach and identify the lots that will be used.**

**vii. We would also recommend that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot, and that the same lots be used for equivalence testing, quality range testing, and visual assessment of graphical displays.**

**viii. Please note that high assay variability would not be a justification for a large $\sigma_R$. In such a situation, the assay would need to be optimized and/or the number of replicates increased to reduce variability.**

**ix. In cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range.**

**One potential statistical approach to evaluate quality attributes is based on a standard statistical test of equivalence with the margin defined as a function of the reference product variability (e.g., $c * \sigma_R$). The constant c would be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and the reference product, when a moderate number of reference product and biosimilar lots are available for testing. If, for example, we selected $\delta = 1.5$ $\sigma_R$ for all sample sizes used in equivalence testing to illustrate this potential statistical approach, the test would yield a positive result if the 90%**

**confidence interval about the difference in sample means lies within (-1.5 $\sigma_R$, 1.5 $\sigma_R$). If 10 biosimilar and 10 reference product lots, this test would have approximately 84% power when the true underlying mean difference between the proposed biosimilar and reference product lots was equal to $\sigma_R$ /8, assuming a test with $\alpha = 0.05$.**

**Note that with this potential approach, the margin would be a function of the reference product variability as demonstrated in testing by the biosimilar applicant; therefore, a larger margin would be used for attributes with larger variability. In addition, the confidence level would depend on the number of lots available for testing. For a more limited number of lots, as described in your briefing package, you may consider calculating the confidence interval with a lower confidence level to ensure adequate power. In this situation, the lower confidence level would be expected to be appropriately addressed by the final manufacturing control strategy. In contrast, when a moderate or greater number of lots are available for testing, the equivalence test would be based on a 90% confidence interval.**

***Question 2 - Non-clinical: Suitability of non-clinical package to support biosimilarity***
*Does the Agency concur that the non-clinical package is suitable to support review of LA-EP2006 as a biosimilar product submitted under Section 351(k) of the PHS Act?*

***FDA Response:***

**The pharmacology/ toxicology package appears acceptable for a 351(k) BLA filing. However, a final determination as to whether pharmacology/toxicology data is sufficient to support demonstration of biosimilarity will be made during the BLA review.**

**Discussion:**
There was no discussion.

**Question 3 – Clinical: Phase 1 data package**
*Sandoz conducted a large three-arm PK/PD study in 279 healthy volunteers (93 subjects/arm) to assess PK bioequivalence and PD equivalence between LA-EP2006 and US-licensed and EU-authorized Neulasta. The study showed superimposable ANC responses, comparable CD34+ cell responses as well as similar PK profiles for all three products. While equivalence was demonstrated in terms of pharmacodynamics, the high variability of the pharmacokinetics being consistent across all three pegfilgrastim products (inter-subject CV% > 80%) precluded showing bioequivalence between any of the products.*
*Does the Agency agree that the PK/PD data generated in study LA-EP06-101 are sufficient to assess initial biosimilarity between LA-EP2006 and Neulasta?*

***FDA Response:***

**No, we do not agree that the data generated in Study LA-EP06-101 are sufficient to support a demonstration of biosimilarity between LA-EP2006 and US-licensed Neulasta. While you state that the reason for the observed PK findings is due to intersubject CV% >**

**80%, we do not agree that this explanation alone is sufficient to explain the observed results and support a demonstration that there are no clinically meaningful differences in safety, purity and potency between LA-EP2006 and US-licensed Neulasta.**

**You should address how analytical differences, including differences in potency and purity, could account for the observed differences in PK in Study LA-EP06-101. Other factors, including but not limited to, the contribution of the PEG moiety, and PK bioanalytical assay issues, should also be explored. Your justification and data to support that there are no clinically meaningful differences will be considered along with the other analytical, nonclinical, clinical PD similarity comparisons, and comparative clinical studies to support a demonstration of biosimilarity between LA-EP2006 and US-licensed Neulasta. Whether the totality of evidence is adequate to support a demonstration of biosimilarity will be a review issue.**

**We note that Study LA-EP06-101 did not include a pairwise comparison between the US-licensed Neulasta and EU-approved pegfilgrastim arms in the PD analysis. If you seek to use data from nonclinical or clinical studies comparing LA-EP2006 is biosimilar to EU-approved pegfilgrastim to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, you should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and establish an acceptable scientific bridge to the US-licensed reference product.**

**The type of bridging data needed to provide adequate scientific justification for this approach would likely include a bridging clinical PK and/or PD study as well as include a direct physico-chemical comparison of all 3 products: US-licensed Neulasta to LA-EP2006, EU-approved pegfilgrastim to LA-EP2006 and EU-approved pegfilgrastim to US-licensed Neulasta. All three comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity (see FDA response to question 1, paragraphs n, o, and p).**

**The adequacy of the PK and PD data from Study LA-EP06-101 will be a review issue.**

**Discussion (Slides 31-41:**
Sandoz stated that they intend to provide the Agency in a subsequent submission the results of a pairwise comparison of PD between the US-licensed Neulasta and EU-approved pegfilgrastim arms from Study LA-EP06-101, as was done in Table 5-2 on page 55 of the Briefing Book for the BPD Type 3 meeting for the comparison between LA-EP2006 with US-licensed Neulasta and between LA-EP2006 and EU-approved pegfilgrastim.

Sandoz presented information to support their position that there is high intersubject variability in PK between LA-EP2006, US-licensed Neulasta and EU-approved pegfilgrastim. They also presented information to evaluate the clinical relevance of observed PK differences by examining PD responses of other filgrastim-based products. Although Sandoz stated they could not currently identify a cause for the higher exposure observed with LA-EP2006, Sandoz stated that in any future submission they would address analytical differences (including but not limited

to the PEG moiety, PK bioanalytical assay issues, difference in delivered dose or content), which may or may not account for the observed PK differences in Study LA-EP06-101.

Sandoz stated their position that they would focus on a discussion of how there are no clinically meaningful differences resulting from the observed differences in PK results based on the demonstration of PD similarity in Study LA-EP06-101. In addition, Sandoz presented information to support their claim that the 6 mg dose used in Study LA-EP06-101 was not in the saturated part of the dose response curve.

***Question 4 – Clinical: Phase 3 data package***
*Sandoz conducted two independent Phase 3 studies in a total of 626 evaluable female patients (318 evaluable patients in study LA-EP06-301 and 308 evaluable patients in study LA-EP06-302) with breast cancer receiving myelosuppressive chemotherapy to assess the equivalence of LA-EP2006 or EU-authorized Neulasta with respect to the duration of severe neutropenia (DSN) in Cycle 1 as the primary endpoint. In both studies, equivalence in DSN was established with tight confidence intervals being well within the pre-defined limits along with highly similar results for all secondary efficacy, safety, and immunogenicity endpoints. Based on these data, Sandoz considers that the similarity in efficacy, safety, and immunogenicity between LA-EP2006 and Neulasta has been convincingly confirmed in a clinically relevant setting addressing any residual uncertainty.*
*Does the Agency concur?*

***FDA Response:***

**As a preliminary matter, the BPCI Act defines the "reference product" for a proposed biosimilar biological product to mean the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act). FDA's use of the term "reference product" or "Neulasta" refers to US-licensed Neulasta.**

**We do not agree that the results from Studies LA-EP06-301 and LA-EP06-302 are adequate to support a demonstration of no clinically meaningful differences. Refer to FDA's response to Question 3 regarding the types of data needed to support the relevance of comparisons to EU-approved pegfilgrastim in Studies LA-EP06-301 and LA-EP06-302 to support a demonstration of biosimilarity to US-licensed Neulasta, the issues regarding PK similarity, and advice regarding an adequate PD similarity analysis.**

**The adequacy of the two comparative clinical studies to support a demonstration of no clinically meaningful differences between LA-EP2006 and US-licensed Neulasta will be a review issue.**

**Discussion (Slides 42-46):**

Sandoz acknowledged FDA's comments. In addition, they affirmed the need to provide adequate scientific justification based on the advice provided in FDA's response to Question 3 to support the relevance of the data obtained using EU-approved pegfilgrastim.

***Question 5 - Regulatory: Use of EU-authorized Neulasta***
*In the two Phase 3 clinical trials and pre-clinical studies, EU-authorized Neulasta was used as active comparator. Physicochemical characterization and Phase 1 data comparing EU-authorized and US-licensed Neulasta indicate that EU-authorized Neulasta is representative of the US-licensed Neulasta.*
*Does the Agency agree that the bridging data to the US-licensed reference Neulasta described below are sufficient to justify the use of EU-authorized Neulasta in both Phase 3 trials and animal studies?*

***FDA Response:***

**FDA does not agree that the bridging data described in your background package is sufficient to justify the relevance of comparative data obtained using EU-approved pegfilgrastim in your two comparative clinical studies and animal studies. See FDA's response to Questions 1 and 3 regarding the use of EU-approved pegfilgrastim**

**Discussion:**
There was no discussion.

***Question 6 - Regulatory: Totality of Evidence***
*The sponsor considers the physicochemical, biological, non-clinical and clinical results for LA-EP2006 adequate to demonstrate biosimilarity to the US reference product Neulasta based on the totality-of-evidence provided, and thus to support licensure under the 351(k) PHS Act.*
*Does the Agency agree that the overall data package will be sufficient to allow review of the LA-EP2006 registration application under Section 351(k) of the PHS Act?*

***FDA Response:***

**FDA does not agree that the overall data package will be adequate to support a demonstration of biosimilarity. Refer to FDA's responses to Questions 1, 3 and 4.**

**We remind you that your 351(k) application must be complete at the time of filing. Please clarify if the application will include the 6 month safety follow-up data from Study LA-EP06-301.**

**Discussion:**
There was no discussion.

***Question 7 – CMC: Suitability of overall CMC package apart from the biosimilarity exercise***
*Sandoz provides herewith an overview on the totality of analytical CMC data generated in the course of the development of LA-EP2006. Does the Agency consider the data suitable to support review as a biosimilar product?*

*Furthermore Sandoz proposes to provide the CMC information with regards to the content and structure as outlined in the annotated table of content (see Section 7). Does the Agency concur with Sandoz's proposal?*

***FDA Response:***

**Regarding the suitability of the analytical CMC data, we have the following recommendations:**

**a.** (b) (4)

**b. The determination of comparability between LA-EP2006 drug substance manufactured at Sandoz GmbH (Kundl, Austria) and at Lek Pharmaceuticals (Slovenia) should include evaluation of release and stability results of LA-EP2006 drug product lots manufactured from these LA-EP2006 drug substance lots.**

**c. Because the potency of LA-EP2006 is a critical quality attribute, you should perform the in vitro bioassay at every time point of the stability protocols in all your comparability exercises.**

**d. Comments i and m(iii) in the response to Question 1, regarding RP-HPLC and peptide mapping results, apply to all comparability exercises.**

**In general we agree with the content and structure outlined in the annotated table of contents. However, a final determination of the adequacy of the information will be made upon review of the 351(k) BLA.**

**Please include the following additional information in the relevant CTD sections:**

| CTD section | Comment |
|---|---|
| **1.1.2 FDA form 356h** | **Indicate if the manufacturing and testing sites are ready for inspection and in operation during the review cycle.** |
| **1.3 Administrative information** | **A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections. Submit an environmental Assessment or a request for categorical exclusion.** |
| **3.2.S.4.3 Validation of analytical procedures** | **Assessment of hold time on recovery of spiked endotoxin in undiluted DS (if formulation contains polysorbate).** |

| | |
|---|---|
| **3.2.S.2.5 Process validation and/or evaluation** | **Three successful consecutive in-process product pool hold time validation runs at manufacturing scale from microbiology perspective**<br>**Information on reuse of membranes and columns, including microbiology data.** |
| **3.2.P.3.5 Process validation and/or evaluation** | • **Bacterial filter retention study report for the sterilizing filter**<br>• **Hold time validation at scale from microbiology perspective**<br>• **Isolator decontamination, if applicable**<br>• **A description of the routine environmental monitoring program**<br>• **Shipping validation data, including container closure integrity data** |
| **3.2.P.5.3 Validation of analytical procedures** | **Assessment of hold time on recovery of spiked endotoxin in undiluted DP** |
| **3.2.P.8.2 Post-approval Stability Protocol and Commitment** | **Container closure integrity test in lieu of sterility test on the stability program.** |

**In addition, section 351(k)(2)(A)(i)(II) of the PHS Act requires that a 351(k) application for a proposed biosimilar product include information demonstrating that the proposed biosimilar product and the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product. In FDA's draft Guidance for Industry, *"Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012),"* we explain: "If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays should reflect these mechanisms of action to the extent possible." Accordingly in your BLA submission, provide functional assays, including mechanism(s) of action, comparing LA-EP2006 to the reference product (US-licensed Neulasta) and include a justification that LA-EP2006 utilizes the same mechanism(s) of action as US-licensed Neulasta. This data and information should not be limited to the "primary" mechanism of action if other mechanism(s) of action are known or can reasonably be determined. Provide a summary of the data under Module 2.6 ("Nonclinical Written and Tabulated Summaries") and Module 2.3 ("Quality Overall Summary") with a link to the relevant section(s) of Module 3.**

**Discussion:**
There was no discussion.

***Question 8 - CMC: Stability data***
*Sandoz intends to provide 24 months stability data with the initial submission. Does the Agency concur with Sandoz´ proposal to submit 30 and 36 months stability data from currently ongoing stability studies at the time of the official acceptance of the initial 351(k) application?*

***FDA Response:***

**It is not clear when you intend to submit the 30 and 36 months stability data. Applications are expected to be completed at the time of submission. It is possible to reach agreements regarding delayed submission of certain components of the application during a BPD type 4 meeting. These components should be submitted not later than 30 calendar days after receipt of the original application. Therefore, it is possible to submit updates to the stability data within 30 days of the original submission and contingent upon previous agreement from the Agency during a BPD type 4 meeting. You may submit additional stability updates upon request from the Agency.**

**Your alternative proposal to submit a shelf extension protocol is acceptable. However, the adequacy of the protocol constitutes a review issue and will be determined upon evaluation of the submission.**

**Discussion:**
There was no discussion.

***Question 9 - CMC:*** (b) (4)

***FDA Response:***

(b) (4)

**Discussion:**
There was no discussion.

***Question 10 - CMC: Combination Product***
*Sandoz intends to provide objective evidence that the device components (syringe and needle safety device) of the product can be handled safely and effectively. This evidence is based on a handling study conducted by Novartis using the identical device components but different drug product. Does the Agency concur that the proposed extrapolation from the Novartis handling study is sufficient to provide evidence for the safety and efficiency of the device components of LA-EP2006?*

***FDA Response:***
**From a device handling perspective, you have adequately addressed our questions regarding additional information on the syringe being used.**

**However, we have concerns regarding whether Novartis's handling study can be extrapolated to this product due to multiple differences between the two products (i.e., indication, dose, patient population, and training) that ultimately may affect the results of the Human Factors study. However, we recommend you complete systematic evaluation of use-related risk. Based on that assessment, make a determination of the necessity of a Human Factors validation study (considering that identical device components with different drug products are already marketed and this patient population is familiar with the use of prefilled syringes). Please provide justification of your decision regarding the necessity of a Human Factors validation study.**

**Discussion:**
There was no discussion.

***Question 11 - Non-clinical: Data format***
*Does the Agency agree that for licensure of LA-EP2006 as a proposed biosimilar product to Neulasta under 351(k) of the PHS Act, the pharmacology and toxicology information can be submitted as study reports in PDF format, without providing additional electronic, individual animal data listings?*

***FDA Response*:**

**Your proposal to submit study reports in PDF format is acceptable.**

**Discussion:**
There was no discussion.

***Question 12 – Clinical: ISS and ISE***
*ISE/ISS are not planned. Rather, pooled data from the two Phase 3 studies will be included in the Summary of Clinical Efficacy and the Summary of Clinical Safety in Modules 2.7.3 and 2.7.4, and the statistical analysis plan (SAS) and post-text tables will be presented in Module 5.3.5.3 as described in the "Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (2009)." Does the Agency concur with this approach?*

***FDA Response:***

**This approach is acceptable.**

**Discussion:**
There was no discussion.

***Question 13 – Bioanalytical: Anti-Pegfilgrastim binding Assay***
*An anti-pegfilgrastim antibody assay has been developed and validated to detect antibodies against pegfilgrastim, including the characterization of the antigenic epitope (PEG, filgrastim). Is the validated anti-pegfilgrastim antibody assay acceptable for characterization of the immune response in clinical studies?*

***FDA Response:***

**Your anti-pegfilgrastim antibody screening assay is acceptable to assess for the presence of anti-pegfilgrastim binding antibodies in clinical samples. Your confirmatory assay is acceptable for demonstrating that the response is antigen specific. However, your data show that your rabbit anti-pegfilgrastim positive control antiserum only binds G-CSF and does not bind PEG. Therefore, this positive control is inadequate for in-study monitoring to support that your assay performs as expected with regards to detection of anti-PEG antibodies. You need to implement and validate an appropriate system suitability control for an anti-PEG confirmatory assay. Alternatively, you may develop and validate a different assay to test for the presence of anti-PEG antibodies in your clinical samples. An assay to detect anti-PEG antibodies will need to be provided to the Agency with the original 351(k) BLA for LA-EP2006.**

**Discussion:**
There was no discussion.

***Question 14 – Bioanalytical: Anti-Pegfilgrastim neutralizing Assay***
*All samples which are tested positive for anti-pegfilgrastim antibodies are further analyzed regarding their neutralizing capacity in a validated cell-based neutralizing antibody assay. Is the validated filgrastim neutralizing antibody assay acceptable for characterization of the neutralizing capacity of anti-pegfilgrastim antibodies in clinical studies?*

***FDA Response:***

**No, your approach to characterizing the neutralizing capacity of anti-pegylated G-CSF antibodies in clinical studies using a neutralizing antibody assay validated for G-CSF rather than pegylated G-CSF is not acceptable. You need to develop and validate an assay for use with pegylated G-CSF.**

**The lack of a suitable neutralization assay would result in an inadequate assessment of immunogenicity. If this issue is not resolved prior to submission of your 351(k) BLA, it may have implications for the fileability of your 351(k) BLA.**

**With regards to the anti-G-CSF neutralizing antibody assay validation report, we note that analysis of your data showed significant differences between analysts that resulted in the use of analyst-specific cut points. This approach is not acceptable, as it indicates that either your assay robustness is poor or your analyst training is deficient. You should identify the root cause of this variation and establish adequate measures to overcome it.**

**Discussion (slides 50-53):**

The sponsor provided slides to support their position that their G-CSF neutralizing antibody (Nab) assay is suitable to assess for anti-pegylated G-CSF Nab, and asked for Agency agreement.

FDA stated that the new immunogenicity information provided in the slides would need to be considered and would be addressed in a post-meeting addendum to the minutes. The FDA commented however that the NAb bioassay needed to include pegylated G-CSF as a stimulator. No bioassay data were submitted in the meeting package comparing the responsiveness of the NSF-60 cell line to pegylated G-CSF versus G-CSF, and this was necessary before the Agency could fully evaluate the sponsor's proposal.

With regard to the use of analyst specific cut points, the sponsor contended that this practice is accepted in the literature when using cell-based bioassays, if the assay variability is high. For NAb assessment for clinical study LA-EP2006-301, the sponsor proposed using the lowest patient cut-point value for sample analysis and asked for agency concurrence. The Agency commented that such an approach would require putative NAb positive samples to be subsequently confirmed; otherwise false positive samples could be included in analyses of the impact of ADA on safety and efficacy, which could confound those analyses.

For clinical study LA-EP2006-302, the sponsor stated that the assays were performed by a single analyst to ensure meaningful and reliable assessment of NAbs, and asked for Agency concurrence.

The Agency stated they would provide a response to the questions as a post-meeting addendum to the minutes.

**Post meeting addendum:**
The sponsor submitted the following background and questions for the meeting held October 15, 2014, concerning FDA's response to question 14 (see slide 52).

***PEG part of pegfilgrastim is not immunogenic*** → *After hyperimmunization of rabbits with pegfilgrastim only anti-filgrastim antibodies developed;* ***no neutralizing anti-PEG antibodies*** *are commercially available or described in literature.*

- *Lack of positive control antibodies to confirm suitability of an anti-pegfilgrastim NAB assay to detect potential neutralizing anti-PEG / pegfilgrastim antibodies.*
- *For the development of a neutralizing anti-pegfilgrastim antibody assay only anti-filgrastim control antibodies available.*
- *A neutralizing anti-pegfilgrastim assay will have the same specificity as the established and used anti-filgrastim neutralizing antibody assay.*

***Filgrastim is the (bio)active component of pegfilgrastim****; antibodies directed against the PEG portion of pegfilgrastim can only neutralize by steric interference of filgrastim receptor binding.*
***PEG has no pharmacological activity.***
*Only anti-filgrastim antibodies present a safety issue → cross-reactivity to endogenous counterpart.*

***No effect on PD seen in patients tested positive for anti-PEG / anti-pegfilgrastim antibodies*** *(in the binding antibody ELISA) in studies LA-EP06-301 and LA-EP06-302.*

*Question: Based on these arguments, Sandoz believes that the filgrastim NAB assay is suitable to further characterize the relevant neutralizing capacity of anti-pegfilgrastim antibodies. Does the Agency agree?*

**FDA Response to question on slide 52:**
No, we do not agree. In order for you to use the G-CSF NAb assay to detect neutralizing antibodies to pegylated G-CSF, you will need to demonstrate that the NFS-60 cell line responds similarly to pegylated G-CSF (LA-EP2006, US-licensed Neulasta and EU-approved pegfilgrastim) as it does to G-CSF (EP-2006, US-licensed Neupogen and EU-approved filgrastim). You will need to use an anti-pegylated G-CSF antibody as a system suitability control for the assay. In addition, you will need to demonstrate that the presence of anti-PEG antibodies will not interfere with the assay when using pegylated G-CSF as a stimulator.

*Concerning the Agency's preliminary written responses provided for the meeting about user specific cut-point in the G-CSF NAb assay, the sponsor provided the following information and raised the following questions:*

- *Cut-point for antibody assay (AA, stimulus: filgrastim) and specificity assay (SA, stimulus: IL-3) were determined.*
- *Cell-based assays are more susceptible to variability. Therefore analyst-specific cut-points are suitable to balance this variability.*
- *Analyst-specific cut-points are recommended by Shankar et al, 2008 in case of differences between the analysts.*

***Proposal Sandoz:***

- ***Study LA-EP06-301:*** *Analysis was done by two analysts. Sandoz proposes to apply a conservative approach using the lowest patients cut-point value for evaluation. Does the agency agree?*
- ***Study LA-EP06-302:*** *Analysis was done by one analyst only. Thus, this ensures a meaningful and reliable assessment of NABs. Does the agency agree?*

**FDA Response to Questions on slide 53:**
The use of analyst-specific cut points, especially when they are as disparate as 26.2% and 42.5% is problematic, and suggests either poor analyst training or lack of assay robustness. The Agency discourages the use of analyst-specific cut points.

A. Concerning your proposal to use the lowest patient cut-point value (26.2%) for evaluation of samples from study LA-EP06-301, this is potentially acceptable, but you will need to confirm the NAb positivity of those samples, and your NAb validation study has no confirmatory step described. You will need to include such a step in your validation report.
**B.** Concerning study LA-EP06-302, your proposal to have the analysis done by only one analyst is potentially acceptable but you will need to clarify in your report which analyst-specific cut point will be used and if it is the lowest cut-point value, you will need to confirm positive samples if any are detected.

**Additional FDA comments:**

**Product Quality Microbiology:**

**All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule of the product should be provided in Module 1 of the BLA. Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers.**

**The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:**

- **Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).**
- **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).**
- **Column** (b) (4) **membrane sanitization and storage validation data and information (3.2.S.2.5).**
- **Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).**
- **Data summaries of shipping validation studies (3.2.S.2.5).**
- **Drug substance bioburden and endotoxin release specifications (3.2.S.4).**
- **Qualification data for bioburden and endotoxin test methods performed for in-process intermediates, buffers, and drug substance (3.4.S.4).**
- **If the formulation contains polysorbate, the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated (3.4.S.4).**

**The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. 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 study protocols and validation data summaries should be included in Section 3.2.P.3.5:**

- **Bacterial filter retention study for the sterilizing filter.**
- **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.**
- **In-process microbial controls and hold times. Hold times should be validated at manufacturing scale from microbiology perspective. Pre-sterile filtration bioburden limits should be monitored and should be less than 10 CFU/100 mL.**
- **Isolator decontamination, if applicable.**
- **Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.**
- **A description of the routine environmental monitoring program.**
- **Shipping validation studies, including container closure integrity data.**

**The following method validation information should be provided:**

- **Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry (3.2.P.8.2).**
- **Qualification data for bioburden, sterility and endotoxin test methods performed for in-process intermediates and buffers (where applicable) and the drug product, as appropriate (3.2.P.5).**
- **Rabbit Pyrogen Test results from three batches of drug product in accordance with 21CFR 610(b).**
- **Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold.**

**Immunogenicity**

**In the meeting package, you indicate that immunogenicity safety data for your 351(k) BLA submission for LA-EP2006 will come from two clinical studies in patients with breast cancer and a single dose parallel arm PK and PD study in healthy volunteers. All of these data sets are suboptimal for assessing immunogenicity.**

**Regarding your assessment of immunogenicity in a patient population, we note that during the clinical studies it appears that you obtained samples for ADA testing at baseline, day 15**

**of cycle 6 and 30 days after the last treatment. For a proposed biosimilar to US-licensed Neulasta, FDA would expect that samples for ADA testing be obtained more frequently during a clinical study to capture IgM and transient ADA responses. The adequacy of your immunogenicity data set will be a review issue.**

**To compare treatment emergent anti-drug antibody (ADA) incidence in a study conducted in healthy volunteers, subjects should have two exposures to either LA-EP2006 or US-licensed Neulasta in a parallel arm study, because treatment emergent ADA responses to therapeutic proteins tend to occur after a second dose of a product. Therefore, a two dose study in healthy volunteers is more informative than a single dose study.**

**Discussion (slides 47-49):**
**There was no discussion.**

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidaces/UCM360507.pdf). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

**DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm ).

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

## 5.0 ACTION ITEMS

No Action Items were identified.

## 6.0 ATTACHMENTS AND HANDOUTS

Sponsor Presentation Slides are attached.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ALBERT B DEISSEROTH
11/14/2014