

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125553Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## MEMORANDUM

**To:** File for Sandoz, Inc.'s 351(k) Application, BLA # 125553, Referencing Neupogen (filgrastim)

**From:** The CDER Exclusivity Board

**Re:** Exclusivity Expiry for Neupogen (filgrastim) BLA 103353

**Date:** June 26, 2014

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The CDER Exclusivity Board (Board) was asked by the Therapeutic Biologics and Biosimilars Team (TBBT) in CDER's Office of New Drugs to determine if there is any unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Neupogen (filgrastim) (BLA 103353; Amgen, Inc.) that would prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Neupogen (filgrastim).

Section 351(k)(7)(A) of the PHS Act states that "approval of ... [a biosimilar application] may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a)." Section 351(k)(7)(B) of the PHS Act states that ... [a biosimilar application] may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a)." Section 351(k)(7)(C)(i) of the PHS Act states that "[s]ubparagraphs (A) and (B) shall not apply to a license for or approval of ... a supplement for the biological product that is the reference product."

After reviewing the record, the Board concludes that BLA 103353 for Neupogen (filgrastim) was first licensed by FDA under section 351(a) of the PHS Act on February 20, 1991. The product was indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. A supplement (no. 1036) that added acute myeloid leukemia as an indication was approved by FDA on April 2, 1998. Additional supplements for changes and updates to the approved labeling were approved between May 29, 2002, and September 13, 2013.

The dates that are 4 and 12 years after the date of first licensure of Neupogen (filgrastim) are February 20, 1995, and February 20, 2003, respectively. A licensure of a supplement does not trigger a separate period of exclusivity. Accordingly, section 351(k)(7) of the PHS Act does not prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Neupogen (filgrastim).

**Cc:** The Therapeutics Biosimilar Biologics Team, Office of New Drugs, CDER  
Sandra Benton, Marlene Schultz-DePalo

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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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MARLENE T SCHULTZ-DEPALO

12/30/2014

Memo entered into DARRTS on behalf of the CDER Exclusivity Board

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

BLA#: 125553 Supplement Number: 0 BLA Type (e.g. SE5): 351(k)

Division Name: OHOP/DHP PDUFA Goal Date: 3/8/2015 Stamp Date: 5/8/2014

Proprietary Name: Zarxio

Established/Generic Name: TBD

Dosage Form: 300 mcg PFS, 480 mcg PFS

Applicant/Sponsor: Sandoz, Inc

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

None

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Number of indications for this pending application(s): 5

**Indications:**

1. Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
2. Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
3. Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation
4. Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
5. Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmps@fda.hhs.gov](mailto:cderpmps@fda.hhs.gov)) OR AT 301-796-0700.

**justification):****# Not feasible:**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\* Not meaningful therapeutic benefit:**

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**† Ineffective or unsafe:**

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ Formulation failed:**

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	None	< 36 kg	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): Preliminary Protocol: 3/06/15 Final Protocol Submission: 6/06/15 Study Completion: 3/06/16 Final Report Submission: 6/06/16							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	≥36 kg	None	All studies using US-licensed Neupogen	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

Zarxio is a biosimilar candidate. US-licensed Neupogen is the reference product. Extrapolation of efficacy and safety of the drug product is based on the finding that the data submitted in the BLA provides for a determination of biosimilarity.

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

**This page was completed by:**

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 6/2008)**

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/s/  
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JESSICA L BOEHMER  
02/20/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # N/A BLA # 125553	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zarxio Established/Proper Name: filgrastim-sndz Dosage Form: 300 mcg/0.5 mL in single use prefilled syringe and 480 mcg/0.8 mL in single use prefilled syringe		Applicant: Sandoz Inc. Agent for Applicant (if applicable): N/A
RPM: Jessica Boehmer, Lara Akinsanya		Division: Division of Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)               <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>March 8, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		N/A
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	N/A
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Approval: March 6, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	August 14, 2014 - Letter August 11, 2014 - Review
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: July 22, 2014 DMEPA: February 25, 2015 and December 23, 2014 DMPP/PLT: March 3, 2015 OPDP: February 17, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None CMC Labeling: March 4, 2015
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	July 22, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	Exclusivity Board Memo December 30, 2014
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>February 18, 2015</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	March 4 (2), 3, and 2, 2015; February 27, 26 (2), 23, 20, 19, 17 (2), 13, 11, 6 (2), 4, and 3, 2015; January 29, 27, 21, 20, 13 (2), 9, and 6, 2015; December 27, 16, and 11, 2014; November 18 (2), 12, 10, and 7, 2014; October 31 (2), 29, 16, 9, 6, and 2, 2014; September 17, 2014; August 13, 5, 2014; July 22, 16, and 7, 2014; June 27, 25, 24, 20, 16, 11, 9, 4, 2014; May 29, 22, and 21, and 20, 2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	March 5, 2015; January 13, 2015; November 13, 2014
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> November 19, 2013 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	<input type="checkbox"/> No AC meeting January 7, 2015
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	March 5, 2015
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	February 26, 2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	7
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See February 9, 2015 Clinical Review, page 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	N/A
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	November 26, 2014
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Cosigned January 30, 2015 and September 11, 2014 Reviews
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Cosigned January 30, 2015 and September 11, 2014 Reviews
Statistical Review(s) ( <i>indicate date for each review</i> )	January 30, 2015 Clin Stats; January 30, 2015 CMC Stats; September 11, 2014 CMC Stats
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	February 5, 2015
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Cosigned January 29, 2015 Review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	January 29, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	January 20, 2015; September 16, 2014; July 15, 2014

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	January 30, 2015
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	January 30, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Cosigned February 10, 2015 Review
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	February 10, 2015
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	February 6, 2015 Amendment January 30, 2015
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> ) <input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	February 2, 2015 (DP) January 30, 2015 (DS)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	CDRH: February 27, 2015; February 20, 2015 (2) Immunogenicity: January 30, 2015
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See January 30, 2015 Product Quality Review, Page 6
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: March 5, 2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	N/A
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Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	N/A
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

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JESSICA L BOEHMER  
03/06/2015

## Memorandum

Date: March 5, 2015

From: Biological Product Naming Working Group

Subject: BLA 125553 (submitted under section 351(k) of the Public Health Service (PHS) Act)

To: File

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FDA has determined that the use of a distinguishing suffix (“-sndz”) in the nonproprietary name for Sandoz, Inc.’s (Sandoz) Zarxio (filgrastim-sndz), a biosimilar product submitted in a 351(k) biologics license application (BLA), is necessary to distinguish this product from Neupogen (filgrastim). Neupogen (filgrastim) is the reference product for this 351(k) application, and is licensed under BLA 103353 held by Amgen, Inc.

Zarxio (filgrastim-sndz) is a human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology. Sandoz has requested licensure of Zarxio (filgrastim-sndz) for each of the indications previously approved for Neupogen (filgrastim). Specifically:

- to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever;
- to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia;
- to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation;
- to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and
- to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

FDA has concluded that a nonproprietary name for Sandoz’ product that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance. This nonproprietary name for Zarxio (filgrastim-sndz) indicates its relationship to Neupogen (filgrastim), and also indicates that the products are distinct. The use of this nonproprietary name containing a distinguishing suffix also is expected to reduce confusion among healthcare providers who,

based on their experience with small-molecule drugs and generic versions of those drugs, may consider use of the same nonproprietary name to mean that the biological products are interchangeable. Additionally, the placement of the identifier as a suffix should result in this biosimilar product and its reference product being grouped together, yet remaining distinguishable, in electronic databases to help health care providers identify these products. If Zarxio and Neupogen were to share the same proper name, this could increase the likelihood that a patient could receive a product different from what was intended to be prescribed and lead to medication errors.

FDA also has concluded that a nonproprietary name containing a distinguishing suffix will facilitate postmarketing safety monitoring by providing a clear means of determining which “filgrastim” product is dispensed to patients. Due to the fact that health care providers often use nonproprietary names instead of proprietary names when prescribing and ordering products, particularly in the settings in which filgrastim products are used, and pharmacovigilance systems often do not require inclusion of proprietary names, the use of distinct proprietary names is insufficient to address these concerns.

On February 6, 2015, FDA advised Sandoz that the nonproprietary name of Zarxio should contain a unique suffix attached with a hyphen to the core name “filgrastim.”<sup>1</sup> FDA advised that the nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should Sandoz’ 351(k) BLA be approved. FDA explained that its comments on the nonproprietary name for this product did not reflect the Agency’s decision on a general naming policy for biosimilar products. That general policy is still under consideration.<sup>2</sup> As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, FDA advised that it would work with Sandoz to minimize the impact this would have to Sandoz’ manufacture and distribution of this product, should it be licensed.

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<sup>1</sup> FDA has previously incorporated distinguishing features in the nonproprietary names of biological products that contain drug substances related to those found in previously licensed products to help minimize medication errors by (1) preventing a patient from receiving a product different than what was intended to be prescribed and (2) reducing avoid confusion among healthcare providers who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable from a clinical standpoint. For example, FDA has used three-letter prefixes to distinguish Granix (tbo-filgrastim) from Neupogen (filgrastim) and Zaltrap (ziv-aflibercept) from Eylea (aflibercept).

<sup>2</sup> FDA also has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars (see Docket No. FDA-2014-P-0077). The citizen petitions submitted by the Generic Pharmaceutical Association and Novartis request that FDA require biosimilar products to be identified by the same nonproprietary name as their reference products (see Docket Nos. FDA-2013-P-1153 and FDA-2013-P-1398). Although FDA is designating a proper name that contains a distinguishing suffix for Zarxio, FDA is continuing to consider the issues raised by these citizen petitions and the comments submitted to the corresponding public dockets with respect to establishing a general naming convention for biological products.

On February 14, 2015, Sandoz proposed the suffix “-sndz”, i.e., a suffix composed of four lowercase letters derived from the name Sandoz. FDA evaluated the proposed suffix “-sndz” and determined that it was unlikely to be a source of error: the suffix is distinct from the names of other drug substances, does not look similar to the names of other currently marketed products, and does not include any abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order. In addition, the suffix does not make promotional representations with respect to safety or efficacy of this product.

FDA also considered whether a proper name that includes an abbreviation derived from the prospective license holder’s company name would be inconsistent with statutory requirements or FDA’s practices for naming biological products. A biological product’s proper name is not expressly described in the PHS Act or FDA’s regulations for biological products as nonproprietary, although FDA’s longstanding practice is to designate proper names that are nonproprietary in nature. Importantly, the largest portion of the proper name will be the “core” name for the drug substance. The core name (“filgrastim”) reflects the drug substance name adopted by the United States Adopted Name (USAN) Council for the reference product, which is, by definition, nonproprietary. The name as a whole communicates the relationship between biological products that share this “core” name, with the added identifier derived from the name of the prospective license holder to indicate that this is a distinct product. Thus, FDA considers the inclusion of a distinguishing suffix composed of four letters that also are contained within the name of the prospective license holder to not be inconsistent with the description of the proper name as nonproprietary.<sup>3</sup>

For these reasons, FDA agrees that Zarxio will be identified as “filgrastim-sndz.” This nonproprietary name containing the distinguishing suffix will be the proper name designated in the license.

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<sup>3</sup> We note that FDA’s regulations at 21 CFR 299.4(d) reference the 1985 USAN Guiding Principles, which do not expressly address the use of a suffix derived from the manufacturer name, but do contain general statements distinguishing the adopted name from trademarked names. In FDA’s view, “filgrastim-sndz” is not inconsistent with the USAN Guiding Principles because, as discussed above, the name as a whole is nonproprietary. Further, we conclude that 21 CFR 299.4(d) does not describe a process that FDA must apply in order to designate a proper name for a biological product under section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k).

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/s/  
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JESSICA L BOEHMER  
03/05/2015

LEAH A CHRISTL  
03/05/2015



BLA 125553

**ACKNOWLEDGE CORPORATE  
ADDRESS CHANGE**

Sandoz Inc.  
Attention: John M. Pakulski, RPh  
Head US, Regulatory Affairs  
US Biopharmaceuticals  
100 College Road West  
Princeton, NJ 08540

Dear Mr. Pakulski:

We acknowledge receipt on October 28, 2014, of your October 28, 2014 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

506 Carnegie Center Drive  
Suite 400  
Princeton, NJ 08540

to

100 College Road West  
Princeton, NJ 08540

for the following Biologics License Application (BLA):

BLA 125553 for Zarxio (filgrastim-sndz).

We have revised our records to reflect this change.

Please cite the BLA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology  
Products  
Center for Drug Evaluation and Research

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/s/  
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JESSICA L BOEHMER  
03/04/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, March 04, 2015 5:32 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** FDA proposed minor edits to Zarxio PI and PPI/IFU - BLA 125553- biosimilar to Neupogen - response due noon March 5 (also officially submitted March 5)  
**Attachments:** ZarxioPI\_FDA\_Edits\_4Mar2015.docx; Zarxio\_IFU\_FDA\_Edits\_4Mar2015.docx  
**Importance:** High

Dear John,

Please reference your BLA for EP2006, BLA 125553.

Please see attached revised draft of the PI and PPI/IFU. Please review the Agency's very minor changes/comments, outlined below:

PI: deleted a duplicated word in the pregnancy category of “pregnancy” and minor editorial revisions (all in tracked changes)

PPI/IFU: relocated “Step 13” above the enlarged figure for better flow (in tracked changes)

If you agree with all the proposed edits you should provide a clean version of the PI and PPI/IFU via email. Any additional edits should be in tracked changes. If you accept all changes please officially submit these to the BLA as final labeling.

Please provide the labeling to me via email and officially submit by **12:00 PM EST, March 5, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
03/04/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, March 03, 2015 6:03 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** FDA proposed edits to Zarxio PI and PPI/IFU - BLA 125553- biosimilar to Neupogen - response due noon March 4  
**Attachments:** FDA\_edits\_Zarxio\_PI\_3Mar2015.docx; Zarxio\_PPI\_IFU\_3Mar2015.docx  
**Importance:** High

Dear John,

Please reference your BLA for EP2006, BLA 125553.

Please see attached revised draft of the PI and PPI/IFU. Please review the Agency's changes/comments and do the following to the same drafts:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). If you agree with all the proposed edits you should provide a clean version of the PI. Any additional edits should be in tracked changes.

Please provide the labeling to me via email by **12:00 PM EST, Wednesday, March 4, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
03/03/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, March 02, 2015 5:38 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** Zarxio, BLA 125553 - PMRs and PMCs  
**Attachments:** PMR-1\_PMCs\_2-3-4-5-6-7\_2Mar2015.docx

**Importance:** High

Dear John,

The review team agrees with your edits to the PMCs 2, 3, and 7 received by email March 2, 2015. The review team also agrees with your edits to PMR-1 and PMCs 4,5, and 6, received by email February 27, 2015. Please see the attached minor edits proposed from FDA for PMCs 3 and 7. If you agree, please accept changes and officially submit the final versions of all PMR and PMCs: PMR-1, PMCs 2, 3, 4, 5, 6, and 7 to the BLA.

We ask you to submit both by email and officially to the BLA, **a copy of the PMR and PMC studies** to us (attached) **with a statement that you agree to perform the trials as described and within the timelines that you specify**. Please contact me if you have any questions.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)



study:	Zarxio ( <a href="#">filgrastim-sndz</a> ), in the presence of 2 mg/ml human serum albumin, in glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Testing will include potency and sub-visible particles.	
PMC Schedule Milestone:	Final Report Submission:  The final study report(s) will be reported according to 21CFR601.12	05/2016

**PMC 4**

PMC - 4 PMC Description of study:	To re-adjust the (b) (4) bioburden limit of (b) (4) for the (b) (4) drug substance based on process capability from 10 batches of product.	
PMC Schedule Milestones:		
	Study Completion:	08/2017
	Final Report Submission:	Annual Report May, 2018

**PMC 5**

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits for (b) (4) after data from more than 10 <sup>1)</sup> batches are available and provide the limits in an Annual Report.	
PMC Schedule Milestones:		
	Study Completion:	03/2017
	Final Report Submission:	08/2017

<sup>1)</sup> In case that less than 10 batches are manufactured by the date set for study completion, a preliminary action limit for bioburden and endotoxin will be set and re-assessed as soon as required number of batches is available.

**PMC 6**

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times (b) (4) at scale from a microbiology perspective. Provide study results in an Annual Report.	
PMC Schedule Milestones:		

	Study Completion:	12/2015
	Final Report Submission:	Annual report 05/2016

### PMC 7

PMC - 7 PMC Description of study:	To update the stability program for <a href="#">Zarxio (filgrastim-sndz)</a> , pre-filled syringe drug product to include the syringe force measurements glide force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.	
PMC Schedule Milestone:	<p>Final Report Submission:</p> <p>For functional testing on the devices constituent parts of the combination product:</p> <p>Implementation of analytical test for stability and inclusion of functional tests in the post-approval stability commitment (with test frequency t0 and thereafter once a year until end of shelf life) on one commercial batch per strength:</p> <ul style="list-style-type: none"> <li>- Syringe freedom of movement inside the needle safety device;</li> <li>- Removability of the flag label</li> <li>- Activation of the needle safety device</li> </ul> <p>For break loose and glide force on the pre-filled syringes (combination product):</p> <ul style="list-style-type: none"> <li>- Implementation of analytical test for stability and inclusion of test in the post-approval stability commitment (with test frequency t0 and thereafter once a year until</li> </ul>	<p>Annual report 05/2016</p> <p>Annual report 05/2016</p> <p>05/2020</p>

Deleted: EP2006

end of shelf life)  - Shelf life specification will be set and specification included in the post-approval stability commitment after testing of sufficient commercial batches (i.e. 10 batches each per 300 mcg/0.5mL and 480 mcg/0.8mL strength <sup>1</sup> ).  The updated annual stability protocol including testing and acceptance criteria (specifications) will be reported according to 21CFR601.12	
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<sup>1</sup>) In case that less than 10 batches each per 300 mcg/0.5mL and 480 mcg/0.8mL strength are manufactured and have reached end of shelf life by the date set for study completion, a preliminary action limit for break loose and glide force will be set and re-assessed as soon as required number of batches is available.

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/s/  
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JESSICA L BOEHMER  
03/02/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, February 27, 2015 3:38 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** Please respond: Information request and response to Feb 25 email Sandoz proposed edits to Proposed PMR and PMCs - BLA 125553 for EP2006: - due noon March 2nd  
**Attachments:** PMCs\_2\_3\_7\_FDA\_Edits\_27Feb2015.docx  
**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006.

Please see the attached FDA proposed edits and comments regarding PMC-2, PMC-3, and PMC-7 in response to your February 25, 2015 email correspondence with proposed edits to the proposed PMR and PMCs.

Please also provide a response to the Information Request, below.

### CMC Information Request:

1. You are committing to implement an analytical method to assess [REDACTED] (b) (4) concentration for release or in-process testing of your product under PMC-2 and plan to submit the final report as an annual report. An annual report is not the appropriate reporting category for implementation and establishment of specifications for your drug product. Please refer to 21CFR 601.12 for appropriate reporting category. The reporting category may be determined at the time of submission.

The proposed date for submission of the final study report of May 2020 is acceptable.

2. PMC 3 refers to an in-use stability study for your product under the conditions described in the dilution section of your product labeling (section 2.5). Please note that the in-use stability study that we are requesting in PMC 3 may be conducted in a laboratory setting simulating clinical conditions and the conditions described in the dilution section of your product labeling. Additionally, the results of this study should be submitted according to 21 CFR 601.12. [REDACTED] (b) (4)
3. We have the following comments regarding PMC-7:
  - a) You are committing to implement functional testing for the device constituents of Zarxio drug product (syringe freedom of movement inside the needle safety device, removability of the flag label and activation of the needle safety device) and propose submission of the study report in the 2020 annual report. You also commit to implementing analytical testing for break loose and glide force of Zarxio pre-filled syringes and propose to submit the study report in the 2017 annual report. FDA requests submission of an updated annual stability protocol for Zarxio drug product that incorporates testing for the device constituents and analytical testing for break loose and glide force of Zarxio drug product by 2016. The updated stability protocol may be submitted

in the 2016 Annual report. The results of these tests conducted on commercial Zarxio batches should be submitted within annual reports.

You propose to implement shelf life specifications (acceptance criteria) for functional testing of the device components and analytical testing of break loose and glide force and include them in the post-approval stability commitment after 10 batches each per 300 mcg/0.5 ml and 480/0.8 ml strengths are manufactured. The proposed testing frequency for these tests is at time zero and thereafter once a year until the end of shelf life. You plan to submit the study report in the (b) (4)

(b) (4) . The updated stability protocol that includes acceptance criteria for the above referred tests should be submitted according to 21 CFR 601.12 by May 2020.

Please respond to the information request and proposed edits to the PMCs via email by **12:00 PM March 2, 2015**. Please also officially submit this information to your BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)



**PMC 7**

<p>PMC - 7 PMC Description of study:</p>	<p>To update the stability program for EP2006 pre-filled syringe drug product to include the syringe force measurements glide force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.</p>	
<p>PMC Schedule Milestone:</p>	<p>Final Report Submission:</p> <p><u>For functional testing on the devices constituent parts of the combination product on one commercial batch with testing frequency after production (t0) and thereafter once a year until end of shelf life:</u></p> <ul style="list-style-type: none"> <li>- <u>Syringe freedom of movement inside the needle safety device;</u></li> <li>- <u>Removability of the flag label</u></li> <li>- <u>Activation of the needle safety device</u></li> </ul> <p><u>For break loose and glide force on the pre-filled syringes (combination product):</u></p> <ul style="list-style-type: none"> <li>- <u>Implementation of analytical test for stability and inclusion of test in the post-approval stability commitment (with test frequency t0 and thereafter once a year until end of shelf life)</u></li> <li>- <u>Shelf life specification will be set and specification included in the post-approval stability commitment after testing of sufficient commercial batches (i.e. 10 batches each per 300 mcg/0.5mL and 480 mcg/0.8mL strength).</u></li> </ul> <p><u>The updated annual stability protocol including testing and acceptance criteria</u></p>	<p><u>Annual report 05/2016</u></p> <p><u>Annual report 05/2016</u></p> <p><u>05/2020</u></p>

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(specifications) will be reported according to  
21CFR601.12

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/s/  
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JESSICA L BOEHMER  
02/27/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, February 26, 2015 5:25 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** Please respond: BLA 125553 for EP2006: Response to Feb 25 email Sandoz proposed edits to Proposed PMR and PMCs - due February 27  
**Attachments:** PMR\_1\_BLA\_125553.docx; PMC\_4\_BLA\_125553.docx; PMC\_5\_6\_125553.docx  
**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006.

Please see the attached FDA proposed edits and comments regarding PMR-1, PMC-4, PMC-5, and PMC-6 in response to your February 25, 2015 email correspondence with proposed edits to the proposed PMR and PMCs. Additional FDA comments regarding PMC-2, PMC-3, and PMC-7 will be forthcoming.

Please respond via email by **4:00 PM February 27, 2015**.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

**PMR 1**

PMR - 1 PMR Description of study:	To develop a presentation that can be used to directly and accurately administer filgrastim-sndz to pediatric patients who weigh less than 36 kg requiring doses that are less than 0.3 mL (180 mcg), and conduct any necessary human factors studies to evaluate the ability of caregivers to measure the appropriate doses.
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**Comment [A1]: To Applicant:** FDA does not agree with your proposed timeframes for the PMR milestones (b) (4) from the time originally proposed by FDA. We advise you to submit a preliminary protocol to assess both of the two options you have proposed. Depending on the option you choose, you can contact FDA to renegotiate the other milestone dates based on the need to refine the protocol and the availability of representative samples for testing.

PMR Schedule Milestones:	Preliminary Protocol Submission:	06/06/2015
	Final Protocol Submission:	09/06/2015
	Study Completion:	06/06/2016
	Final Report Submission:	09/06/2016

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**PMC 4**

PMC - 4 PMC Description of study:	To re-adjust the (b) (4) bioburden limit of (b) (4) for the (b) (4) drug substance based on process capability from <b>10</b> batches of product.	
PMC Schedule Milestones:		
	Study Completion:	<u>03/2017</u>
	Final Report Submission:	<u>Annual Report</u> <u>May, 2018</u>

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**PMC 5**

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits for (b) (4) after data from more than <u>10</u> batches are available and provide the limits in an Annual Report.	
PMC Schedule Milestones:		
	Study Completion:	<u>03/2017</u>
	Final Report Submission:	(b) (4) <u>08/2017</u>

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**PMC 6**

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times (b) (4) at scale from a microbiology perspective. Provide study results in an Annual Report.	
PMC Schedule Milestones:		
	Study Completion:	<u>12/2015</u>
	Final Report Submission:	<u>Annual report</u> <u>05/2016</u>

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/s/  
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JESSICA L BOEHMER  
02/26/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, February 26, 2015 11:56 AM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CMC Labeling Information Request - BLA 125553- biosimilar to Neupogen - due Feb 27

**Importance:** High

Dear John,

Please reference BLA 125553 for Zarxio (filgrastim-sndz). Please provide a response to the Information Request, below.

### [CMC Labeling Information Request:](#)

We have the following comment regarding your revised carton labeling submitted on February 24, 2015.

#### **A. All Carton Labeling**

1. Add the statement “No U.S. Standard of Potency” to the bottom panel, per 21 CFR 610.61(r).

Please provide revised carton labels to me by email and officially submit them to the BLA by **12:00 PM, February 27, 2015.**

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/26/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, February 23, 2015 4:24 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** Information Request - BLA 125553- biosimilar to Neupogen - due Feb 25

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

### Information Request:

Submit an amendment to your 351(k) BLA to include information found in the “action package” for the Neupogen BLA (see draft guidance on Biosimilars: Questions and Answers Regarding Implementation of the BPCI Act, Q+A I.13). For your convenience, your amendment may provide a Web link to the SBA and FDA reviews currently available at Drugs@FDA, accompanied by a list of the documents that you intend to reference (identified by title and date), and this information will be incorporated by reference into your 351(k) BLA.

Please respond to me via email and officially submit your response to the BLA by **4:00 PM ET February 25, 2015**.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/23/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, February 20, 2015 3:42 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** Proposed PMR and PMCs - BLA 125553- biosimilar to Neupogen

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

As we continue our review of your application, our normal policy is to consider post-marketing studies and labeling at this time, in order to gain agreement in advance of an action date. We have determined that the following studies are necessary as post-marketing commitments (PMCs) or post-marketing requirements (PMRs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies are intended to describe the main objective and study characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key elements. It is also necessary for you to provide schedule milestone dates as indicated. Most milestones only require the applicant to provide the month and year for completion of each category (however, PREA milestones require month, day, and year). For milestone calculation purposes only, assume that an approval occurs on the BsUFA action date. Please note that we have provided proposed milestones for the PREA PMR per normal policy. We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMC and PMR studies description to us with a statement that you agree to perform the studies as described and within the timelines that you specify for the studies.

Final PMC and PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For PMR/PMCs, reply to our drafts as soon as possible, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document submitted by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits that FDA has proposed with which you agree.
2. Assuming and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMCs and PMRs agreed upon. We ask the following:
  - a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

- b. Send the RPM an email courtesy copy of the draft version of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you by FDA that you agree with, and only return to us YOUR edits in track changes.
- c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR/PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

PMR - 1 PMR Description of study:	To develop a presentation that can be used to directly and accurately administer filgrastim-sndz to pediatric patients who weigh less than 36 kg requiring doses that are less than 0.3 mL (180 mcg), and conduct any necessary human factors studies to evaluate the ability of caregivers to measure the appropriate doses.	
PMR Schedule Milestones:	Preliminary Protocol Submission:	03/06/2015
	Final Protocol Submission:	06/06/2015
	Study Completion:	03/06/2016
	Final Report Submission:	06/06/2016

PMC - 2 PMC Description of study:	To enhance the control strategy of (b) (4) development, validation, and implementation of an analytical method to assess (b) (4) concentration for release or in-process testing of Zarxio drug product	
PMC Schedule Milestone:	Final Report Submission:	MM/YYYY

PMC - 3 PMC Description of study:	To confirm the stability of Zarxio drug product in 5% glucose at concentrations ranging from (b) (4) mcg/ml to 15 mcg/ml of Zarxio, in the presence of 2 mg/ml human serum albumin, in glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Testing will include potency and sub-visible particles.	
PMC Schedule Milestone:	Final Report Submission:	MM/YYYY

PMC - 4 PMC Description of study:	To re-adjust (b) (4) bioburden limit of (b) (4) for the (b) (4) drug substance based on process capability from 20 batches of product.	
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PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 5 PMC Description of study:	Establish bioburden and endotoxin action limits for [REDACTED] (b) (4) after data from more than 20 batches are available and provide the limits in an Annual Report.	
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PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 6 PMC Description of study:	Conduct studies to support the worst-case hold times [REDACTED] (b) (4) at scale from a microbiology perspective. Provide study results in an Annual Report.	
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PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

PMC - 7 PMC Description of study:	To update the stability program for EP2006 pre-filled syringe drug product to include the syringe force measurements glide force and injection force and functional testing of the needle safety device. The update to the stability program will include establishment of appropriate specifications and verification activities for these attributes.	
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PMC Schedule Milestone:	Final Report Submission:	MM/YYYY
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Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/20/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, February 19, 2015 5:17 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** FDA Advice and proposed edits to labeling - BLA 125553- biosimilar to Neupogen - response due noon Feb 20  
**Attachments:** FDA\_edits\_Zarxio\_PI\_track\_change\_Feb19\_2015.docx  
**Importance:** High

Dear John,

Please reference your BLA for EP2006, BLA 125553.

The nonproprietary name of your product should contain a distinguishing suffix. FDA agrees with your proposed nonproprietary name, filgrastim-sndz, for your product. The nonproprietary name containing the distinguishing suffix will be the proper name designated in the license should your 351(k) BLA be approved.

FDA's comments on the nonproprietary name for this product do not reflect the Agency's decision on a general naming policy for biosimilar products. That general policy is still under consideration. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

Revise the nonproprietary name to filgrastim-sndz wherever it appears in the proposed labels and labeling for your product.

Please see attached revised draft of the PI. Additional FDA comments regarding the PPI/IFU will be forthcoming.

Please review the Agency's changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). Do not officially submit the revised labeling at this time.

Please provide a revised labeling to me via email by **noon Friday, February 20, 2015**.

These are the Agency's preliminary revisions, and there may be additional proposed revisions during continued labeling discussions.

Please confirm receipt of this message.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/19/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, February 17, 2015 9:38 AM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** DMEPA Information Request - BLA 125553- biosimilar to Neupogen - due Feb 17

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[DMEPA Information Request:](#)

Please provide your response to me by email by **4:00 PM ET today, February 17, 2015.**

We continue to recommend to better differentiate between the 300 mcg/0.5mL and 480 mcg/0.8mL strengths of the product to help prevent wrong strength selection errors. Per revised container labels and carton labeling, the only difference between the strengths of the product is the use of a blue color for 300 mcg/0.5mL and grey for 480 mcg/0.8mL which is insufficient differentiation. The remainder of the labels and labeling appear very similar. Additionally, using the same <sup>(b) (4)</sup> color for the proprietary name for 300 mcg/0.5mL and 480 mcg/0.5mL strengths adds to the similarity between the labels and labeling.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/17/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, February 17, 2015 10:48 AM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CMC Labeling Information Request - BLA 125553- biosimilar to Neupogen - due Feb 17

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

### CMC Labeling Information Request:

#### **BLA 125553/0 Zarxio (filgrastim-bflm<sup>[1]</sup>) Container Label and Carton Labeling Comments**

We have the following comments regarding your revised container labels and carton labeling emailed on February, 11, 2015.

#### **A. All Syringe Container Labels, Blister Foil and Tray and Carton Labeling**

1. Ensure the font size of “filgrastim-bflm” is at least half the size font size of the proprietary name “Zarxio” per 21 CFR 201.10. Currently, the font size of “filgrastim-bflm” is less than half the size of “Zarxio.”
2. Relocate the dosage form to appear directly under “filgrastim-bflm.” To further clarify, the proper name for CDER-regulated biological products should not include the finished dosage form. The finished dosage form, injection, can appear on the line below the proper name.<sup>[2]</sup> For the small syringe container label, omission of the dosage form is acceptable.
3. Relocate “MFD” (manufacturing date) away from the lot and expiration date and other important information on the label to avoid potential for confusion.

#### **B. Blister Foil Labeling 1-Pack of 300 mcg and 480 mcg strengths**

1. Relocate the NDC from under the strength statement to the top of the principal display panel above the strength statement, similar to the 10-count blister foil labeling, per 21 CFR 201.2.

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<sup>[1]</sup> Note that we are using “filgrastim-bflm” as a placeholder nonproprietary name in the comments. We acknowledge the continued discussion between Sandoz and the FDA with regard to the nonproprietary name. The nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should your 351(k) BLA be approved.

<sup>2</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. April 2013. Draft Guidance. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Please provide your response to me by email by **4:00 PM ET today, February 17, 2015.**

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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<sup>[1]</sup> Note that we are using “filgrastim-bflm” as a placeholder nonproprietary name in the comments. We acknowledge the continued discussion between Sandoz and the FDA with regard to the nonproprietary name. The nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should your 351(k) BLA be approved.

<sup>[2]</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. April 2013. Draft Guidance. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

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/s/  
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JESSICA L BOEHMER  
02/17/2015

**Boehmer, Jessica**

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**From:** Boehmer, Jessica  
**Sent:** Friday, February 13, 2015 1:42 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553- due Feb 20

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[CMC Information Request:](#)

Please provide your response to me by email by **12:00 PM ET, February 20, 2015.**

You provided freeze/thaw testing results from six process validation batches of EP2006 drug product manufactured by the proposed commercial process. The results indicate that

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/13/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, February 11, 2015 4:30 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** RE: CDRH Information Request - BLA 125553- biosimilar to Neupogen - due Feb 16

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[CDRH Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, February 16, 2015.**

In your response to the Agency information request dated February 6, 2015, you committed to implementing additional testing to assess device constituent part functionality of the combination product. You proposed that these tests would not be incorporated into ongoing stability assessments, but rather will be provided within future annual reports. To support this determination, you stated that “test methods are not yet fully developed and implemented, they are not included in the stability protocol in [Module 3.2.P.8.2]. These tests are not part of the shelf life specification”. The Agency notes that information provided within Module 3.2.P.8.3 of your submission does assess gliding force measurements for the combination product. Please include assessment of gliding force measurements within the shelf life specification for the combination product and update the Post-approval Stability Protocol and Stability Commitment to include this change.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
02/11/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, February 06, 2015 1:30 PM  
**To:** Pakulski, John  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CDRH Information Request - BLA 125553- biosimilar to Neupogen - due Feb 9

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

[CDRH Information Request:](#)

Please provide your response to me by email by **4:00 PM ET, February 9, 2015.**

In your January 30, 2015 submission to BLA125553, you provided a *Post-approval Stability Protocol and Stability Commitment* to evaluate the drug constituent part of the combination product. We note that the proposed assessment does not appear to explicitly challenge the functionality of the device constituent parts of the combination product after exposure to aging. Revise this *Post-approval Stability Protocol and Stability Commitment* to evaluate essential performance of the device constituent parts of your combination product, including examinations of glide forces and activation of the needle safety device.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
02/06/2015



BLA 125553

## GENERAL ADVICE

Sandoz Inc.  
Attention: John M. Pakulski, RPh  
Head, US Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for EP2006.

We also refer to your May 8, 2014 and January 22, 2015, submissions containing draft carton and container labels and draft labeling text.

We have reviewed the referenced material and have the following comments and recommendations:

- A. The nonproprietary name of your product should contain a unique suffix. The suffix is intended to uniquely identify your product, and is not intended to convey any meaning. FDA recommends that the nonproprietary name of your product be filgrastim-bflm. While FDA recommends "bflm" as the suffix, you may also consider "dtsm" or "zbdm" as acceptable alternatives. Note that we are using filgrastim-bflm as the recommended nonproprietary name in the comments below. The nonproprietary name containing an acceptable and unique suffix will be the proper name designated in the license should your 351(k) BLA be approved.

If you choose to propose an alternate suffix, notify the Regulatory Project Manager prior to any submission. However, please note that additional time would be needed for FDA to review and confirm the acceptability of the proposed suffix.

FDA's comments on the nonproprietary name for this product do not reflect the Agency's decision on a general naming policy for biosimilar products. That general policy is still under consideration. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

- B. Revise the nonproprietary name to filgrastim-bflm wherever it appears in the proposed labels and labeling for your product.

We have the following comments regarding your proposed container labels and carton labeling submitted on May 8, 2014.

**C. All Syringe Container Labels, Blister Foil and Tray and Carton Labeling (300 mcg/0.5 mL and 480 mcg/0.8 mL)**

1. The nonproprietary name should be displayed in a contiguous manner using the same font size, weight, and color on all container and carton labeling as "filgrastim-bflm". Please also ensure the font size of filgrastim-bflm is at least half the size font size of the proprietary name "Zarxio" per 21 CFR 201.10.
2. Change the (b) (4) font color of the letter "O" in "ZARXIO" to match the color currently used for the letters in "ZARXI." We recommend this change to improve the readability of the product's name and reduce the likelihood of confusing "ZARXIO" with "Zarxi O", "Zarxi 0," or "Zarxi."
3. Consider capitalizing only the first letter of the proprietary name followed by lower case letters (i.e. "Zarxio" instead of "ZARXIO") as discussed in Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. Draft Guidance.  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>
4. Revise the color fonts utilized in the strength presentation to provide better differentiation between 300 mcg and 480 mcg strengths. Currently, the 300 mcg strength uses a blue (b) (4) color font to display the strength and the 480 mcg strength uses a grey color font. Thus, the two strengths are not adequately differentiated from each other, which can lead to wrong strength selection errors. See Guidance referenced in comment A.3.
5. Revise the dosage form statement located underneath the expression of strength, (b) (4) to "injection" in accordance with United States Pharmacopeia (USP) 12/1/14-4/30/15, USP 37/NF 32, General Chapter, Injection <1>, Nomenclature and Definitions, which FDA generally applies to determine appropriate dosage form terms. Additionally, revise the font size of the dosage form "injection" to be identical to the font size you plan to use to display filgrastim-bflm.

6. Relocate the dosage form to appear directly under filgrastim-bflm. For the small syringe container label, the dosage form may be omitted (see comment E.2.).
7. Clarify the meaning of "MFD" that appears on the side panels with the Lot and EXP.

**D. Carton Labeling for 10-Pack of 300 mcg and 480 mcg strengths**

1. Add the appropriate warning to the principal display panel (PDP) for devices that contain natural rubber with regard to Natural Rubber Latex (NRL) vs. Dry Natural Rubber (DNR) per FDA Guidance: User Labeling for Devices that Contain Natural Rubber (21 CFR 801.437).

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070929.pdf>

2. Revise the route of administration statement [REDACTED] (b) (4) " to read "For Subcutaneous Use or Intravenous Use Only".
3. Add the statement "Single-Use Only" to the PDP directly below the route of administration statement.
4. Remove the following statement from the side panel, [REDACTED] (b) (4) [REDACTED] since the PDP states the carton contains "10 prefilled syringes with a needle safety guard." We recommend removing this statement to provide clarity and reduce the likelihood with confusion regarding the correct net quantity provided in the carton.
5. Consider adding the following statement to the PDP:

"Refrigerate. Do Not Freeze"

We recommend this revision based on post marketing data related to wrong storage of similar products using the same delivery method.

6. Revise manufacturing information to comply with per 21 CFR 600.3(t), 21 CFR 610.61. For example:

"Manufacturer:" or "Manufactured by:" (Licensee or Applicant on the 356h form)

Sandoz

Princeton NJ 08540

US License No. 2003

at: (if you wish to list the drug product facility)

GP Grenzach Produktions GmbH  
Grenzach-Wylen, Germany

Product of xxxx (Consider adding the country of origin for your product per U.S. Customs Border and Protection 19 CFR 134.11)

7. Add the statement "No preservative."
8. Delete the statement [REDACTED] (b) (4) from the bottom panel.
9. Add the statement "Do Not Freeze. Do Not Shake" with the storage and handling information on the bottom panel.
10. Delete the statement [REDACTED] (b) (4) This information should appear in the Prescribing Information in section 2 – Dosage and Administration along with the preparation instructions per 21 CFR 201.57(c)(3).
11. Add the amounts of inactive ingredients to comply with 21 CFR 201.100(b)(iii) and USP Official 12/1/2014 –4/30/2015, USP 37/NF 32, <1091> Labeling of Inactive Ingredients, by listing the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). For example, revise "Each prefilled syringe contains 480 micrograms filgrastim-bflm in 0.8 mL (600 mcg/mL). Inactive ingredients: glutamic acid... and sorbitol (E420)" to read as:

Each 0.8 mL prefilled syringe contains 480 mcg filgrastim-bflm, glutamic acid (1.178 mg), polysorbate 80 (0.032 mg), sorbitol (40 mg), and water for injection. Sodium hydroxide may be added to adjust pH.

Note deletion of [REDACTED] (b) (4)

12. Add the statement "A recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) derived from *E Coli*." to comply with per 21 CFR 610.61(q).

**E. Carton Labeling 1-Pack of 300 mcg and 480 mcg strengths**

1. Relocate the NDC from the side panels to the top of the PDP per 21 CFR 201.2.
2. See comments D1, D2, D3, D5, D6, D7, D8, D9, D10, D11, and D12.

**F. Blister Foil Labeling 300 mcg and 480 mcg strengths**

1. Relocate the statement "Single-Use Only" to appear under the route of administration statement.

2. See comments D1 and D7.
3. Add the statements "Do Not Freeze. Do Not Shake." with the storage and handling information.
4. Revise manufacturing information to comply with per 21 CFR 600.3(t), 21 CFR 610.61(b). For example:

"Manufacturer:" or "Manufactured by:" (Licensee or Applicant on the 356h form)  
Sandoz  
Princeton NJ 08540  
US License No. 2003

**G. Syringe Label for 300 mcg and 480 mcg strengths**

1. We consider the PFS Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
2. Consider deleting  <sup>(b) (4)</sup>  

3. Revise **▲ SANDOZ** to appear as Sandoz US Lic. No 2003.
4. Delete the abbreviations "SC/IV" that appear in red font. Consider expanding the abbreviation to read "Subcutaneous or Intravenous Use" and relocating under the dosage form statement (see comment G.2.) or strength statement to reduce the likelihood of confusing the abbreviations for other terms as discussed by ISMP.<sup>1</sup> This can be achieved by reducing the prominence of the manufacturer information as in comment G.3.
5. Remove the volume statements  <sup>(b) (4)</sup> on the right side of the label as this information is redundant and occupies space.

We have the following comments regarding your proposed labeling (prescribing information) submitted on January 22, 2015.

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<sup>1</sup> ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 September 8]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

H. Please see the attached recently approved labeling for US-licensed Neupogen in PLR format, available at [Drugs@FDA](mailto:Drugs@FDA). We recommend that you incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, in your draft proposed labeling. You may use this PLR format labeling as a template to facilitate a consistent approach to your draft proposed PLR format labeling. Submit to your BLA annotated labeling that describes the areas where your proposed labeling differs from the approved Neupogen labeling. Please also submit your proposed labeling in tracked changes where the areas that differ are noted.

Please respond via email by 12:00 PM ET, February 11, 2015.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD  
Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Attachment:  
US-licensed Neupogen labeling in PLR format, available at [Drugs@FDA](mailto:Drugs@FDA)

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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ANN T FARRELL  
02/06/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, February 04, 2015 12:56 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** DMEPA Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Feb 5

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

### DMEPA Information Request:

Please provide your response to me by email by **1:00 PM ET, February 5, 2015**.

1. The information you have provided in January 22, 2015 submission did not address Question 4 from Agency's Information Request sent to you on January 9, 2015. As a result, we reiterate the request: For the 8 patients that were unable to set at least one of the doses within acceptable tolerance, please provide information on what doses those participants prepared/dialed. Otherwise, state that you did not collect that data.
2. For the product marketed in Europe as Zarzio, please provide the following information:
  - a. It appears that Zarzio is marketed in Europe in a syringe with an active needle guard and a syringe without needle guard. Please provide information describing the design of both prefilled syringes, and if possible images that display the actual syringes. Also, comment on why two syringe designs are marketed in Europe when you have sought a single syringe design in the US.
  - b. Please state whether the syringe with an active needle guard used for Zarzio in Europe is the same syringe design, including the same needle guard, proposed to be marketed in US.
  - c. Please describe whether you have had any reports of medication errors, specifically dosing errors reported with partial dosing for the Zarzio product in Europe. In providing this information, if possible, please identify the type of syringe presentation associated with the report.
3. Please state whether you aware of any other products that are marketed (in the US or outside the US) in the same syringe presentation, with the same active needle guard, that you propose to market your proposed product in the United States.
4. Please provide ten (10) syringes of each strength, bearing your updated labeling, for our review.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
02/04/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, February 03, 2015 1:17 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Feb 5

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

### CMC Information Request:

Please provide your response to me by email by **12:00 PM ET, February 5, 2015.**

1. Your proposed release and stability specification for extractable volume of EP2006 drug product (DP) is “not less than (b) (4)” (300 mcg/0.5 mL strength) and “not less than (b) (4)” (480 mcg/0.8 mL strength). The proposed acceptance criteria would result in (b) (4) lower total amount of product for the 300 mcg/0.5 ml strength and (b) (4) lower total amount of product for the 480 mcg/0.8 mL strength. The amount of product could be even lower if the protein concentration of the EP2006 DP is at the lower end of the specification. Revise your acceptance criteria to ensure that your drug product will deliver the stated amount of “not less than (b) (4)” (300 mcg/0.5 mL strength) and not less than (b) (4) (480 mcg/0.8 mL strength).
2. Your proposed acceptance criteria for sum of impurities by RP-HPLC are (b) (4) for release and stability of EP2006 DP, respectively. Historical data of EP2006 DP provided in the submission show that sum of impurities of EP2006 DP are 0.9-2.4% at release and 3.4-5.3% at stability (36 months). These data include clinical EP2006 DP and process validation EP2006 DP batches. We are concerned that your current acceptance criterion for sum of impurities at release of (b) (4) can lead you to fail a stability specification for sum of impurities. Based on the stability data of EP2006 DP process validation batches, the sum of impurities can increase up to 2.7 % by the 24 month time point. This means that the sum of impurities of EP2006 DP lots released with a sum of impurities result of (b) (4) will likely result in an out of specification. In addition, your analysis of US-licensed Neupogen by RP-HPLC indicates that the sum of impurities in the reference product is 3.5-5.9% for lots of different shelf life collected from the market. (b) (4)  
(b) (4) Revise your acceptance criteria for sum of impurities determined by RP-HPLC taking into consideration your analysis of US-licensed Neupogen and your clinical and manufacturing experience with EP2006 DP.
3. Your justification for maintaining the (b) (4) as criterion for assignment of equipotency of in house primary and secondary reference materials considering standard error of the last four reference materials is not appropriate because the variability is enhanced. You should establish acceptance criteria for assignment of equipotency from testing a single primary reference standard that has been calibrated using an international reference standard for GCSF. Revise your criterion for assignment of equipotency to be more stringent ( (b) (4) ). The variability of the biological activity data may be controlled, for example, by increasing the number of replicates in the bioassay conducted to qualify the reference standard.

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
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/s/  
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JESSICA L BOEHMER  
02/03/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, January 27, 2015 6:29 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 28

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below.

### CMC Information Request:

Please provide your response to me by email by **4:00 PM ET, January 28, 2015**.

You provided a post-approval stability protocol for EP2006 drug product (DP) in section 3.2.P.8.2 and in a document entitled "3.2.R Shelf life extension protocol" proposed to extend the shelf life of EP2006 DP to 36 months. There is a discrepancy in the analytical testing proposed in section 3.2.P.8.2 (Table 1-2) and in document "3.2.R Shelf life extension protocol" (Table 5-2). Additionally, we note these protocols skip testing for appearance, clarity, extractable volume, IEF and particulate matter at specific testing points. We are concerned that your proposed stability testing protocol is not adequate to ensure that the product will maintain its purity, potency and safety over the proposed shelf life. To address our concern provide the following:

1. Clarify which proposed stability protocol (Table 1-2 in section 3.2.P.8.2, or Table 5-2 in document "3.2.R Shelf life extension protocol") will be used in the stability commitment and for extension of the shelf life of EP2006 DP, and update the two sections of the BLA to be consistent.
2. Revise your post-approval stability protocol to be consistent with the revised shelf life specifications (e.g. inclusion of potency testing). Additionally, revise your protocol to test quality attributes such as appearance, clarity, and particulate matter at all testing points. Extractable volume and IEF testing may be conducted less frequently (b) (4).

Please respond to me via email and officially submit your response to the BLA **by January 30, 2015**.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)

FDA/CDER/OND/OHOP

(301) 796-5357 (phone)

(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
01/30/2015



BLA 125553

**GENERAL ADVICE**

Sandoz, Inc.  
506 Carnegie Center Drive  
Suite 400  
Princeton, NJ 08540

ATTENTION: John Pakulski, RPh.  
Head, US Biopharmaceutical Regulatory Affairs

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for EP2006.

On January 20, 2015, at 11:09 am, an information request intended for you was inadvertently emailed to a U.S. Agent not associated with Sandoz. The information request was subsequently emailed to you on January 20, 2015, at 2:38 pm.

On January 20, 2015, at 11:14 am, the recipient of the information notified us that he had received the email in error. The recipient agreed to delete the email. The recipient further agreed not to retain any copies of the information or to use, distribute, or disclose the email or the contents thereof. On January 20, 2015, the Office of New Drugs (OND) sent a letter to the recipient, requesting that he provide OND with a letter 1) confirming this agreement, and 2) indicating that he has deleted the email and any copies. OND also informed the recipient that we would be notifying you of the inadvertent disclosure of this information.

We apologize for the inadvertent disclosure of your information. CDER takes its disclosure responsibilities very seriously and we make every effort to ensure that information is disclosed only in accordance with applicable laws and regulations.

If you have any questions, please call me at 301-796-0869.

Sincerely,

Leah Christl, Ph.D.  
Associate Director for Therapeutic Biologics  
Therapeutic Biologics and Biosimilars Team  
Office of New Drugs  
Center for Drug Evaluation and Research

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/s/  
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LEAH A CHRISTL  
01/29/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, January 21, 2015 3:55 PM  
**To:** Pakulski, John  
**Cc:** Liu, Zhengyu; Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 27

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and officially submit your response to the BLA.

### [CMC Information Request:](#)

Please provide your response to me by email by **4:00 PM ET, January 27, 2015**.

1. You did not provide leachable and extractable data for the drug substance (DS) container closure system. To address this deficiency provide the following:
  - a. Extractable and leachable data from the container closure system and leachables data from the EP2006 DS process using suitable methods. Analysis of extractables and leachables should include evaluation of organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semivolatile (e.g., GC-MS) species, and metals (e.g., ICP-MS) (refer to Markovic, I. Evaluation of safety and quality impact of extractable and leachable substances in therapeutic biologic protein products: a risk-based perspective. Expert Opin. Drug Saf. (2007) 6(5)). The extractable and leachable assessment should include their chemical identification and quantification.
  - b. Risk assessment of extractables and leachables identified in your proposed container closure system for EP2006 DS and leachables from the EP2006 DS process. You may consider the extractable data conducted by the manufacturers of the components of the container closure system and the materials used in the manufacture of EP2006 DS (b) (4) ) to conduct an initial risk assessment of potential extractables and leachables.

Additional information regarding extractables and leachables should be provided per *FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999)*.

2. Revise your release and stability specifications for drug substance (DS) and drug product (DP) to address the following:

- a. Establish objective and quantitative (when possible) acceptance criteria for identity methods (molecular size, hydrophobicity and isoelectric point). Acceptance criteria such as “correspond to reference” are not appropriate.
  - b. Provide method validation and transfer reports (if applicable) for the peptide mapping method intended to be included as orthogonal identity tests in the DS release specifications.
  - c. Process-related impurities such as E. coli host cell proteins and residual DNA are not expected to change during storage. Consider removing these tests from the stability specifications of EP2006 DS.
  - d. Your release and stability specification for extractable volume of EP2006 DP is “not less of (b) (4) (300 mcg/0.5 ml strength) and “not less than (b) (4) (480 mcg/0.8 ml strength). Revise your acceptance criterion for extractable volume to include two significant figures. In addition, specify the rounding procedures applied to extractable data.
  - e. Describe your control strategy for the levels of sub-visible particles (b) (4) in the EP2006 DP.
  - f. You proposed to revise the acceptance criterion for pH of the EP2006 DP as (b) (4) based on manufacturing experience of lots of EP2006 DP manufactured for the US market and for other markets. The data provided in Table 7-1 of the response to information request (question 1) dated January 14, 2015 indicate that your process is able produce EP2006 DP with pH in the range of (b) (4). Revise the upper limit of the acceptance criterion to better reflect manufacturing experience of the EP2006 DP for the US market.
  - g. You proposed to introduce the relative retention time (0.8-0.9 min.) and relative peak heights (60-140%) of two EP2006 peptide peaks (G4, G12) as acceptance criterion for the peptide mapping method used as orthogonal identity test in the release specification of EP2006 DS. Your peptide map method has at least 12 well resolved peptide peaks. Additionally, based on the peptide map method data provided, it appears that your method is also quite reproducible. Revise your acceptance criterion for peptide mapping to include all major EP2006 peptide peaks to account for the complete sequence of the EP2006 protein.
3. You control the concentration of the excipients in the final EP2006 drug product in (b) (4) steps: (b) (4)
- (b) (4)
- You should establish a more appropriate control strategy for the concentration of excipients in the final EP2006 DP. Establish a control strategy for the excipients of the final EP2006 DP that includes (b) (4)
- (b) (4)
4. The reference standards or materials section and the response to IR dated October 10, 2014 describe the procedures to declare the biological activity of EP2006 in-house primary and secondary reference materials. In the response to the above referred IR you state the following regarding the evaluation of the in vitro assay used to declare the potency of the EP2006 in-house reference materials:

“The in-vitro assay is evaluated as follows: If the mean relative potency of the new EP2006 in house primary reference material is between (b) (4) of the used reference material, the new reference material will be assigned as having 100% potency, corresponding to 100% of the biological activity of the previous

reference material (U/mg EP2006). If the mean relative potency of the new in-house primary reference material is outside this range, a correction factor may be introduced”.

The range of (b) (4) proposed for declaration of 100% potency of your EP2006 in-house primary and secondary reference materials is too wide. Revise your proposed range to be more stringent (b) (4). The variability of the biological activity data may be controlled by, for example, by increasing the number of replicates in the bioassay conducted to qualify the reference standard.

Additionally, clarify whether the EP2006 in-house primary reference material will be calibrated against an international reference standard for GCSF and provide information about the procedures for declaration of potency of the EP2006 in house primary reference material.

5. The method validation report for host cell proteins (b) (4) entitled “Validation of the Sandwich ELISA to Determine the Concentration of Host Cell Proteins (HCP) in EP2006 test Items” states that “the reference item of this study was (b) (4). The IgG antibodies used were affinity purified (b) (4). (b) (4). Provide information regarding the source of (b) (4) antibodies used in the HCP ELISA assay.

6. Provide expansions of the  $^1\text{H}$ - $^{15}\text{N}$  HSQC spectra of EP2006, US-licensed Neupogen and EU-approved Neupogen (Figures 5-14 through 5-21, section 3.2.S.3.1). The expansions may be provided by quadrant (e.g. 4 quadrants per spectrum). In addition, please draw the cross-peaks in the overlaid spectra in different color and “transparent” so the cross-peaks of each product can be easily distinguished.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
01/21/2015



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/s/  
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JESSICA L BOEHMER  
01/20/2015

**Boehmer, Jessica**

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, January 13, 2015 5:26 PM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica; Liu, Zhengyu  
**Subject:** CMC/Micro Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 21

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[CMC Micro Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, January 21, 2015.**

- 1) The SDN 14 (eCTD sequence 0013) response to Question 3c stated that the method sensitivity for the dye ingress test method was determined to be 25  $\mu\text{m}$  based on studies conducted with vials. Clarify how this value was determined.

2)

[Redacted content] (b) (4)

3)

[Redacted content] (b) (4)

- 4) The SDN 14 response to Question 10b states that

[Redacted content] (b) (4)

5) Regarding the 2010 – 2013 (b) (4) validation data presented in the SDN 14 response to Question 11b:

a) Table 11-3 of the response describes (b) (4) whereas Table 5-4 of Module 3.2.P.3.5.5.7.2 describes (b) (4). Clarify how the validation (b) (4) presented in Table 11-3 correlate with those presented in Table 5-4.

b) Clarify why an Fo acceptance criterion of (b) (4) was used for the initial 2010 validation studies, whereas a criterion of (b) (4) was used for the 2011, 2012 and 2013 requalification studies.

6) Regarding media fill validation:

a) Module 3.2.P.3.5.6.2 states that (b) (4) whereas footnote 2 of Module Table 6-1 indicates that a (b) (4) that (b) (4). Clarify what occurred (b) (4).

b) Tables 6-2 and 6-4 indicate that the (b) (4). Clarify how these deviations impacted evaluation of the media fill results.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
01/13/2015

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** December 3, 2014

**Application Number:** BLA 125553/0

**Product Name:** EP2006, Proposed Biosimilar to US-licensed Neupogen

**Sponsor/Applicant Name:** Sandoz, Inc.

**Subject:** Immunogenicity testing results

### FDA Participants

#### Division of Hematology Products

Albert Deisseroth, MD, PhD, Cross-Discipline Team Leader  
Jessica Boehmer, MBA, Senior Regulatory Project Manager

#### Office of Biotechnology Products (OBP)/Division of Therapeutic Proteins

Susan Kirshner, PhD, Review Chief  
Frederick Mills, PhD, Biologist  
Faruk Sheikh, PhD, Staff Fellow

#### OND Therapeutic Biologics and Biosimilars Team

Carla Lankford, MD, PhD, Science Policy Analyst

### Sponsor/Applicant Participants

Catherine Cornu-Artis – Head Global Clinical Development  
Ingrid Schwarzenberger – Head Global Regulatory Affairs  
Joerg Windisch – Chief Scientific Officer  
Gregor Schaffar - Head Clinical Bioanalytics  
Sigrid Balsler - Head Biostatistics & Clinical Submission  
Stefan Kramer – Global Program Leader  
Hannes Wallnoefer – Global Regulatory Manager  
Zhengyu (Eddy) Liu – US Manager Regulatory Affairs  
John Pakulski – Head US Regulatory Affairs

### 1.0 BACKGROUND:

FDA requested the teleconference with Sandoz to discuss their immunogenicity testing results. Specifically, FDA wanted to discuss:

- a) Additional testing of samples
- b) Obtaining patient data from the 301 and 302 studies.

## **2.0 DISCUSSION:**

Sandoz indicated they have reanalyzed the study 302 data using a reset cut-point; in addition, Sandoz will test all positive samples with a confirmatory assay. Any sample that is confirmed positive will be tested with a neutralizing antibody assay. The Agency indicated the proposed plan is acceptable.

Sandoz indicated they will send the missing Excel data files that should have been included with their November 17, 2014 response to FDA's Immunogenicity information request.

## **3.0 ACTION ITEMS:**

Sandoz will send the missing Excel data sheets.

Sandoz will send the new immunogenicity data by December 24, 2014.

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/s/  
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JESSICA L BOEHMER  
01/13/2015

## Boehmer, Jessica

---

**From:** Boehmer, Jessica  
**Sent:** Tuesday, January 13, 2015 11:24 AM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica; Liu, Zhengyu  
**Subject:** Statistics Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 14th

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[Statistical Information Request:](#)

Please provide your response to me by email by **3:00 PM ET, tomorrow, January 14, 2015.**

- 1) Please send an executable SAS program, as simple as possible, so that we can understand and recreate your ANC profile graph. When data sets are called in the SAS program, identify them by name and date submitted to the BLA.
- 2) Please clarify why the sample sizes on day 2 are larger than the sample sizes on day 1.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
01/13/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, January 09, 2015 4:42 PM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica; Liu, Zhengyu  
**Subject:** DMEPA Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 13th

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### [DMEPA Information Request:](#)

Please provide your response to me by email by **3:00 PM ET, January 13, 2015.**

We are reviewing your Human Factors study results and need the following information:

1. If available, please provide your full Human Factors Study Results report. If unable to provide the full report, at a minimum please provide information from Comments 2 through 5 from this Information Request.
2. Please provide Failure Modes and Effects Analysis Evaluation/Risk Analysis Evaluation
3. For the 11 patients that were able to set correct doses each time, please provide information regarding which ones were caregivers and which ones were patients.
4. For the 9 patients that were unable to set at least one of the doses within acceptable tolerance, please provide information what doses those participants prepared/dialed.
5. If you collected subjective responses from participants regarding their preparation of the product, please submit that information as well. It is unclear from your submission dated December 2, 2014 whether the 0.1 mL and 0.2 mL markings are visible on the 0.8 mL syringe, or whether the spring of the needle interferes with readability of 0.1 mL and 0.2 mL markings on both syringes. Please provide information to clarify.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
01/09/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, January 06, 2015 3:29 PM  
**To:** Liu, Zhengyu; Pakulski, John  
**Cc:** Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 13th

**Importance:** High

Dear John and Eddy,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### [CMC Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, January 13, 2015.**

1. The proposed bioburden (b) (4) and endotoxin (b) (4) limits for (b) (4) are alert limits. Please commit as a post-market commitment to update the BLA with bioburden and endotoxin action limits for (b) (4) in an Annual Report when data from more EP2006 batches are available. Tighten the endotoxin limit (b) (4).
2. You indicate in Table 0-3, "Overview of changes introduced to the BLA application STN125553/0" in amendment dated 11/12/2014 (Sequence 19) that (b) (4) (b) (4)  
  
(b) (4)  
. Update the BLA with the correct information.
3. Provide the protocol for validation of (b) (4) hold times at scale from microbiology perspective. Please note that the bioburden and endotoxin level (b) (4) should not increase during the hold time.
4. You committed in an amendment dated 8/22/2014 (sequence 10) to update the bioburden specification of the (b) (4) (b) (4). The specification is still not updated. Please update the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
01/06/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Saturday, December 27, 2014 8:56 PM  
**To:** john.pakulski@sandoz.com; zhengyu.liu@sandoz.com  
**Cc:** Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Jan 5th and 12th

**Importance:** High

Dear John and Eddy,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### [CMC Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, January 5, 2015. Responses to Items 2 and 7 may be provided by January 12, 2015.**

1. Revise your release and stability specifications for EP2006 drug substance (DS) and EP2006 drug product (DP) to address the following:
  - a. You did not include a specification for potency in your proposed release and stability program for EP2006 DP. Establish release and stability specifications for potency for EP2006 drug product.
  - b. You propose SE-HPLC, RP-HPLC, and IEF as orthogonal identity tests. These tests are not sufficient to confirm the identity of EP2006 because they do not assess a unique characteristic of your product. In addition, EP2006 DP is manufactured at a CMO (GP Grenzach Produktions GmbH (GPG), Germany) where other products may also be manufactured. Thus, an identity test that unequivocally distinguishes EP2006 from other products manufactured at the facility is critical. Include an identity test that evaluates a unique characteristic of your product, such as peptide mapping, in the release specifications of EP2006 DS and DP. Your specifications for identity should include quantitative (when possible) and objective acceptance criteria. An acceptance criterion such as “*correspond to reference*” is not appropriate.
  - c. Your specifications for purity by RP-HPLC for release and stability of EP2006 DS and DP include acceptance criteria for sum of impurities (%) and largest individual impurity (%). Based on your characterization studies, the RP-HPLC method evaluates product-related substances and impurities including oxidized and deamidated EP2006 species as well as nor-leucine EP2006 variants. Because the impact of these species on safety and efficacy may be different [REDACTED] (b) (4) [REDACTED], you should establish acceptance criteria for individual species. Please revise your acceptance criteria for release and stability of EP2006 DS and DP to include acceptance criteria for the individual species evaluated by the RP-HPLC method. The acceptance criteria should consider

the impact of the individual species on safety and efficacy, the results of your analysis of the reference product, US-licensed Neupogen, and your manufacturing experience with EP2006 DS and DP.

- d. Your release and stability specification for bioactivity for EP2006 DS is (b) (4). Revise your acceptance criterion for bioactivity to include (b) (4). In addition, specify the rounding procedures applied to the bioactivity data.
  - e. The methods to assess purity included in your release and stability specifications for EP2006 DS and DP are not suitable to evaluate (b) (4) EP2006 species. Include SDS-PAGE as an orthogonal method for purity in the release and stability specifications of EP2006 DS and DP to evaluate (b) (4) EP2006 species that can be unnoticed by SEC and to monitor other process- and product-related impurities.
  - f. Your stability acceptance criterion of (b) (4) by IEF, for EP2006 DP does not reflect the results of the analytical testing you conducted on the reference product, US-licensed Neupogen, or your clinical and manufacturing experience with EP2006 DP. Based on your results, there are (b) (4) with intensity of (b) (4) in US-licensed Neupogen lots collected from the market (different shelf lives). The number of bands with intensity of (b) (4) in the release and stability results of EP2006 DP was (b) (4), respectively. Revise the acceptance criterion for stability of EP2006 DP taking into consideration the results of your analysis of US-licensed Neupogen and your clinical and manufacturing experience with EP2006 DP.
  - g. The proposed acceptance criterion for EP2006 DS and DP pH is (b) (4). The proposed upper limit is not supported by your clinical and manufacturing experience, where the maximum measurement for the upper limit was to (b) (4). Please revise the upper limit of the acceptance criterion for pH for both EP2006 DS and DP.
2. You provided in-use stability data (“*Compatibility of EP2006 DP with solutions containing glucose and HSA; stability in various container materials*”) of EP2006 DP and EU-approved Neupogen in 5% glucose in containers of different materials. Content, by RP-HPLC, was the only quality attribute evaluated. Your in-use stability studies did not include evaluation of potency, purity, aggregates, and particulates. Provide the in-use stability data of EP2006 in 5% glucose and 2 mg/ml HSA that includes evaluation of potency, purity, aggregates, and particulates. We recommend that you conduct your in-use stability study using dilution conditions (e.g., concentration of GCSF and HSA) similar to those described in the US-licensed Neupogen labeling.
  3. Your characterization studies of EP2006 include characterization of EP2006 product-related substances and EP2006 product-related impurities. Please specify which EP2006 species are product-related substances and which are product-related impurities.
  4. You provided a summary of the manufacturing process validation exercise for EP2006 DP and reported the results of in-process and release control tests as well as additional testing on (b) (4) to support process validation and hold times. However, you did not provide the process parameters used to control the manufacturing process. Provide information and justify the process parameters and operating

ranges (b) (4) used to manufacture each of the EP2006 DP process validation batches. In addition, provide the process validation protocol executed in the EP2006 DP process validation exercise.

5. You provided data from a retrospective shipping validation study to support shipping of EP2006 DP from its (b) (4)

Update your drug product shipping procedure to specify an upper limit for the temperature during shipping and provide a justification for the proposed temperature upper limit. In addition, provide qualification data for the containers used to ship EP2006 DP.

6. In addition to a retrospective shipping validation study, you proposed a prospective shipping validation study (b) (4)

. Please provide your protocol for the prospective shipping validation study of EP2006 DP that you plan to execute.

7. You evaluated extractables and leachables from the container closure system, and leachable from the EP2006 DP manufacturing process, by the routine RP-HPLC purity method used for release and stability testing of EP2006 DP. Your RP-HPLC method does not appear to be suitable for evaluation of all types of extractables and leachables in your product. Analysis of extractables and leachables should include evaluation of organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species, and metals (e.g., ICP-MS) (*Markovic, I. Evaluation of safety and quality impact of extractable and leachable substances in therapeutic biologic protein products: a risk-based perspective. Expert Opin. Drug Saf. (2007) 6(5)*). The extractable and leachable assessment should include their chemical identification and quantification. To address this deficiency provide the following:

- a. Extractable and leachable data from the container closure system and leachables data from the EP2006 DP process using suitable methods.
- b. Risk assessment of extractables and leachables identified in your proposed container closure system for EP2006 DP and leachables from the EP2006 DP process. You may consider the extractable data conducted by the manufacturers of the components of the container closure system and the materials used in the manufacture of EP2006 DP (b) (4) to conduct an initial risk assessment of potential extractables and leachables.
- c. Since the presence of (b) (4) (b) (4) in syringes can impact product quality and stability, we recommend that you evaluate and control the levels of (b) (4) in your pre-filled syringes and provide a risk assessment for the impact of (b) (4) (b) (4) on the quality, stability and safety of your drug product.
- d. Provide information on the strategy to control the levels of (b) (4) leached into your product from the container closure system.

Additional information regarding extractables and leachables should be provided per *FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999)*.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
12/27/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, December 16, 2014 4:50 PM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due December 19th

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[Clinical Information Request:](#)

Please provide your response to me by email by **2:00 PM ET, December 19, 2014.**

You have stated that the needle safety device (NSD) utilized for your product is the UltraSafe Passive Needle Guard (b) (4), manufactured by (b) (4) and cleared in CDRH under (b) (4). Within the 510(k) process, a manufacturer may be able to make changes to a device while only documenting the changes internally. Your submission does not contain information related to a change control process as it relates to the use of the aforementioned 510(k) device. Please provide the change control procedures that are in place that will ensure continued compatibility of your product with the UltraSafe passive Needle Guard (b) (4).

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
12/16/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, December 11, 2014 5:10 PM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due December 15th

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### [Clinical Information Request:](#)

Please provide your response to me by email by **4:00 PM, December 15, 2014.**

1. Regarding about SN0020 submitted 12/2/2014:
  - a) On Annex 5, you cite the following human factors study:

EP2006\_PFS\_30\_48\_in (b) (4) system, Training Definition Study Report 8116 0016a WIP01, 12th March 2014

The citation is not hyperlinked. Please identify where in the BLA this study can be found. If it is not in the BLA, please submit the full study report.

- b) In item #7 of the cover letter, you indicate that you are submitting corrected datasets for EP06-101, EP06-102, EP06-104, EP06-105, and EP06-301. Please describe the actual corrections made for each of the data sets. Are the corrections to variable names (if so, which variable names were changed), data elements (under which variables), etc?
2. During the review of records at Sandoz Pharmaceuticals in Holzkirchen, Germany, November 17-21, 2014, the FDA Inspector determined that subject 703-07 in Protocol EP06-302 received commercial filgrastim rather than study drug in Cycle 2. This subject was not identified as having received commercial filgrastim in your prior revised ex.xpt file. Please clarify if this new major protocol deviation will alter the results of any of the efficacy analyses in your study report for Protocol EP06-302.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/

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JESSICA L BOEHMER  
12/11/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, November 18, 2014 3:37 PM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 21

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email **by 2:00 PM November 21, 2014**, and then officially submit your response to the BLA.

### [CMC Information Request:](#)

1. Please provide the following information about the EP2006, US-licensed Neupogen and EU-approved Neupogen batches (unless otherwise specified) used in clinical studies EP06-101, EP06-102, EP06-103, EP06-105, EP06-109, EP06-301 and EP06-302:
  - a. Content
  - b. Bioactivity
  - c. Expiry (US-licensed Neupogen and EU-approved Neupogen) and manufacturing date (EP2006)

Provide the data using the same units (e.g. percentage of bioactivity) for all the three products.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/

-----  
JESSICA L BOEHMER  
11/18/2014

## Boehmer, Jessica

---

**From:** Boehmer, Jessica  
**Sent:** Tuesday, November 18, 2014 1:23 PM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** FDA Advice re: July 1 submission - HF study - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006.

### [DMEPA Advice:](#)

With reference to your July 1, 2014, submission of data from Novartis' Human Factors study for its proposed secukinumab injection, we do not agree that this data can be extrapolated to EP2006 due to multiple differences between the two products (i.e., indication, dose, patient population, and training) that ultimately may affect the applicability of the results of the Human Factors study. However, EP2006 is proposed to be marketed in a similarly designed prefilled syringe that is currently marketed for Neupogen. Since the Neupogen prefilled syringe is used in a similar manner in the same patient population without any concerning trends in reported use errors, we do not think a Human Factors study for EP2006 is needed.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
11/18/2014

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** November 13, 2014

**Application Number:** BLA 125553

**Product Name:** EP2006, Proposed Biosimilar to Neupogen

**Sponsor/Applicant Name:** Sandoz, Inc.

**Subject:** OSI/ORA Holzkirchen inspection

### FDA Participants

#### Office of Scientific Investigations

William H. Taylor, PhD, DABT, CAPT, U.S. Public Health Service, Director, Division of Bioequivalence and Good Laboratory Practice Compliance  
Nicola Fenty-Stewart, PhD, Project Manager

#### Division of Hematology Products

Jessica Boehmer, MBA, Regulatory Project Manager

### Sponsor/Applicant Participants

#### Sandoz Inc.

John M. Pakulski, RPh, Head, U.S. Biopharmaceutical Regulatory Affairs

### 1.0 BACKGROUND:

OSI/ORA is conducting inspections at the site in Holzkirchen, Germany. According to the June 18, 2014 amendment to BLA 125553, records should be located at this site and OSI/ORA planned their inspections accordingly. Sandoz indicated the requested documents for EP06 103 are at the Cologne site and that they were not willing to send source documents from the Cologne site.

ORA is awaiting documents from the EP06 109 and EP06 101 studies that will be shipped to Holzkirchen.

### 2.0 DISCUSSION:

FDA requested that the Applicant ship the requested records to the Holzkirchen, Germany site, as the June 18, 2014 amendment to BLA 125553 indicated this is where the records would be located.

FDA noted that failure to comply with this request could have significant implications to review of the application.

Sandoz indicated that they would provide an update by the end of the day, November 13, 2014.

**3.0 ACTION ITEMS:**

Sandoz will update the Agency regarding the requested records and if/when they will be shipped and available for review.

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/s/  
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JESSICA L BOEHMER  
11/13/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, November 12, 2014 3:53 PM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica  
**Subject:** RE: BLA 125553 EP2006 - Response timing for CMC Information Requests dated Nov 7 and Oct 31

**Importance:** High

Dear John,

Regarding the proposed response timing for the CMC Information Requests:

For November 7 request regarding bioactivity/potency:

1. Please provide your responses for request # 1a and #2 by **2:00 PM, Nov 14 2014**
2. Please provide your responses for request # 1b by **12:00 PM, Nov 17 2014**

For October 31 request regarding content:

Your proposed timeframe for a response in **early December** is acceptable.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

---

**From:** Pakulski, John [<mailto:john.pakulski@sandoz.com>]  
**Sent:** Wednesday, November 12, 2014 9:59 AM  
**To:** Boehmer, Jessica  
**Subject:** RE: BLA 125553 EP2006 - Response timing for CMC Information Requests dated Nov 7 and Oct 31

Dear Jessica,

As discussed on phone, please follow-up with the reviewer regarding the November 7 request to confirm that we can provide both data and explanation on November 17<sup>th</sup>. We cannot provide data today as indicated below.

And we look forward to receiving the feedback on our proposed timing for the October 31 request.

Thanks, John

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**From:** Pakulski, John  
**Sent:** Monday, November 10, 2014 4:31 PM

To: [Jessica.Boehmer@fda.hhs.gov](mailto:Jessica.Boehmer@fda.hhs.gov)

Subject: BLA 125553 EP2006 - Response timing for CMC Information Requests dated Nov 7 and Oct 31

Dear Jessica,

This email concerns the timing of Sandoz' responses to the following CMC Information Requests.

November 7 request regarding bioactivity/potency

We will provide the data as requested on Wednesday, November 12. However, the explanation on the difference between Neupogen PFS and vials will be provided next Tuesday, November 18.

October 31 request regarding content

We plan to provide at the beginning of December. Is this timing OK?

Best regards, John

**John M. Pakulski, R.Ph.**

**Head US Biopharmaceutical Regulatory Affairs**

Sandoz Inc., a Novartis company

100 College Road West

Princeton, NJ 08540

USA

Phone: +1 609 627 8861

Cell: (b) (6)

Email: [john.pakulski@sandoz.com](mailto:john.pakulski@sandoz.com)

Web: <http://www.novartis.com>

Learn more about biosimilars @ [www.sandoz-biosimilars.com](http://www.sandoz-biosimilars.com)

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JESSICA L BOEHMER  
11/12/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, November 10, 2014 10:52 AM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** Immunogenicity Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 17 (#1) and Dec 1 (#2)

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### Immunogenicity Information Request:

1. In your 9th Oct, 2014 correspondence, in response to FDA's concern over the low rate of samples that screened positive for anti-drug antibodies (ADA) in study EP06-302, you provided a summary of the analyses you performed to evaluate the cut-point for the ADA assay. You reported that the lower number of samples screening positive for ADA was considered to be a result of the chemotherapy treatment. However, in study EP06-301, which also evaluated samples from chemotherapy-treated breast cancer patients, 14 of 643 (2.1%) samples screened positive. Therefore, based on the information provided to date, it remains unclear as to whether the assay did not perform as expected when analyzing samples from study EP06-302. In order to further understand the assay performance, FDA has determined that we should perform our own analysis of the primary data from some of your immunogenicity studies. To this end, provide the following information by **3:00 PM ET, November 17, 2014:**
  - a. Primary data generated from studies EP06-109, EP06-301 and EP06-302, including the data for all non-specific binding and negative controls used in the cut-point determination during the study sample analysis. The data should be provided in EXCEL format.
  - b. Details about the equations and the calculation process you used in the determination of cut-point in clinical sample analysis in both facilities.
2. The Neupogen label reports that 11/333 (3%) of cancer patients receiving Neupogen developed anti-Neupogen antibodies. Similarly, literature reports (Laricchia-Robbio et al. J. Cell Physiol 173: 219-226, 1997; Revoltella RP et al. Leukemia and Lymphoma 26: 29-34, 1997) indicate that anti-GCSF antibodies can be found in healthy humans. However, in all your studies, you reported only a single subject who tested positive for anti-GCSF antibodies. Provide your explanation as to why only a single anti-GCSF positive subject was observed in your studies, and provide your assessment of the anti-GCSF antibody prevalence and incidence you expected to observe. The information should be provided by **3:00 PM ET, December 1, 2014.**

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
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/s/  
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JESSICA L BOEHMER  
11/10/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, November 07, 2014 9:52 AM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CMC Stats Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 12

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### [CMC Statistical Information Request:](#)

Please provide your response by **November 12, 2014**.

1. In your response, dated October 16, 2014, to our request for information, dated October 02, 2014, you provided additional data to support analytical similarity of EP2006 and the reference product, US-licensed Neupogen and to establish an analytical bridge between EP2006, the reference product and EU-approved Neupogen.

Provide the following additional information for the bioactivity potency data present in Table 2-8.

- a. Clarify how many replicates were obtained to calculate the reportable result for each lot.
  - b. For bioactivity data in the table, the five data points of US-licensed Neupogen of Vial are consistently lower than those data from US-licensed Neupogen of PFS. Provide an explanation as to why such difference is observed between the vial and PFS presentations of US-licensed Neupogen. In addition, please submit all available potency data for US-licensed Neupogen for both Vial and PFS presentations.
2. Specify the expiry date for the tested US-licensed Neupogen and EU-approved Neupogen as well as the manufacturing date for the EP2006 in your Table 2-2 for Content and Table 2-8 for Bioactivity. Also specify the testing date for each lot value listed in Table 2-2 and Table 2-8.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)

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JESSICA L BOEHMER  
11/07/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, October 31, 2014 4:40 PM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** Clin Pharm Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen - due Nov 5

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

[Clinical Pharmacology Information Request:](#)

For studies EP06-109, EP06-101, EP06-103, and EP06-105, complete statistical analyses using the 90% CI, (b) (4) limits for the single dose ANC and multiple dose CD34+ PD AUEC and Emax parameters. Please submit these results by **Wednesday, November 5, 2014**.

Also, you may submit your response to the Clinical Pharmacology Information Request dated October 29, 2014 on November 5, 2014, as requested.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
10/31/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, October 31, 2014 4:24 PM  
**To:** john.pakulski@sandoz.com  
**Cc:** zhengyu.liu@sandoz.com; Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to me via email and then officially submit your response to the BLA.

### CMC Information Request:

Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the “strength” of the proposed biosimilar product is the same as that of the reference product. Accordingly, we expect your proposed biosimilar product to have both the same total content of GCSF (in mass or units of activity in a container closure) and the same concentration of GCSF (in mass or units of activity per unit volume) as US-licensed Neupogen (see Q+A I.12 in draft guidance on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009).

You stated that your equivalence testing results for “content” (i.e., concentration as expressed in milligrams per milliliter) of EP2006 in pre-filled syringes (PFS) against US-licensed Neupogen in PFS, and between EP2006 in PFS against the US-licensed Neupogen in both PFS and vials are “inconclusive”. In addition, FDA analysis of content of drug product batches manufactured at Lek Pharmaceuticals d.d., Slovenia (LEK), IDT Biologika GmbH, Germany (IDT) and GP Grenzach Produktions GmbH, Germany (GPG) (section 3.2.P.5.4) indicates that the EP2006 drug product validation batches manufactured at GPG (b) (4) have (b) (4) content compared to EP2006 drug product batches manufactured at IDT ( (b) (4) ) and LEK ( (b) (4) ). The (b) (4) content of EP2006 drug product manufactured at GPG appears to be a manufacturing issue. Address the (b) (4) “content” (i.e., concentration as expressed in milligrams per milliliter) of EP2006 drug product manufactured at GPG and submit data to demonstrate that EP2006 drug product manufactured at GPG, the proposed site for your intended commercial product, has the same “strength” as US-licensed Neupogen.

Please provide a time frame for when you plan to provide the requested data.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)

FDA/CDER/OND/OHOP

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JESSICA L BOEHMER  
10/31/2014

**From:** Miller, Mara Bauman  
**To:** [Pakulski, John \(john.pakulski@sandoz.com\)](mailto:john.pakulski@sandoz.com); [Liu, Zhengyu \(zhengyu.liu@sandoz.com\)](mailto:zhengyu.liu@sandoz.com)  
**Cc:** [Boehmer, Jessica](mailto:Boehmer, Jessica)  
**Subject:** BLA 125553 for EP2006, Information Request  
**Date:** Wednesday, October 29, 2014 5:56:00 PM  
**Importance:** High

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Hello John-

Regarding BLA 125553 for EP2006, we have the following Information Request. Please respond by Monday, November 3, 2014. Provide a response to Jessica Boehmer via email by the due date and then officially submit your response to the BLA.

Regarding the PK substudy within Study EP06-302,

1. Provide summary tables that compare the demographics (e.g., race, age, height, weight, BMI, etc.) and baseline laboratory values of a) the patients included in the two treatments of the PK substudy (EP2006 and Neupogen arms) and b) a comparison of those patients in the PK substudy arms to the overall patients enrolled in those respective treatment arms. Please include the following stratum as an additional factor for these comparisons: adjuvant vs. neoadjuvant.
2. Provide summary tables that compare the actual total dose of each drug administered in Cycle 1 (i.e., chemo, EP2006, and Neupogen) of the patients included in the two treatments of the PK substudy (EP2006 and Neupogen arms).
3. Provide a list of the EP2006 and US licensed Neupogen lots used in the PK substudy.

Thank you,

Mara

Mara Miller, MA  
Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
WO22, Room 2309  
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Silver Spring, MD 20993  
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MARA B MILLER  
10/29/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, October 16, 2014 4:35 PM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica; zhengyu.liu@sandoz.com  
**Subject:** CMC/Micro Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Jan5

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond by **January 5, 2015**. Please respond to me via email by the due date and then officially submit your response to the BLA.

### [CMC/Microbiology Information Request:](#)

Your 09/30/2014 Amendment response to Question 13d (eCTD sequence 0013) only stated theoretical reasons for [REDACTED] <sup>(b) (4)</sup> t. Data from confirmatory validation studies were not provided. Submit data demonstrating that container closure integrity is maintained and [REDACTED] <sup>(b) (4)</sup> is not breached during worst case shipping conditions.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
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JESSICA L BOEHMER  
10/16/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, October 09, 2014 8:44 AM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica  
**Subject:** Immunogenicity Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Oct 21 and Nov 4

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to Item 1 by **October 21, 2014** and to Item 2 by **November 4, 2014**. Please respond to me via email by the due date and then officially submit your response to the BLA.

### [Immunogenicity Information Request:](#)

Regarding anti-drug antibody binding assay please address the following issues:

1. You submitted results of the immunogenicity screening assay and reported that two of 1583 samples (0.001%) from cancer patients in study EP06-302 screened positive for anti-drug antibodies. FDA recommends a 5% false positive detection incidence for anti-drug antibodies (ADA) screening assays to minimize false negative results (see draft guidance for industry titled "Assay Development for Immunogenicity Testing of Therapeutic Proteins" (2009)). We also note that of 81 samples from study EP06-109 in healthy volunteers 3 samples (3.7%) screened positive. This result is inconsistent with the results obtained in study EP06-302. Overall, we conclude that your screening assay does not perform consistently and that it is not adequate to assess the immunogenicity of EP-2006 or the reference product. Therefore, in light of our concerns regarding your screening assay, the data may not support a demonstration of no clinically meaningful differences between reference product and EP-2006 in terms of the safety, purity, and potency of the product.

To address this deficiency you should provide immunogenicity data for EP2006 and the reference product using a screening assay cutpoint that has a 5% false positive rate and provide evidence that the screening assay is validated. We note that it may be possible to recalculate the cut-point and re-evaluate results from clinical study ADA samples using existing data to begin to address this issue. If recalculation of the cut-point is sufficient to achieve a 5% false positive rate with a validated assay, then additional testing would be necessary to confirm specificity. Any samples that confirm positive should be tested using the neutralizing antibody assay.

Regarding Neutralizing antibody assay:

2. The neutralizing antibody assay cut-point validation results showed considerable variability between analysts. This resulted in your establishing analyst specific cut-points. It is unusual to require analyst specific cut-points for ADA assays. Therefore, our assessment is that your assay was not appropriately optimized and/or that your analysts are not suitably trained. You should revise the assay so that analyst

specific cut-points are unnecessary or explain why your assay provides a meaningful and reliable assessment of neutralizing antibody activity despite the use of analyst specific cut-points.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
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JESSICA L BOEHMER  
10/09/2014

**Boehmer, Jessica**

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**From:** Boehmer, Jessica  
**Sent:** Monday, October 06, 2014 5:34 PM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Oct 20

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond by **October 20, 2014**. Please respond to me via email by the due date and then officially submit your response to the BLA.

[CMC Information Request:](#)

Please establish in-process bioburden and endotoxin limits (b) (4), as committed during the pre-license inspection and update the BLA accordingly.

Please provide a table listing all the in-process bioburden and endotoxin limits for the (b) (4) (b) (4) and update the BLA accordingly. List the bioburden action limits as, (b) (4) and endotoxin action limits as (b) (4).

The endotoxin release data for the (b) (4) provided in Section 3.2.S.4.4, "Batch analyses" are in EU/mL. Please provide endotoxin release data for the (b) (4) in EU/mg and update the BLA accordingly.

The buffer hold time study data obtained from (b) (4) was used to support the hold time validation at scale (b) (4) (b) (4)

(b) (4). Therefore, commit to conduct a hold time study under a QA approved protocol with pre-established bioburden and endotoxin acceptance criteria to demonstrate that (b) (4) (b) (4) can be held at scale without compromising microbial quality of the process streams. Hold time data should be collected during routine production runs (b) (4). Validation data should be reported in a validation report at the end of the study. Provide the hold time study protocol during the review cycle and provide the projected study completion date. Completion of the study report may be submitted in an Annual Report.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
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(301) 796-9845 (fax)

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JESSICA L BOEHMER  
10/06/2014

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, October 02, 2014 1:07 PM  
**To:** Pakulski, John  
**Cc:** Boehmer, Jessica  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE Oct 16 and 23

**Importance:** High

Dear John,

Please reference BLA 125553 for EP2006. Please provide a response to the Information Request, below. Please respond to Questions 1 and 10 by **October 16, 2014** and Questions 2 – 9 by **October 23, 2014**. Please respond to me via email by the due date and then officially submit your response to the BLA.

### [CMC Information Request:](#)

1. You provided data to support analytical similarity between EP2006, US-licensed Neupogen and an EU-approved filgrastim product. The data are derived from two evaluations. Evaluation 1 compared 6 batches of EP2006 drug product (DP), 4 batches of US-licensed Neupogen and 2 batches of the EU-approved filgrastim product. Evaluation 2 compared 6 batches of EP2006 drug substance (DS) and 5 batches of EP2006 DP with 4 batches of the EU-approved filgrastim.

We are reviewing your analytical similarity data (i.e., evaluation 1 and 2) to evaluate whether you have demonstrated that EP2006 is “highly similar” to US-licensed Neupogen and whether you have provided adequate analytical data to scientifically justify the relevance of other comparative data obtained using EU-approved filgrastim to support a demonstration that EP2006 is biosimilar to US-licensed Neupogen.

In your critical quality attribute (CQA) assessment, you identified potency (specific activity in U/mg) and protein concentration (protein content in µg/ml), both with a criticality score of 140, as two of the most critical quality attributes. However, based on the data you submitted, the min-max ranges for potency and protein content of EP2006 appear to be lower than those of US-licensed Neupogen. One possible explanation for these observations may be the limited number of batches of US-licensed Neupogen (4 batches) included in your similarity exercise.

As you have additional US-licensed Neupogen reference lots that were identified during inspection, you should include these lots of US-licensed Neupogen in your similarity exercise. We further recommend that you conduct a statistical analysis of the analytical similarity data, including data from these additional lots, to provide more robust support for your efforts to demonstrate that EP2006 is “highly similar” to the reference product with respect to quality attributes, including but not limited to potency and protein content. We currently recommend that you use a statistical approach to evaluate quality attributes of EP2006 that is consistent with the risk assessment principles set forth in the International Conference on Harmonisation 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  $\pm$  X  $\sigma$ , 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 EP2006 is highly similar to the reference product. This could include, for example, considering the ages of the 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 the proposed biosimilar and the reference product. You may propose alternative statistical approach(es) to evaluate quality attributes and support a demonstration that EP2006 is highly similar to US-licensed Neupogen.

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:

**Tier 1 (Equivalence Test):** One needs to test against the following null hypothesis.

$H_0: \mu_B - \mu_R \leq -\delta$  or  $\mu_B - \mu_R \geq \delta$  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.

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 ( $\sigma_R$ ). The equivalence test should be based on the normal distribution, unless the data clearly deviate from the normal distribution.

**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.

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.

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.

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.

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.

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.

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 were tested, this would have approximately 84% power of passing equivalence testing 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 the more limited number of lots 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.

2. Provide validation reports for the following methods:
  - a. Bioactivity by proliferation with NFS-60 cells
  - b. Content and purity by RP-HPLC
  - c. Host cell proteins (HCP) by ELISA
  - d. Purity by SE-HPLC
3. Your acceptance criterion for identification of various raw materials tested in-house is “complies with test”. Revise your specifications for identification of raw materials to specify the method and acceptance criteria applied. Acceptance criteria should be objective and quantitative (e.g. complies with USP <>).
4. You determined that the (b) (4) used in the manufacture of EP2006 DS is a critical raw material because its quality has the potential to influence the levels of EP2006 norleucine variants. In section 3.2.S.2.6, you indicate that a (b) (4) was implemented to select lots (b) (4) of optimal quality. Provide information on the (b) (4) for (b) (4) as well as information as to how the specifications for the (b) (4) (Table 3-20, section 3.2.S.2.3) provide the optimal quality needed to control for EP2006 nor-leucine variants.
5. The proposed action limit for residual (b) (4) (Table 1-7, section 3.2.S.2.4). This action limit was justified based on a toxicology assessment for levels up to (b) (4) and the impact (b) (4) levels have on EP2006 (b) (4).

The levels of residual (b) (4) in process validation batches B034028, B034029 and 034030 (Table 1-31, section 3.2.S.2.5) are (b) (4) which are above the proposed action limit. To address this discrepancy, please provide the following:

- a. Toxicology assessment of (b) (4)

- b. Clarify and justify the proposed in-process control action limit for (b) (4) content
  - c. A justification as to how the results of residual (b) (4) in the process validation batches demonstrate that the (b) (4) is capable of reducing (b) (4) levels effectively
6. On August 22, 2014, you provided a protocol for validation of (b) (4) lifetime at commercial scale. According to your protocol, the functionality of the (b) (4) is verified by (b) (4). The parameters to be trended, the testing frequency, and the trending rules that will be applied to monitor (b) (4) performance were not specified. The number of theoretical plates (N), height equivalent of a theoretical plate (HEPT) and symmetry factor were excluded from the protocol. As a result, we find your protocol deficient.

Your protocol should include the following:

- a. The parameters to be trended (e.g. purity by RP-HPLC and SE-HPLC, EP2006 content, step yield, residual DNA, HCP), the testing frequency, and the trending rules that will be applied to monitor (b) (4) performance.

- b.
- c.

7. The process validation (PV) data for the manufacture of EP2006 DS (fermentation, isolation and purification) provided in the 351(k) BLA was generated from (b) (4)

Please update your 351(k) BLA with the (b) (4) PV data. In addition, please confirm whether this process is the proposed commercial manufacturing process for the EP2006 product for which you are requesting licensure by FDA in your 351(k) BLA.

8. Provide the following information regarding all analytical methods used for control of the DS and DP including:
  - a. Date of full validation
  - b. Summary of change history and whether the changes impacted validation status of the analytical method. A justification that the changes did not impact method validation should also be provided.
  - c. The testing sites where each method is executed. Method transfer or re-validation reports (if applicable) should also be provided

Provide this information in tabular format with hyperlinks to module 3.2.R where the method transfer or re-validation reports should be located.

9. Provide information on the qualification of characterization assays used in the analytical similarity exercises including “Method characterization of EP2006 affinity to G-CSF determination by SPR”. Although these documents were provided on inspection, they should be formally submitted to the 351(k) BLA to support that the characterization assays used in the analytical similarity assessment are fit for the intended use.
10. On June 24, 2014, we sent you the following Information Request: “We note that the United States Pharmacopeial Convention recently published a monograph for filgrastim in United States Pharmacopeia 36 -National Formulary 31, Supp. 2 (official 12/1/13). FDA has not yet determined whether the USP monograph for filgrastim is applicable to your proposed biosimilar product. However, we request that you describe whether your proposed biosimilar product meets the standards set forth in the monograph.” Please advise FDA of the date by which you intend to submit a response.

Please provide a response by the due date indicated above. Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/

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JESSICA L BOEHMER  
10/02/2014

1) Please submit a Letter of Authorization permitting Agency review of DMF (b) (4). The DMF referenced (b) (4) refers to a CBER DMF.

2) Regarding the proposed (b) (4) rubber syringe stoppers:  
a) The referenced DMF (b) (4) only provides information regarding the stopper formulation. Submit a Letter of Authorization for the review of DMF (b) (4) describing validation (b) (4).

b) (b) (4) Please clarify which configuration is to be used for EP2006 drug product manufacture.

3) Regarding validation of container closure integrity of the prefilled syringe system by the microbial and dye ingress methods:

- a) Submit a description of the positive control used for the microbial ingress test. Include the perforation diameter.
- b) Submit the method sensitivity limit (minimum detectable perforation diameter) for the microbial ingress test.
- c) Submit the method sensitivity limit (minimum detectable perforation diameter) for the dye ingress test.
- d) Submit the detection limit (minimum detectable dye concentration) for the dye ingress test.

4) Regarding formulation of bulk EP2006 drug product:

- a) Specify the established hold times and hold temperatures for the (b) (4) and excipient (b) (4).
- b) Submit microbiology quality data supporting the formulation hold time limit stated in Module 3.2.P.3.5.4.2.2. Readjust the (b) (4) bioburden limit (b) (4). It is noted that the limit (b) (4) stated in Table 1-2 of Module 3.2.P.3.2.1.4.2 (b) (4) appears to be (b) (4) not in line with process capability.

5) Regarding the (b) (4) drug product in the (b) (4):

- a) Modules 3.2.P.3.3.3 (Page 5, item 15), 3.2.P.3.3.7 (Page 7), and 3.2.P.3.4.1.4.1 (Page 9, Table 1-1 (b) (4)) state that the allowable storage period (b) (4). Clarify the allowable hold time and hold temperature.
- b) Clarify whether bioburden and endotoxin testing will be routinely performed (b) (4).

7) (b) (4)

8)

9)

10)

11)

- 12) Rabbit pyrogen test data as required in 21CFR610.13(b) were not provided in the BLA submission. Please submit the data from three drug product lots to demonstrate that the drug product does not contain pyrogenic substances.

- 13) Regarding shipping validation:
- a) Describe how EP2006 drug product manufactured at the Grenzach facility will be shipped to the U.S. Include the mode of transport, the drug product packaging configuration, and a summary of the shipping validation studies and data. The information should include the location of temperature probes during shipping validation and during routine transport.
  - b) Submit a summary of the number and locations of the temperature probes used to record the data presented in Figure 9-1 of Report 3.2R, *Medical Device Part Summary of the Combination Product/Medical Device Aspects of EP2006\_PFS\_30\_48* (b) (4). In the response specify the locations considered to be worst case.
  - c) The data presented in Figure 9-1 indicates that the maximum allowable temperature of 8°C was exceeded for shipment (b) (4). Describe any product impact and how the deviation was resolved. Specify the maximum excursion temperatures and excursion duration.
  - d) Submit validation studies demonstrating that the syringe stopper movement during shipping does not (b) (4). Describe the allowable distance that the syringe stopper can move before it (b) (4).
- 14) Regarding media fill simulation:
- a) Submit the microorganisms used for medium growth promotion testing.
  - b) Submit the procedures conducted in the event of a media fill failure. In your response include a description of the impact of failure on product release and product fills.
- 15) Regarding endotoxin testing of EP2006 drug product:
- a) Submit a justification for why (b) (4) rather than EP2006 (b) (4) were used in the endotoxin recovery studies presented in SDN 9 (Module 1.11.1, eCTD sequence 0008).
  - b) Submit the gel clot data for the endotoxin recovery studies presented in SDN 9.
  - c) Submit the validation study report for determination of drug product endotoxin levels by the USP <85> kinetic chromogenic method. Include data supporting the maximum validation dilution and standard dilution for release testing.
- 16) Submit a description of the container closure integrity test (CCIT) method proposed for drug product stability testing in Module 3.2.P.8.2.

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/s/  
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MONSURAT O AKINSANYA  
09/17/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 125553/0

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Sandoz, Inc.  
506 Carnegie Center Drive  
Suite 400  
Princeton, NJ 08540

ATTENTION: John Pakulski, RPh.  
Head, US Biopharmaceutical Regulatory Affairs

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated and received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for EP2006, 600 mcg/ mL.

We also refer to your May 23, 2014, correspondence, received May 23, 2014, requesting review of your proposed proprietary name, Zarxio.

We have completed our review of the proposed proprietary name, Zarxio and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your May 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Lara Akinsanya, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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KELLIE A TAYLOR  
08/14/2014

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Wednesday, August 13, 2014 5:54 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara  
**Subject:** CDRH OC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 08/27

Hello John,

Please provide the following by **Wednesday, August 27, 2014** for FDA desk reviews of the Device component of the EP2006 300 mcg/0.5 mL and 480 mcg/0.8 mL solution for injection:

1. A detailed design control information describing where in your design and development process the device became subject to your design control program according to 21 CFR 820.30 Design Controls.
2. A detailed summary of how management with executive responsibility establishes its policy, objectives for, and commitment to quality in compliance with 21 CFR 820.20, Management Responsibility.
3. A detailed summary of procedures established and maintained to ensure that all purchased or otherwise received product and services conform to specified requirements as indicated per 21 CFR 820.50, Purchasing Controls.
4. A detailed summary of how corrective and preventive actions are identified, investigated, verified or validated, implemented, and documented in compliance with 21 CFR 820.100, Corrective and Preventive Action.
5. Clarification and details of which facilities in the submission are responsible for developing the design specifications of the device constituent part and maintenance of the design history file.

Please refer to suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations, available in the guidance document "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA

Staff," February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.ht>

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
08/13/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Tuesday, August 05, 2014 3:30 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 8/22

Hello John,

Please respond to the below CMC Information Request by **Friday, August 22, 2014**:

1. Please provide a diagram showing the in-process bioburden and endotoxin sampling locations, the locations of the (b) (4), and the (b) (4) process. The bioburden of the manufacturing process should be monitored (b) (4).
2. Please implement an in-process bioburden limit for the (b) (4) step or justify the lack of in-process bioburden limit at that step.
3. Please provide information and microbiology validation data at scale for the proposed maximum hold times (b) (4).
4. Please include bioburden and endotoxin monitoring of the (b) (4) lifetime study at commercial scale. Provide the bioburden and endotoxin limits for the study.
5. The bioburden release test uses (b) (4) (b) (4) sample volume. Please update the bioburden specification to (b) (4). Similarly, the bioburden release test results should be expressed as CFU/volume tested.
6. With regard to bioburden release data provided in Section 3.2.S.4.4, "Batch analysis", 13 batches had results of (b) (4). Please provide the exact CFU/volume tested for those batches.
7. Please provide the summary qualification results for the bioburden test of the in-process and (b) (4) drug (b) (4). Please clarify if (b) (4) time is for the qualification samples or routine product bioburden samples.
8. With regard to the endotoxin qualification study of the (b) (4) (b) (4) sample, please provide the (b) (4) used for the (b) (4) calculation. Provide the summary qualification data for the (b) (4) (b) (4) sample. In addition, provide the dilution you will use for the routine testing of the (b) (4) (b) (4) sample.
9. With regard to the endotoxin qualification study (b) (4)

10. Please provide the bioburden and endotoxin limits [REDACTED] (b) (4). In addition, provide microbiology validation data at scale for the maximum hold times [REDACTED] (b) (4).
11. The [REDACTED] (b) (4) endotoxin limit [REDACTED] (b) (4) is too high based on the historical data. Please tighten the [REDACTED] (b) (4) endotoxin limit [REDACTED] (b) (4).

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
08/05/2014



BLA 125553/0

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

Sandoz Inc., a Novartis Company  
Attention: John Pakulski, RPh  
Head, Regulatory Affairs  
US Biopharmaceuticals  
506 Carnegie Center, Suite 400  
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated May 8, 2014, received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for EP2006.

EP2006 is a proposed biosimilar to Neupogen (filgrastim) (BLA 103353).

We refer to the July 7, 2014 filing notification letter informing you that your 351(k) BLA has been accepted for review with a standard review classification and a March 8, 2015 user fee goal date.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 8, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. For Protocol EP06-302, we identified 25 subjects who were treated with an alternate form of leukocyte growth factor rather than the assigned study agent. How these protocol violations affect the interpretation of the study results will be a review issue.

2. Your application requests licensure for 300 mcg/0.5 mL and 480 mcg/0.8 mL in single-use prefilled syringes only. Clarify how your prefilled syringe presentations can support dosing and administration in pediatric patients, such as young children with congenital neutropenia, who will require a daily subcutaneous injection. Your instructions for use of the prefilled syringe in the patient labeling do not address this circumstance.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Product Quality - CMC

1. You provided summary data of the qualification of the Master Cell Bank (MCB) and Manufacturer's Working Cell Bank (MWCB). Certificates of analysis for these cell banks were also provided. Update your submission to include full qualification reports for the MCB and MWCB, including bacteriophage testing.
2. Provide bacteriophage testing results of your current MWCB EP2006; (b) (4)  
[REDACTED]
3. You provided an overview of the protocol for qualification of a future manufacturer's working cell banks (MWCB). Your protocol does not include comparability assessment of drug substance manufactured at full scale using approved and proposed MWCBs and lacks (b) (4)  
[REDACTED]. The comparability data are needed to verify that EP2006 produced using a new MWCB is comparable to EP2006 produced using an approved MWCB. Update your protocol to include testing of drug substance manufactured at full scale with current and proposed MWCBs and to include (b) (4)  
[REDACTED] and submit the revised protocol for review.
4. [REDACTED] (b) (4)
5. Based on the data provided in Section 3.2.S.5 Reference Standards or Materials, it appears that you have a one-tier reference material system. You should develop a two-tier in-house reference material system consisting of primary and working reference materials. Each subsequent working or primary reference material should be calibrated against an in-house primary material appropriately characterized that is representative of

production and clinical materials (ICH Q6B). Calibrating against a single primary reference material assures that the bioactivity determined for the test samples is consistent over time and limits the potential drift in product potency that may occur when each new standard is compared to the current working standard. To address this deficiency, provide a protocol for qualification of primary and working reference materials. Additionally, clarify the intended purpose(s) of your in-house primary/working reference materials (e.g. determination of potency, assay system suitability).

6. Your bioactivity assay for drug substance (EP2006-32s42-bioactivity-790-1-0) uses (b) (4) used in analytical procedure EP2006-32s42-bioactivity-790-1-0.
7. You propose a hold time (b) (4) (b) (4) You provided stability data for (b) (4) stored under these conditions at small scale and state that “stability (b) (4) was also proven by using (b) (4) stored up to (b) (4) for the production of drug substance and consecutively drug product leading to products which comply with the specifications and are similar to the batches produced with (b) (4) (b) (4). To further support the proposed hold time for (b) (4), provide the release, stability and characterization data (if available) of the DS and DP batches manufactured with the (b) (4) stored up to (b) (4) compared to DS and DP lots manufactured with (b) (4).

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (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 an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted a pediatric assessment with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Monsurat Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Edvardas Kaminskas, M.D.  
Deputy Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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EDVARDAS KAMINSKAS  
07/22/2014

## Wright, Kevin

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**From:** Liu, Zhengyu <zhengyu.liu@sandoz.com>  
**Sent:** Wednesday, July 16, 2014 5:11 PM  
**To:** Wright, Kevin  
**Cc:** Kang, Sue  
**Subject:** RE: Question on Request for Proprietary Name for BLA 125553

Hi Dr. Wright,

Thank you for your clarification. Good to know that re-evaluation is no longer required within the same review cycle.

Best regards, eddy

**Zhengyu (eddy) Liu, Ph.D.**  
Regulatory Affairs  
US Biopharmaceuticals, Sandoz Inc.  
506 Carnegie Center, Suite 400  
Princeton, NJ 08540  
USA

Phone +1 609 6278679  
Cell (b) (6)  
Fax +1 609 6278659  
[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)  
[www.novartis.com](http://www.novartis.com)

---

**From:** Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]  
**Sent:** Wednesday, July 16, 2014 1:19 PM  
**To:** Liu, Zhengyu  
**Cc:** Kang, Sue  
**Subject:** RE: Question on Request for Proprietary Name for BLA 125553

Dr. Zhengyu,

Please see my responses below.

---

**From:** Liu, Zhengyu [mailto:[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)]  
**Sent:** Tuesday, July 15, 2014 1:53 PM  
**To:** Wright, Kevin  
**Cc:** Kang, Sue  
**Subject:** RE: Question on Request for Proprietary Name for BLA 125553

Dear Dr. Wright,

Thank you for your answer. I would like get one more clarification from you. According to FDA's practice, the trade name is **re-evaluated** 90 days before product approval (given the action date of March 8, 2015, reevaluation will probably happen in December 2014). DMEPA no longer re-evaluates proprietary names for marketing applications within a single application review cycle.

Assuming the decision is made to conditionally approve "Zarxio" by August 23, my understanding from your answer is that after reevaluation, if the acceptance is not overturned then the acceptance will become final and DMEPA won't issue a second letter. If the name is found acceptable, acceptance will be final for this review cycle and letter will be sent stating the proprietary name was found acceptable.

However if the acceptance is overturned after reevaluation, DMEPA will inform us right away. Is my understanding correct? If the name is found unacceptable, then we will notify you by letter.

Thank you very much.

Best regards, eddy

**Zhengyu (eddy) Liu, Ph.D.**

Regulatory Affairs  
US Biopharmaceuticals, Sandoz Inc.  
506 Carnegie Center, Suite 400  
Princeton, NJ 08540  
USA

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[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)

[www.novartis.com](http://www.novartis.com)

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**From:** Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]  
**Sent:** Friday, July 11, 2014 1:31 PM  
**To:** Liu, Zhengyu  
**Cc:** Pakulski, John; Kang, Sue  
**Subject:** RE: Question on Request for Proprietary Name for BLA 125553  
**Importance:** High

Dr. Liu,

Thank you for your inquiry. Please see my responses below.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | [kevin.wright@fda.hhs.gov](mailto:kevin.wright@fda.hhs.gov)

 Thinking green when printing

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**From:** Liu, Zhengyu [<mailto:zhengyu.liu@sandoz.com>]  
**Sent:** Friday, July 11, 2014 12:14 PM  
**To:** Wright, Kevin  
**Cc:** Pakulski, John

**Subject:** Question on Request for Proprietary Name for BLA 125553

**Importance:** High

Dear Dr. Wright,

My name is Eddy Liu. I work for John Pakulski of Regulatory Affairs group from Sandoz. We submitted a Request for Proprietary Name for BLA 125553 in May. The proposed name "Zarxio" received a "conditional acceptable" opinion from FDA during IND phase in 2013. We have two questions regarding the name request:

1) Is DMEPA going to issue an opinion on the name within 90 days of receipt of the Request, i.e. by August 23? Yes, DMEPA will issue a decision on the proposed proprietary name by August 23.

2) When we approach the BLA action date of March 8, 2015, will DMEPA issue another comment on the name? If yes what is the approximate timeline?. No, DMEPA will not issue a second letter *if* the proposed proprietary name, Zarxio, is found acceptable by DMEPA.

Thank you for your help.

Best regards, eddy

**Zhengyu (eddy) Liu, Ph.D.**

Regulatory Affairs

US Biopharmaceuticals, Sandoz Inc.

506 Carnegie Center, Suite 400

Princeton, NJ 08540

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Phone +1 609 6278679

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[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)

[www.novartis.com](http://www.novartis.com)

---

**From:** Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]

**Sent:** Tuesday, May 20, 2014 3:14 PM

**To:** Pakulski, John

**Cc:** Kang, Sue; Akinsanya, Lara

**Subject:** BLA 125553 EP 2006: Request for Proprietary Name

Hello John,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to BLA 125553 if you intend to market this product with a proprietary name.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME", on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage, frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | [kevin.wright@fda.hhs.gov](mailto:kevin.wright@fda.hhs.gov)

 Thinking green when printing

**THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.**

**If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.**

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/s/  
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KEVIN WRIGHT  
07/17/2014



BLA 125553/0

**FILING NOTIFICATION LETTER**

Sandoz Inc., a Novartis Company  
Attention: John Pakulski, RPh  
Head, Regulatory Affairs  
US Biopharmaceuticals  
506 Carnegie Center, Suite 400  
Princeton, NJ 08540

Dear Mr. Pakulski:

Please refer to your Biologics License Application (BLA) dated May 8, 2014, received May 8, 2014, submitted under section 351(k) of the Public Health Service Act for EP2006.

EP2006 is a proposed biosimilar to Neupogen (filgrastim) (BLA 103353).

We also refer to your amendments dated May 23, June 5, 12, 16, 18, 24 (2), and July 1, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. This filing communication constitutes the notification described in section 351(l)(2) of the Public Health Service Act that your 351(k) BLA has been accepted for review. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 8, 2015.

We plan to send a separate filing communication that provides additional information and describes any potential review issues identified during the initial filing review within 74 calendar days from the date of FDA receipt of the original submission in accordance with the performance goal established under the Biosimilar User Fee Act (BsUFA).

If you have any questions, call Monsurat Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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ANN T FARRELL  
07/07/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Friday, June 27, 2014 12:32 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara  
**Subject:** ClinPharm Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 07/28

Hello John,

Please respond to the below Clinical Pharmacology Information Request by **Monday, July 28, 2014:**

- Regarding the G-CSF PK data from Study EP06-01, submit the individual concentration-time data and PK parameter data in a SAS-compatible dataset and variable definitions.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
06/27/2014

**Akinsanya, Lara**

---

**From:** Akinsanya, Lara  
**Sent:** Wednesday, June 25, 2014 11:45 AM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara  
**Subject:** CMC Microbiology Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 7/1

Hello John,

Please respond to the below CMC Microbiology Information Request by **COB Tuesday, July 1, 2014:**

1) The EP2006 formulation contains excipients (b) (4) that could result in low endotoxin recovery (LER) (see K.L. Williams, Endotoxin Test concerns of Biologics, American Pharmaceutical Review, October 28, 2013). In the 11/14/2013 type 4 BPD meeting package response for IND 109197 (pages 14 and 15) you were advised to conduct studies regarding the effect of hold time on endotoxin recovery for (b) (4) (b) (4) spiked with known amounts of endotoxin in containers with compositions similar to those used for manufacture and sampling. This information was not provided. Please submit.

2)  (b) (4)

3) 

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
06/25/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Tuesday, June 24, 2014 8:02 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara  
**Subject:** CMC Information Request (device) - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen

Hello John,

Please respond to the below CMC Information Request as soon as the information is available:

We note that the United States Pharmacopeial Convention recently published a monograph for filgrastim in United States Pharmacopeia 36 -National Formulary 31, Supp. 2 (official 12/1/13). FDA has not yet determined whether the USP monograph for filgrastim is applicable to your proposed biosimilar product. However, we request that you describe whether your proposed biosimilar product meets the standards set forth in the monograph.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
06/25/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Friday, June 20, 2014 3:44 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara; Liu, Zhengyu (zhengyu.liu@sandoz.com)  
**Subject:** Clinical Information Request (device) - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/24

Hello John,

Please respond to the below Clinical Information Request regarding the delivery device by **June 24, 2014**:

The submission contains basic technical information regarding the container closure system. The provided information references separate DMF's for the syringe barrel/hypodermic needle and the plunger rod/rubber stopper; however, there is no information provided regarding any functional testing that has been conducted on the final, finished device. FDA requires that functional testing be provided for the final, finished device in order to adequately review all characteristics of the device. FDA Guidance "Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4" provides an overview of functional testing that is recommended for a product of this type (in particular, please see Section V.B.3).

Please provide the requested testing for review.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
06/21/2014

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Monday, June 16, 2014 11:56 AM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara; Liu, Zhengyu (zhengyu.liu@sandoz.com)  
**Subject:** Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/24

Hello John,

Please respond to the below Clinical Information Request by **June 24, 2014**:

- I. Provide a copy of the study protocol and amendments for Study Protocols 101, 103 and 109, respectively, and a corresponding sample Case Report Form (CRF), as applicable.
- II. Provide a copy of the sample informed consent form and amendments for Study Protocols 101, 103 and 109, respectively.
- III. Provide study patient data listings organized by clinical site number to include the elements below in PDF electronic format. The PATIENT DATA LISTINGS should be GROUPED and submitted to the Agency according to CLINICAL STUDY SITE (PER COUNTRY). The study subject data listings should capture the following, as applicable:
  - 1) Subject discontinuation (If applicable per treatment group: site subject number, screening visit date, informed consent date, assent date, date of first dose/last dose, length of date or discontinuation, reason for discontinuation).
  - 2) Prohibited medications (non-study medications): (If applicable per treatment group: site subject number, type (prohibited meds), medication (preferred term), indication/reason taken, date started, date stopped).
  - 3) Adverse events, (If applicable per treatment group: preferred term/investigator entry, detailed drug name, blinded-phase active dose, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no)).
  - 4) Clinical, laboratory and other diagnostic safety events or endpoints, as applicable: (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1...etc).
  - 5) G-CSF, CD34 and anti-rhG-CSF antibody assay laboratory testing and results as applicable to the study protocol.
  - 6) Clinical, laboratory and other data relevant to the primary efficacy endpoints: body temperature, neutrophil counts (If applicable per treatment group: site subject number, visit # and corresponding date in MM/DD/YY format (baseline, week 1...etc).
  - 7) Protocol deviations.

For Part III, the requested patient data listings are for the following clinical study sites:

1. Ralf Freese, Hamburg, Germany, Protocol 101
2. U. Fuhr, Kol, Protocol 103
3. F. Sorgel, Protocol 101,103,109 and 302
4. Richard Larouche, Montreal, Canada, Protocol 109
5. Caroline Hebert, Protocol 109
6. Vera Koppenburg , Protocol 109 and 302
7. Josef Cseh, Szekesfehervar, Hungary, Protocol 302 Site 204
8. Irina Davidenko, Krasnodar, Russia, Protocol 302 Site 703 (n=29 enrolled patients)
9. Vladimir Semiglazov, St. Petersburg, Russia, Protocol 302 Site 706 (n=44 enrolled patients)

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
06/17/2014

## Akinsanya, Lara

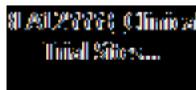
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**From:** Akinsanya, Lara  
**Sent:** Wednesday, June 11, 2014 4:24 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara; Liu, Zhengyu (zhengyu.liu@sandoz.com)  
**Subject:** Clinical Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/16

Hello John,

Please respond to the below Clinical Information Request by **June 16, 2014**:

1. Please review the clinical trial site contact list attached. Please update the contact information for each site. Note that for the clinical trial sites, we are seeking the contact information for the study subjects' medical records (primary source documentation) and for the investigator's study records.
2. For each of the 13 clinical protocols submitted to the BLA, please provide contact information for the site where the sponsor's records will be available for inspection.
3. For each of the 13 clinical protocols submitted in the BLA, please provide a copy of the final version of the protocol that incorporates all interim amendments.
4. We noted that for protocol EP06-302, the deviation file indicates that multiple subjects were treated with G-CSF products other than US-Neupogen or EP2006, but the exposure file ex.xpt shows that all subjects received only study drug. Please provide a corrected version of ex.xpt for protocol EP06-302 that includes one additional column that specifies exactly which G-CSF (manufacturer/brand) was administered each date for each subject. Please also clarify whether a G-CSF product not specified in the protocol was used (as a protocol deviation) in any of the other clinical trials submitted to the BLA.



Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

Site # (Name,Address, Phone number, email, fax#)	Responsibility
<p>Ralf Freese, M.D.  MDS Pharma Services, Hamburg  Clinical Trial Center North  Martinistrasse 52. S10  D-20246 Hamburg. Germany  Phone: +49 (0) 40 42803 1602  Fax: +49 (0) 40 42803 1605  <b>email:</b></p>	<p>Protocol 101 Clinical Site</p>
<p>U. Fuhr, M.D.  ITECRA GmbH&amp;Co KG  c/o Evangelisches Krankenhaus  Weyertal, 7th floor  Weyertal 76  50931 Köln, Germany  Phone: +49 - 221 - 4 78 52 30  FAX: +49 - 221 - 4 78 70 11  <b>email:</b></p>	<p>Protocol 103 Clinical Site</p>
<p>(b) (4)</p>	<p>G-CSF and CD34 assay results</p>
<p>Richard Larouche, M.D.  PharmaNet Canada Inc.  5160, boul. Décarie, Suite 800  Montréal (Québec), Canada  H3X 2H9  Tel.: 001 (514) 485-7500  Fax: 001 (514) 485-7501  <b>email:</b></p>	<p>Protocol 109 Clinical Site</p>
<p>(b) (4)</p>	<p>CD34 assay results</p>
<p>Dr. Vera Koppenburg  HEXAL AG  Keltenring 1+3  82041 Oberhaching  Tel.: +49 89 61 36 70 -135  Fax.: +49 89 61 36 70 -147  <b>email: vera.koppenburg@sandoz.com</b></p>	<p>Anti-rhG-CSF antibodies</p>
<p>Site 204  Jozsef Cseh MD  Fejer Megyei Szent Gyorgy Korhaz,  Onkologiai Osztaly  8000 Szekesfehervar, Seregelyesi u. 3.  Telephone +36 22 535 662  Fax +36 22 535 667  <b>email: onkologiaf@mail.fmkorhaz.hu</b></p>	<p>Protocol 302 Clinical Site</p>

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MONSURAT O AKINSANYA  
06/11/2014

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Monday, June 09, 2014 12:32 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara  
**Subject:** CMC Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/13

Hello John,

Please respond to the below CMC Information Request by **June 13, 2014**:

1. You provided analytical similarity data of EP2006, US-licensed Neupogen, and EU-approved filgrastim in three separate documents (“Biosimilarity with reference product”, “Biosimilarity EU Comparator” and “additional Data Neupogen”). To facilitate the review of these data, please provide all the analytical similarity results (e.g. release, stability and characterization data, including functional studies) in a tabular side-by-side format comparing the three products. Representative primary data (e.g., chromatograms, spectra, electropherograms) and graphical representation of the data (when applicable) should also be provided in a side-by-side format comparing the three products. Additionally, please identify in the tables, figures and representative primary data the “version” of EP2006 included in the studies. These data should be located in a single section in 3.2.R.
2. A comparability report for the transfer of drug product from IDT PFS to GPG PFS was provided in the BLA. These data are intended to support the comparability of EP2006 used in clinical studies 104, 105 and 109 (IDT PFS) to the proposed commercial EP2006 drug product (GPG PFS). In addition to clinical studies 104, 105 and 109, you provided data from other clinical studies (e.g. 101, 102, 103, and 301) and preclinical studies using different “versions” of EP2006 (e.g. LEK vial and PFS) to support your application. In order to justify the relevance of the clinical and pre-clinical data from these studies, comparability between each “version” of EP2006 used in the clinical and pre-clinical studies and the proposed commercial drug product (GPG) should be demonstrated. We acknowledge that some of the analytical data for the early “versions” of the drug product were provided in section 3.2.P.5.4 and 3.2.P.8. In order to facilitate review of these data, please provide all the analytical data intended to support comparability of the proposed commercial drug product and the drug product used in all the clinical and pre-clinical studies intended to support your application in a side-by-side format comparing all “versions” of the EP2006 drug product. Representative primary data (e.g. chromatograms, spectra, electropherograms) and graphical representation of the data (when applicable) should also be provided in a side-by-side format. These data should be located in a single section in 3.2.R.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products

Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
06/09/2014

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Wednesday, June 04, 2014 10:54 AM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara; Tzeng, Linhua  
**Subject:** Statistics Information Request - BLA 125553 (Filgrastim Sandoz) - biosimilar to Neupogen DUE 6/10

Hello John,

Please respond to the below Statistics Information Request regarding Study EP006-302 by **June 10, 2014**:

- Perform subgroup analyses to assess whether results are consistent across subgroups. Currently, you have not submitted them.
- Submit all programs (e.g. SAS) that were used to create the efficacy endpoints, all of the efficacy, safety tables, and figures included in the main test portion of the CSR and in the label.
- Provide ITT flag in your dataset ADEFFIC.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
06/04/2014

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, May 29, 2014 10:43 AM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara; Tzeng, Linhua  
**Subject:** CMC Information Request- BLA 125553 for EP2006 (proposed biosimilar to Neupogen) DUE 6/10

Hello John,

Please respond to the below Clinical Information Request by **June 10, 2014**:

- We are planning to conduct a pre-license inspection of your drug substance manufacturing site (Sandoz, Kundl, Austria) in support of BLA STN125553. The manufacturing facility should be in operation for the production of EP2006 during the inspection. Ideally, the facility should be in operation during the September-November timeframe (2014) in order to meet all review milestones. Please provide a manufacturing schedule for EP2006 drug substance.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
05/29/2014

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, May 22, 2014 5:11 PM  
**To:** Pakulski, John (john.pakulski@sandoz.com)  
**Cc:** Akinsanya, Lara; Tzeng, Linhua  
**Subject:** Clinical Information Request- BLA 125553 for EP2006 (proposed biosimilar to Neupogen) DUE 6/5

**Hello John,**

Please respond to the below Clinical Information Request by **June 5, 2014**:

1. Please provide define files for the datasets for all clinical studies submitted in the BLA. Either a pdf or html version (with appropriate hyperlinks) would be acceptable. For additional information about the define files, please see sections 3.1.2.1 and 3.1.2.2 of “Study Data Specifications” available at: <http://wcms.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>
2. Please ensure that the define files include the MedDRA version number and AE grading system used in the respective data sets.
3. For Protocol EP06-302, the datafile ex-ep06-302.xpt, which lists drug exposure, includes multiple rows for study visits with no drug dose, start date or end date. Please explain why these data fields are blank. If the blank fields are in error, please submit a corrected datafile.
4. Protocols EP06-109 and EP06-302 are foreign clinical trials. Please describe your rationale for assuming that the data from these trials are applicable to the US population.
5. The clinical study reports indicate that 4 sites were audited for Protocol EP06-109 and 16 sites for Protocol EP06-302, but the report does not discuss the findings. Please identify any substantial issues identified in your audits, what corrective actions, if any, were required, and whether implementation of the corrective actions as applicable were successful.
6. For Protocol EP06-302:
  - a) Please confirm that the protocols were approved by the IECs at each institution.
  - b) Please confirm that you have on file written commitment to ensure GCP from each investigator.
  - c) Please provide a description of the monitoring procedures that were used to ensure compliance with GCP.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
05/22/2014



BLA 125553/0

**BLA ACKNOWLEDGEMENT**

Sandoz Inc. a Novartis Company  
Attention: John Pakulski, RPh  
Head Regulatory Affairs  
US Biopharmaceuticals  
506 Carnegie Center, Suite 400  
Princeton, NJ 08540

Dear Mr. Pakulski:

We have received your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act) for the following:

**Name of Biological Product:** “(b) (4) / “EP 2006-filgrastim,” proposed biosimilar to Neupogen (filgrastim)

**Date of Application:** MAY 8, 2014

**Date of Receipt:** MAY 8, 2014

**Our Secondary Tracking Number (STN):** BLA 125553/0

**Proposed Use:** Cancer patients receiving myelosuppressive chemotherapy,  
Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy,  
Cancer patients receiving bone marrow transplant,  
Patients undergoing peripheral blood progenitor cell collection and therapy, and  
Patients with severe chronic neutropenia

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act

by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 125553/0** submitted on May 8, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Monsurat Lara Akinsanya, MS  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MONSURAT O AKINSANYA  
05/21/2014

## Wright, Kevin

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**From:** Pakulski, John <john.pakulski@sandoz.com>  
**Sent:** Tuesday, May 20, 2014 3:38 PM  
**To:** Wright, Kevin  
**Subject:** RE: BLA 125553 EP 2006: Request for Proprietary Name

Hi Kevin,

I am acknowledging receipt and confirming that we will submit Request for Proprietary Name.

Best regards, John

**John M. Pakulski, R.Ph.**  
**Executive Director and Head US Biopharmaceutical Regulatory Affairs**

Sandoz Inc., a Novartis company  
506 Carnegie Center, Suite 400  
Princeton, NJ 08540  
USA

Phone: +1 609 627 8861

Cell: (b) (6)

Email: [john.pakulski@sandoz.com](mailto:john.pakulski@sandoz.com)

Web: <http://www.novartis.com>

Learn more about biosimilars @ [www.sandoz-biosimilars.com](http://www.sandoz-biosimilars.com)

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**From:** Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]  
**Sent:** Tuesday, May 20, 2014 3:14 PM  
**To:** Pakulski, John  
**Cc:** Kang, Sue; Akinsanya, Lara  
**Subject:** BLA 125553 EP 2006: Request for Proprietary Name

Hello John,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to BLA 125553 if you intend to market this product with a proprietary name.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME", on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage,

frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 [kevin.wright@fda.hhs.gov](mailto:kevin.wright@fda.hhs.gov)

 Thinking green when printing

**THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.**

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/s/  
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KEVIN WRIGHT  
05/30/2014



PIND 109197

**MEETING MINUTES**

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

Dear Mr. Pakulski:

Please refer to your Pre-Investigational New Drug Application (PIND) file for EP2006.

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2013. The purpose of the meeting was to discuss the format and content of the planned BLA to support licensure of EP2006, a proposed biosimilar to US-licensed Neupogen, under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)).

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 Lara Akinsanya, Regulatory Project Manager at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, M.D., Ph.D.  
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**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar  
**Meeting Category:** BPD Type 4

**Meeting Date and Time:** November 19, 2013; 10:00 AM – 11:00 AM EDT  
**Meeting Location:** White Oak Building 22, Conference Room: 1419

**Application Number:** PIND 109197  
**Product Name:** EP2006 (proposed biosimilar to US-licensed Neupogen)  
**Indication:** EP2006 is being developed for the same indications as approved for US-licensed Neupogen  
**Sponsor/Applicant Name:** Sandoz Inc.

**Meeting Chair:** Albert Deisseroth, M.D., Ph.D.  
**Meeting Recorder:** Lara Akinsanya, M.S.

**FDA ATTENDEES**

Division of Hematology Products (DHP)

Ann T. Farrell, M.D., Division Director  
Albert Deisseroth, M.D., Ph.D., Clinical Team Leader  
Thomas Herndon, M.D., Medical Officer  
Lara Akinsanya, M.S., Senior Regulatory Health Project Manager

Division of Hematology Oncology Toxicology (DHOT)

Haleh Saber, Ph.D., Supervisory, Pharmacologist  
Pedro DelValle, Ph.D., Pharmacology/Toxicologist Reviewer

Office of Pharmaceutical Science, Office of Biotechnology Products (OBP), Division of Therapeutic Proteins (DTP)

Gibbes Johnson, Ph.D., Team Leader, Product Quality  
Maria Gutierrez Lugo, Ph.D., Product Quality Reviewer

Office of Clinical Pharmacology (OCP)

Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader  
Sarah Schrieber, Pharm.D., Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics V (DBV)

Yuan Li Shen, Ph.D., Statistical Team Leader  
Qing Xu, Ph.D., Statistician

Office of Pharmaceutical Science, Office of Biotechnology Products (OBP), Biotechnology Manufacturing Assessment Branch (BMAB)

Bo Chi, Ph.D., Team Leader, Product Quality  
Patricia Hughes, Ph.D., Product Quality Reviewer

Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Team (TBBT)

Leah Christl, Ph.D., Associate Director for Therapeutic Biologics  
Sue Lim, M.D., Senior Staff Fellow  
Neel Patel, Pharm.D., Regulatory Project Manager  
Tyree Newman, BS, Senior Regulatory Project Manager  
Carla Lankford, M.D., Ph.D. Science Policy Analyst

Office of Regulatory Policy (ORP)

Janice Weiner, J.D., M.P.H., Senior Regulatory Counsel

Center for Device and Radiological Health (CDRH)

LCDR Quynh Nhu Nguyen, Regulatory Reviewer (Human Factor)

**SPONSOR ATTENDEES**

Sandoz Inc:

- Carlos Sattler, Vice President, Clinical Development and Medical Affairs
- John Pakulski, Head Regulatory Affairs, US Biopharmaceuticals
- Zhengyu Liu, Team Leader Regulatory Affairs, US Biopharmaceuticals
- Deborah Ablordeppey, Associate Regulatory Affairs, US Biopharmaceuticals

Sandoz GmbH:

- Mark McCamish, Global Head Biopharmaceutical Development
- Pascale Burtin, Head Global Clinical Development Biopharma
- Sigrid Balsler, Global Head Biostatistics and Clinical Submission Management
- Jens Schletter, Head of Global Regulatory CMC
- Roumen Nakov, Head Clinical Development Hematology
- Ulrich Kronthaler, Preclinical Development Manager
- Stefan Kramer, Global Program Leader

- Hannes Wallnoefer, Regulatory Affairs Manager
- Ursula Krimm, Regulatory CMC Team Leader
- Daniela Pfister, Regulatory CMC Manager
- Katharina Ledermaid, eCTD Business expert

External Consultant (Device Expert) – [REDACTED] (b) (4)

- [REDACTED] (b) (4)

## 1.0 BACKGROUND

On August 22, 2013, the Agency received a meeting request from Sandoz to discuss the format and content of the planned BLA for Sandoz's rhG-CSF product, EP2006, to support licensure as a biosimilar to US-licensed Neupogen under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)). The Agency granted the meeting request on September 7, 2013, as a Biosimilar Biological Product Development (BPD) Type 4 Meeting.

On November 14, 2013, the Division emailed Sandoz the preliminary responses to the questions contained in the meeting information package received August 22, 2013.

## 2. DISCUSSION

### General Introductory Comments:

FDA may provide further clarifications of, or refinements and/or changes to, these preliminary 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 PHS Act.

Please note that for ease of reference and discussion, we have renumbered your questions in sequential order.

### 2.1 Electronic submission – eCTD

Sandoz intends to submit the initial application in electronic form using the eCTD format according to current FDA requirements. In the following the applicant would like to take the chance to point out Sandoz' position and strategy on eCTD.

The applicant will provide a "reviewer's guide" as appendix to the cover letter with the initial submission containing information on the content, hyperlinking strategy, naming conventions, legacy documents, literature references, metadata etc., in order to facilitate a smooth and convenient review of the application for the Agency.

Because Sandoz pursues a global development, it proposes to provide all documentation in

A4 format while guaranteeing that the page layout is compatible with letter format. In other words, all documents will be suitable for printing on letter format paper as well as A4 format paper. Page margins follow the specifications in the guideline (PDF Portable Document Format (PDF) Specifications).

**Question 1:**

**Annotated table of contents**

Sandoz intends to submit an electronic CTD dossier as required by the FDA. In the briefing package submitted together with this meeting request, a table of contents of the dossier is provided as Table 13-1. A brief description of all documents is included into this table of contents.

Does the Agency agree that the proposed documents as described are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required, which have to be included in the eCTD dossier for an application under section 351(k) of the Public Health Service Act?

**FDA Response:**

**No, we do not agree that your proposal is adequate. Please see the responses to the remaining questions for information on additional documents and information that should be included in your planned eCTD submission.**

**Discussion:**

*No discussion occurred.*

**Question 2:**

**Scanned PDFs – OCR**

Some existing documents such as literature references or CRF's are not available in a searchable format (i.e. not created from a readable source or OCR).

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

**FDA Response:**

**Yes, we agree.**

**Discussion:**

*No discussion occurred.*

**Question 3:**

**Hyperlinking**

Sandoz intends to use efficient inter-document hyperlinking between individual dossier documents, besides adequate intra-document hyperlinking. This will facilitate a quick and convenient review. Hyperlinking is planned within Modules 2 and 3 and from Module 2 to the respective sections in Modules 3, 4, and 5. It is not planned to hyperlink documents within Modules 4 and 5 or across Modules 3, 4 and 5 to keep the number of hyperlinks to a reasonable amount.

Does the Agency agree with the proposed hyperlinking strategy?

**FDA Response:**

**No, we do not agree. Please provide hyperlinks within Module 5.**

**Discussion:**

*No discussion occurred.*

**2.1 CMC**

**Question 4:**

Does the Agency agree that the CMC data package is sufficient to permit review of the registration application?

**FDA Response:**

**No, we do not agree. We have insufficient information to determine if the CMC data package is sufficient to permit meaningful review of the BLA. Furthermore, you stated that you intend to include “only selected information of the data packages” in the CTD (page 27). We advise that the CMC data and information expected for review of the proposed biosimilar product should be included in the BLA.**

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

- 1. The “final” analytical similarity assessment strategy, as outlined in the response to our information request dated November 1, 2013, intended to demonstrate that EP2006 is analytically “highly similar” to the reference product, US-licensed Neupogen, and to support an analytical bridge between EP2006, US-licensed Neupogen and the EU-approved filgrastim product (marketed in the EU as “Neupogen”) is based on limited data. We have identified deficiencies including limited product characterization (e.g. lack of tests to evaluate product strength and disulfide bond integrity, and insufficient orthogonal methods for characterization of aggregates and higher order structure) and limited number of lots of EP2006, US-licensed Neupogen and the EU-approved**

**filgrastim product analyzed. We note that the data may not be sufficient to support a demonstration of “highly similar” or to build an adequate scientific bridge.**

**In your response to the information request, you state that you “compare your biosimilar products to the reference product throughout the development process on many more lots over time”. The comparative analytical data generated during development may be considered to support analytical similarity provided the analytical characterization of the products is robust, sufficient lots of EP2006, US-licensed Neupogen and the EU-approved filgrastim product were evaluated, and the EP2006 material used in the assessment includes EP2006 product manufactured by the clinical process and by the proposed commercial process for which you seek approval.**

- 2. We note that you have made changes to the manufacture of EP2006 drug substance and drug product (e.g. scale and site of manufacture), and plan to submit comparability data in your BLA submission. Please be aware that in addition to demonstrating comparability between the pre-change and post-change drug substance (DS) and drug product (DP), analytical similarity of EP2006 manufactured by the clinical processes (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at Lek Pharmaceuticals d.d., Slovenia and IDT Biologika GmbH, Germany) and proposed commercial product (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at GP Grenzach Produktions GmbH, Germany) needs to be demonstrated to US-licensed Neupogen.**

**You plan to submit analytical data comparing EP2006, US-licensed Neupogen and the EU-approved filgrastim product to demonstrate analytical similarity of your product to the reference product, US-licensed Neupogen, and to establish an analytical bridge between EP2006, US-licensed Neupogen, and the EU-approved filgrastim product. In your BLA submission, clearly specify the data you intend to use to demonstrate analytical similarity and the data intended to establish the analytical bridge between your product, the reference product, and the EU-approved filgrastim product. For the analytical bridge, we expect all three comparisons (EP2006 to US-licensed Neupogen, EP2006 to the EU-approved filgrastim product, and the EU-approved filgrastim product to US-approved Neupogen) to meet the pre-specified acceptance criteria for similarity. Additionally, specify whether the analytical similarity assessment was conducted with EP2006 lots manufactured by the clinical and proposed commercial processes.**

**With respect to organization of the CMC data package, address the following in the BLA submission:**

- 1. Module 3 should also include the following data:**
  - i. You propose to provide “Executed Batch Records” upon request. This is not acceptable. Executed batch records should be provided in the BLA submission.**

- ii. **You plan to provide analytical method validation reports for non-compendial methods in Module 3 section 3.2.S.4.3. These reports along with method validation protocols should be located in the regional section (3.2.R)**
- iii. **Table 13-1 does not specify whether analytical comparability and analytical similarity protocols will be provided. Provide analytical comparability and analytical similarity protocols in separate 3.2.R modules.**
- iv. **Functional assays, including mechanism of action, should be provided and a justification that EP2006 has the same mechanism(s) of action as US-licensed Neupogen needs to be included in your BLA submission. 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.**

**2. In addition, include the following additional information in the relevant CTD sections.**

<b>CTD section</b>	<b>Comment</b>
<b>1.1.2 FDA form 356h</b>	<b>Indicate if the manufacturing and testing sites are ready for inspection.</b>
<b>1.3 Administrative information</b>	<b>A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections. Environmental Assessment or a request for categorical exclusion</b>
<b>2 Common Technical document summaries</b>	<b>Summaries of “Executed Batch Records” and summaries of “Analytical Comparability and Analytical Similarity protocols”</b>
<b>3.2.S.2.5 Process validation and/or evaluation</b>	<ul style="list-style-type: none"> <li>• <b>Three successful consecutive (b) (4) hold time validation runs at manufacturing scale from microbiology perspective.</b></li> <li>• <b>Information (b) (4) including microbiology data</b></li> <li>• <b>Data summaries of shipping validation studies</b></li> </ul>
<b>3.2.S.4.3 Validation of analytical procedures</b>	<b>Qualification reports for bioburden and endotoxin tests.</b>
<b>3.2.P.3.5 Process validation and/or</b>	<ul style="list-style-type: none"> <li>• <b>(b) (4) retention study report (b) (4)</b></li> </ul>

<p><b>evaluation</b></p>	<p style="text-align: right;">(b) (4)</p> <ul style="list-style-type: none"> <li>• <b>Hold time validation at scale from microbiology perspective</b></li> </ul> <p style="text-align: right;">(b) (4)</p> <ul style="list-style-type: none"> <li>• <b>Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs,</b></li> <li>• <b>A description of the routine environmental monitoring program</b></li> <li>• <b>Shipping validation data, including container closure integrity data</b></li> </ul>
<p><b>3.2.P.5.3 Validation of analytical procedures</b></p>	<p><b>Qualification of bioburden, endotoxin, and sterility tests.</b>  <b>Results of rabbit pyrogen test using three drug product lots.</b></p>
<p><b>3.2.P.8.2 Post-approval Stability Protocol and Commitment</b></p>	<p><b>Container closure integrity test</b> (b) (4)  <b>(b) (4) on the stability program.</b></p>
<p><b>3.2.A Appendices</b></p>	<p><b>Information about other products manufactured in the facilities and strategies to prevent contamination and cross-contamination should also be described in this section.</b></p>

**Discussion:**

*The sponsor presented the attached slide presentation. The sponsor presented slides 10 – 32 in relation to the FDA response to Questions 4, 7, and 11, and asked the following clarification questions:*

*Is the information sufficient to address the concerns raised in the written feedback regarding the analytical links for EP2006 used across the clinical program?*

*Does the Agency agree that the proposed CMC data for the EP2006 vials establishes an appropriate relationship to the proposed commercial material such that clinical study EP06-302 can be considered pivotal?*

*The FDA acknowledged that the information presented by Sandoz in the slide presentation was more robust than the “final similarity assessment” data that was provided in the meeting briefing package. The FDA noted that the additional data, as presented, appears reasonable to address their concerns raised in the responses to the questions regarding the limited product characterization and limited number of lots. The FDA noted that the submission of the data package as outlined in the slide presentation appears more likely to support a demonstration of “highly similar” and to build an adequate scientific bridge, as described in the response to Question 4; however, the Agency would need to review the data to determine whether the data fully addressed the FDA’s concerns. FDA noted that multiple comparability exercises were conducted since the completion of the clinical studies in 2004.*

*The sponsor noted that lots of US-licensed Neupogen and EU-approved filgrastim were collected and tested over a period spanning several years. The FDA advised the Sponsor to provide information about the number of lots tested and lot information, including but not limited to the lot expiry date and testing date, with the data used to determine the lot-to-lot variability of US-licensed Neupogen, EU-approved filgrastim, and EP2006. The sponsor was also advised to provide sufficient data and justification to establish an adequate analytical bridge between US-licensed Neupogen and EU-approved filgrastim. The FDA referred the sponsor to FDA’s response to Question 4 regarding the expectation of the three pair-wise comparisons among the three products. FDA noted that building an acceptable analytical bridge would be critical to justify the relevance of clinical data generated with EU-approved filgrastim, including the multiple dose data supporting the mobilization indication. In addition, the FDA noted that multiple comparability exercises were conducted with EP2006 since the completion of the clinical studies comparing EP2006 to EU-approved filgrastim in 2004 in order to evaluate and support manufacturing changes to EP2006. The FDA stated that the multiple comparability exercises would add complexity to building an adequate analytical bridge to justify the relevance of clinical data generated using EP2006 pre-change material. The FDA advised Sandoz to clearly identify the data being used to support comparability of the EP2006 material used in the clinical studies to the EP2006 material intended for commercial marketing in the US.*

*The sponsor noted that additional analytical tests using retained samples of the drug product and drug substance lots used in the clinical trials would not be possible. These lots surpassed the (b) (4) shelf life years ago, as these studies were started in 2004 to support the EMA MAA application.*

*Clinical study EP06-302 was conducted with EP2006 in a vial presentation. The FDA noted that this represented a change in the container-closure system to that of the proposed EP2006 commercial product, which will be presented in pre-filled syringes-(PFS). The sponsor noted that no formal comparability exercise was performed between the EP2006 PFS and EP2006 vials. FDA advised that the sponsor would need to build a bridge between the EP2006 PFS and vials in order to justify the relevance of the data generated using the vial presentation to the PFS presentation, and that it was not acceptable to have no comparability assessment between the PFS and the vials. In order to build a bridge between the EP2006 PFS and vials,*

*a head-to-head comparability exercise should be performed as per ICH Q5E to establish the relationship (i.e., comparability) between the PFS and vial products.*

*The sponsor clarified that they do not intend to seek licensure for EP2006 in the vial presentation [REDACTED] (b) (4). As such, the sponsor stated their position that certain tests, such as stability testing, should not be part of the comparability exercise between the PFS and vials recommended by FDA. FDA acknowledged the sponsor's position, and stated that a targeted analysis that includes select methods may be acceptable, but the attributes that are evaluated and methods which are used should be justified. The FDA noted that evaluation of leachables should be included as part of the comparability exercise.*

*FDA noted that Sandoz should clearly identify in the BLA what data are being used to support a demonstration of similarity and what data are being used to support comparability.*

**Question 5:**

Does the Agency concur with Sandoz' proposal to provide the detailed summary reports for biosimilarity studies with the originators as well as the comparability studies performed for quality changes during development as separate 3.2.R modules?

**FDA Response:**

**Your proposal to provide analytical similarity reports and analytical comparability reports as separate 3.2.R. modules is acceptable. However, full analytical similarity, and analytical comparability reports should be provided. Please refer to comment 3 in the response to question 1 above regarding the content of the analytical similarity and analytical bridge data.**

**Discussion:**

*No discussion occurred.*

**Question 6:**

Does the Agency concur with Sandoz' proposal to include more detailed information on the process characterization as separate 3.2.R module(s) (e.g. detailed description of methodology and specific examples from process characterization studies)?

**FDA Response:**

**Yes, we concur.**

**Discussion:**

*No discussion occurred.*

**Question 7:**

Sandoz will provide information on several supportive clinical studies (see also Clinical Question 5). These studies were conducted using [REDACTED] (b) (4) which is different from the product Sandoz is seeking approval for ([REDACTED] (b) (4))

(b) (4)

Does the Agency agree with Sandoz's proposal that inclusion of CMC data on (b) (4) used in supportive clinical studies is not needed?

**FDA Response:**

**No, we do not concur. The purpose of the "supportive clinical studies" is not clear from the information provided in your meeting package. Therefore, it is unclear whether the associated CMC data are required in the BLA. In the event the "supportive clinical data" generated with the different (b) (4) material are required to support your 351(k) application, sufficient CMC data should be provided to establish the relationship between such (b) (4) material and the EP2006 product for which you seek approval.**

**Discussion:**

*See summary of discussion captured under Question 4.*

**Question 8:**

The product concerned is considered a combination product composed of the drug and two device components, in particular a pre-filled syringe and a needle safety guard (b) (4). Sandoz proposes to submit information on the pre-filled syringe and the needle safety guard, and their respective interfaces in a summary document in section 3.2.R of the eCTD. To avoid redundant information, appropriate hyperlinks to Module 3.2.P documents will be set and the respective information will not be repeated in Module 3.2.R. As requested during the pre-IND meeting (see pre-IND meeting minutes dated 28 October 2010), Sandoz will provide objective evidence that the device components can be handled safely and effectively by the intended user groups consisting of patients, healthcare professionals, and caregivers. The summary report that Sandoz intends to provide is based on a simulated use handling study conducted by Novartis Pharma AG for a combination product composed of the identical device components (i.e. pre-filled syringe, needle safety guard) and comparable instructions for use regarding the Novartis product. This study revealed that all intended user groups can safely and effectively handle the device. Although the patient population differs between the Novartis product and EP2006 it can be safely assumed that the device components also suits EP2006 users, because they don't have any special needs from a human factors perspective that is caused by the disease (e.g. such as patients suffering from rheumatoid arthritis (RA)).

Does the Agency concur that the outlined approach to address the requirements for the presented combination product EP2006 is acceptable?

**FDA Response:**

**You stated that that you will provide a summary from a simulated use study that was conducted with a Novartis product. In addition, you stated that the device components (pre-filled syringe and needle safety guard) are identical to the Novartis product. However, it appears that the patient population differs between the Novartis product and EP2006. Different patient population indicates different intended user group. A key component of**

**human factors/usability validation testing is that users who are representative of actual users be used for the testing.**

**At this time, we cannot determine whether your approach is acceptable without information that provides a comprehensive analysis of the intended users for your product and how they are comparable to the users of the Novartis product, and without a comprehensive use-related risks analysis on the use of your product. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.**

**You should submit these detailed analyses for review. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.**

**Discussion:**

***The sponsor presented the attached slide presentation. The sponsor presented slides 33-35 in relation to the FDA response to Question 8.***

***FDA noted that the information and approach presented by the sponsor in the slide presentation would need to be discussed internally, and that FDA would provide comments in a post-meeting note.***

**Post Meeting Note:** You clarified at the meeting that the proposed device is identical to the Novartis device. You also clarified that you intend to use existing human factors data from healthy subjects that were collected using the Novartis device to support the human factors evaluation for the proposed device.

This approach is acceptable. However we advise you that a detailed discussion on how you intend to use the human factors data obtained from existing studies to support the proposed product and a justification as to why existing human factors data are relevant for the proposed product should be included in the BLA. As part of the justification, you may consider providing a comparison of the user interface, intended users, and uses for the two products.

### 2.3 Pharmacology/Toxicology

**Question 9:**

Does the Agency agree that the pharmacology and toxicology package summarized in Table 12-1 is sufficient to permit assessment of biosimilarity at the nonclinical level and the review of the respective sections of proposed biosimilar BLA dossier?

**FDA Response:**

**Yes. The pharmacology and toxicology package is acceptable for BLA filing. However, a final determination of biosimilarity will be made during the BLA review based on the totality of the evidence submitted.**

**Discussion:**

*No discussion occurred.*

**Question 10:**

Does the Agency agree that for licensure of EP2006 as a biosimilar product to Neupogen under 351(k) of the Public Health Service Act, the pharmacology and toxicology information can be submitted as study reports in PDF format, without providing additional electronic, individual animal data listings?

**FDA Response:**

**You may submit the data in the PDF format; however, all data including individual animal data should be submitted to the BLA.**

**Discussion:**

*The sponsor presented the attached slide presentation. The sponsor presented slide 36 in relation to the FDA response to Question 10.*

*Sandoz asked for clarification as to whether the individual animal data could be submitted in PDF format. The Agency confirmed that this was acceptable.*

### 2.4 Clinical

**Question 11:**

Does the Agency agree that the clinical data package is sufficient to permit assessment of biosimilarity at the clinical level and the review of the respective sections of the proposed biosimilar BLA dossier?

**FDA Response:**

**The proposed clinical package presented in the meeting package may not be adequate to support a demonstration of biosimilarity. We have the following concerns:**

- **We note that study EP06-109 only compared a single 10 µg/kg SC dose PK of EP2006 with US-licensed Neupogen. For a PK similarity assessment for a G-CSF**

**product, we strongly recommend that the selected dose (or doses) be in the linear ascending part of the dose-response curve (i.e., lower than 10 µg/kg which is on the plateau of the dose-response curve) and should be justified. In 2010, we recommended that you study both the 5 µg/kg and 10 µg/kg doses. As stated in the draft guidance for industry Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act (p. 7) –as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. The draft guidance for industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product also explains that when the administered dose is on the plateau of a dose-response curve, the clinical trial will not be sensitive in detecting differences between the two products (see lines 749-750).**

- With regard to study EP06-109, for PD sampling for CD34+ in peripheral blood to be adequate, you should characterize the AUC of CD34+ and CD34max following at least five daily doses. If the CD34+ data to support the mobilization indication is limited to single dose evaluation as is described in the meeting packet, you should provide a justification supporting the adequacy of the data in the BLA submission.**
- As described in the draft guidance for industry on Biosimilars -- Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, a sponsor may seek to use data derived from clinical studies comparing a proposed product with a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed to provide adequate scientific justification for this approach would likely include a clinical PK and/or PD study conducted with the U.S. licensed reference product. The adequacy of this scientific justification and bridge to the US-licensed reference product would be a review issue. In addition, a sponsor may submit publicly available information regarding the non-U.S.-licensed product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.**

**We note that a 3-way clinical PK and/or PD bridging study has not been conducted for this development program. Therefore, based on the information contained in the meeting package, we assume that you intend to scientifically justify the relevance of the comparative data obtained using the EU-approved filgrastim product to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge. As outlined in the response to Question 4, we note that the analytical data you intend to submit may not be sufficient to build an adequate scientific bridge. The analytical**

**bridge should include direct physicochemical comparison of all 3 products, US-licensed Neupogen to EP2006, the EU-approved filgrastim product to EP2006, and the EU-approved filgrastim product to US-licensed Neupogen, and all three comparisons should meet the pre-specified acceptance criteria for analytical similarity.**

**Assuming you intend to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge, you will need to provide a justification in your BLA as to the adequacy of the “analytical-only bridge” and why a 3-way clinical PK/PD comparison is not necessary to bridge data from your four PK/PD studies that utilized EU-approved filgrastim as the comparator. The absence of a 3-way bridging PK/PD study will be a review issue. However, if you cannot build an adequate scientific bridge to your four PK/PD studies that utilized EU-approved filgrastim as the comparator, based on the issues described in the first 2 bullets of the response to Question 11, the clinical data generated in study EP06-109 may not be sufficient to support a demonstration of biosimilarity of EP2006 to US-licensed Neupogen.**

**Based on the concerns identified regarding the adequacy of the analytical data to build a sufficient scientific bridge, we strongly encourage you to complete a single dose, three-way clinical PK bridging study, using an appropriate dose level, comparing US-licensed Neupogen, EU-approved filgrastim, and EP2006.**

**We note that the utility of data from the single arm study (EP06-301) in patients with breast cancer is limited due to the reliance on a historical control.**

**Discussion:**

***The sponsor presented the attached slide presentation. The sponsor presented slides 39-41 in relation to the FDA response to Question 11.***

***Sandoz stated their position that the 10 µg/kg dose falls in the linear portion of the dose-response curve. The FDA noted that PK/PD data from doses higher than 10 µg/kg would be needed to conclude that the 10 µg/kg dose falls in the linear portion of the dose-response curve. In addition, FDA noted that there is no difference in the PD response between the 5 µg/kg and 10 µg/kg doses.***

***The FDA emphasized the importance of establishing an adequate scientific bridge between EU-approved filgrastim and US-licensed Neupogen to justify the relevance of data obtained from the studies that used EU-approved filgrastim as a comparator.***

***The Sponsor stated that PK data are available on 54 evaluable patients from clinical study EP06-302 using US-licensed Neupogen and EP2006 at doses of 5 ug/kg. The FDA stated that analyses of these data would be important to support a demonstration of PK/PD similarity.***

*Also, see the summary of discussion regarding the scientific bridge captured under Question 4.*

**Question 12:**

To address Pediatric Research Equity Act (PREA), Sandoz plans to submit a pediatric assessment consisting of scientific rationale and justification for extrapolation to treatment in pediatric patients. Since the underlying mechanism of action of the reference product Neupogen® is identical for all indications it is approved for, Sandoz considers it justified to extrapolate the clinical data from phase III studies and the biosimilarity of EP2006 demonstrated by totality of the overall package to all other remaining indications for which the reference product Neupogen® is approved for.

Does the Agency agree with this approach to address Pediatric Research Equity Act?

**FDA Response:**

**Yes, we agree with your approach in principle. The adequacy of this approach will be a review issue. However, we note that your justification for extrapolation for purposes of demonstrating biosimilarity should focus on extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) in the context of your biosimilar development program rather than extrapolation of efficacy (but not safety or dosing) from adult populations to pediatric populations.**

**Discussion:**

*The sponsor presented the attached slide presentation. The sponsor presented slides 37-38 in relation to the FDA response to Question 12.*

*FDA noted that the approach presented by the sponsor in the slide presentation would need to be discussed internally, and that FDA would provide comments in a post-meeting note.*

**Post Meeting Note:** *You asked if it would be acceptable to submit your proposed 351(k) BLA with the agreed, but not confirmed, initial pediatric study plan (iPSP). We refer you to the draft guidance entitled “Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans” (July 2013), which explains that “[i]f a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.” FDA cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP. However, it should be noted that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP. You should submit an agreed and confirmed initial pediatric study plan with your BLA submission.*

**Question 13: Day-120 safety update**

Sandoz will provide the interim safety reports of the European post-approval studies EP06-401, EP06-402, and EP06-501 during the day-120 safety update if not included in the initial

application. Further, if new safety findings regarding the widely used product class of filgrastim-containing drugs are available for Sandoz, either from public available source or Sandoz data, it will be reported.

Does FDA agree with this proposal?

**FDA Response:**

**Yes, we agree.**

**Discussion:**

***No discussion occurred.***

**Question 14: Format of study data/analysis programs**

Data analyses were performed using SAS® Software. Sandoz intends to provide the Agency with all collected/derived data in CDISC SDTM-format, along with annotated CRFs (please find a sample CRF in Appendix 3 – Case Report Form), and a document including data set descriptions as well as variable descriptions (define.pdf). Data will be provided as SAS transport files (XPT files). All analyses of Sandoz will be built on the provided SDTMs.

Since the studies were originally analyzed based on non-CDISC data, the original SAS programs do not relate to the datasets submitted. Therefore, Sandoz does not intend to provide any SAS programs at the time of filing. The adaptation and validation of these programs is ongoing and specific programs will be provided upon request.

Does the Agency concur with Sandoz' that the data format and the potential to provide SAS programs upon request, is adequate to support the submission, filing, and review of Sandoz' proposed biosimilar BLA for EP2006?

**FDA Response:**

- **We concur with your data format.**
- **Please provide a Statistical Analysis Dataset, in SAS transport format to our Electronic Document Room (EDR). This dataset shall have one record only per subject and need to include at least following information:**
  - **Demographic variables**
  - **Baseline characteristics**
  - **Population flags**
  - **Efficacy outcomes (primary, secondary, etc.)**
  - **Covariates and subgroup variables**
  - **Subject disposition variables**
- **The define.pdf file should contain the descriptions of variable names on data sets. All derived variables should be clearly defined so that these variables can be traced to variables in the raw datasets. Please also include the programs that were used to derive the dataset.**

**Discussion:**

*No discussion occurred.*

**Question 15: Data to be included and summarized**

The clinical overview (Section 2.5) and the summaries (2.7.3 and 2.7.4) in Module 2 of the dossier will primarily be based on the results of five phase 1 studies (EP06-101, EP06-102, EP06-103, EP06-105, and EP06-109) conducted in healthy volunteers and one single-arm phase 3 (EP06-301) study in breast cancer patients. In addition, efficacy and safety results of the comparative Phase 3 trial (EP06-302) in breast cancer patients using vials and interim efficacy and safety data of study EP06-501 in healthy donors will be included as supportive data.

Due to the differences in the application route, frequency, and dose, Sandoz proposes to present the phase 1 study results side-by-side without any integrated analyses.

Based on the completely different setting in the phase 3 study as compared to the healthy volunteer studies and to the stem cell mobilization study and given that the supportive study EP06-302 uses a different presentation, no pooled analyses will be performed across these studies. In particular, Sandoz proposes not to include specific ISE and ISS documents in the file, but to assess and discuss the overall efficacy and safety profile in the clinical summary sections.

The four phase 1 studies conducted in Japan are considered only supportive and the results will not be included in the Module 2, however the study reports will be provided in Section 5.3 of the dossier.

Does the Agency concur with this approach?

**FDA Response:**

**Yes, we agree.**

**As noted in the response to Question 7, in the event the data from the studies conducted in Japan are necessary to support your 351(k) application, sufficient data should be provided to establish the relationship between the material used in the studies and the EP2006 product for which you seek approval.**

**Discussion:**

*No discussion occurred.*

**2.5 Labeling**

**Question 16:**

Does the Agency agree that the biosimilar prescribing information for EP2006 should be essentially the same as the prescribing information of the US reference listed biologic Neupogen®?

**FDA Response:**

**Your proposed approach to draft proposed labeling is a reasonable starting point for submission of your proposed 351(k) BLA. Submit your draft proposed labeling for EP2006 in the PLR format. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your 351(k) BLA.**

**Discussion:**

*No discussion occurred.*

**2.6 Additional Comments**

**Statistics**

The proposed no imputation for missing data is not acceptable. Sensitivity analyses, including an appropriate method of imputation, should be performed to account for the limitation of the data and to examine the potential impact of any missing data. Too much missing data undermine the reliability and confidence of the results. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.

**Discussion:**

*No discussion occurred.*

**Product Quality Microbiology**

All facilities should be registered with FDA at the time of the 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 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:

- 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 (b) (4) 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).
- (b) (4)
- Bioburden and endotoxin data obtained (b) (4) of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

The CMC Drug Product section of the 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”.

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

- [REDACTED] (b) (4) retention study [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4). Hold times should be validated at manufacturing scale.
- [REDACTED] (b) (4)
- 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.

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 for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed [REDACTED] (b) (4) for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed [REDACTED] (b) (4) as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610(b).

- The effect of hold time on endotoxin recovery should be assessed (b) (4)

(b) (4)

**Discussion:**

*No discussion occurred.*

**Immunogenicity**

Table 13-1 does not specify the location of the validation reports for immunogenicity assays used to evaluate human sera samples and the immunogenicity data. Provide validation reports for immunogenicity assays in section 5.3.1. “Reports of Biopharmaceutical Studies” under 5.3.1.4 “Reports of Bioanalytical Methods for Human Studies”. The immunogenicity data should be included under Section 2.7. “Clinical Summary” and a synopsis in section 2.5. “Clinical Overview”.

**Discussion:**

*No discussion occurred.*

**Regulatory**

1. You describe the strength of your proposed product and the reference product in your Briefing Book as 30 MU/0.5mL and 48 MU/0.8 mL for the prefilled syringe. It is unclear why you have chosen different units of measure (“MU” or “Mio. Units”) than appear in the approved product labeling for US-licensed Neupogen, the reference product, which describes the strength of the product in mcg/mL. As stated in FDA’s draft guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the BPCI Act, the total content of drug substance and concentration of drug substance generally should be expressed using the same measure as the reference product (see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259809.htm#Q12>). Revise all references to the strength of your proposed product and the reference product accordingly.
2. You state that the applicant will provide a “reviewer’s guide” as appendix to the cover letter with the initial submission containing information on, among other things, naming conventions. Please note that your 351(k) BLA submission should clearly describe whether the comparator used in each study is the US-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature throughout your 351(k) BLA submission that clearly differentiates these products. A single explanation in the reviewer’s guide will not be adequate. Furthermore, we note that statements such as “Using Neupogen as reference product at every stage in development...” (Briefing Book, page 16) are misleading and erroneous, and require correction.

**Discussion:**

*No discussion occurred.*

***Additional Discussion:***

- *The sponsor noted their plan to submit the 351(k) BLA for EP2006 requesting licensure as a biosimilar to US-licensed Neupogen in May 2014.*
- *The sponsor noted their intention to request a meeting to discuss an interchangeability designation for EP2006 after the original BLA to support a demonstration of biosimilarity is submitted.*

### **3.0 PREA PEDIATRIC STUDY PLAN**

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(n) 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 the submission of your planned 351(k) BLA; see additional comments below regarding expected review timelines.

Section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 505B(e) of the FD&C Act to set forth a process for reaching agreement between applicants and FDA on initial PSPs. This provision of FDASIA has an effective date of January 5, 2013. Section 505B(e)(2)(A) of the FD&C Act as amended by FDASIA provides that applicants should submit an initial PSP no later than 60 calendar days after the date of the end-of-Phase 2 meeting, or at another time agreed upon by FDA and the applicant. As required by FDASIA, FDA has issued guidance on PSP requirements, including timing of PSP submission. Refer to Guidance for Industry 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>

Sections 505B(e)(2)(C) and 505B(e)(3) 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); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. 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.

#### **4.0 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

#### **5.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

#### **6.0 ACTION ITEMS**

None.

#### **7.0 ATTACHMENTS AND HANDOUTS**

A copy of slides presented at the meeting is 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  
12/19/2013



PIND 109197

**MEETING PRELIMINARY COMMENTS**

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

Dear Mr. Pakulski:

Please refer to your Pre-Investigational New Drug Application (PIND) file for EP2006.

We also refer to your August 20, 2013, correspondence, received August 22, 2013, requesting a meeting to discuss and secure FDA's guidance and agreement on the format of the content of the planned BLA in order to support the licensure of Sandoz' rhG-CSF product under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hard copy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Monsurat Lara Akinsanya, M.S.  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## PRELIMINARY MEETING COMMENTS

**Meeting Type:** Biosimilar  
**Meeting Category:** BPD Type 4

**Meeting Date and Time:** November 19, 2013; 10:00 AM – 11:00 AM EDT  
**Meeting Location:** White Oak Building 22, Conference Room: 1419

**Application Number:** PIND 109197  
**Product Name:** EP2006 (proposed biosimilar to US-licensed Neupogen)  
**Indication:** EP2006 is being developed for the same indications as approved for US-licensed Neupogen  
**Sponsor/Applicant Name:** Sandoz Inc.

### Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 19, 2013; 10:00 AM – 11:00 AM EDT between Sandoz and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

### 1.0 BACKGROUND

On August 22, 2013, the Agency received a meeting request from Sandoz to discuss and secure FDA's guidance and agreement on the format of the content of the planned BLA in order to support the licensure of Sandoz' rhG-CSF product under section 351(k) of the Public Health Service Act (PHS Act, 42 U.S.C. 262(k)). The Agency granted the meeting request on September 7, 2013, as a Biosimilar Biological Product Development (BPD) Type 4 Meeting.

On November 14, 2013, the Division emailed Sandoz the preliminary responses to the questions contained in the meeting information package received August 22, 2013.

## **2. DISCUSSION**

### **General Introductory Comments:**

FDA may provide further clarifications of, or refinements and/or changes to these preliminary 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).

Please note that for ease of reference and discussion, we have renumbered your questions in sequential order.

### **2.1 Electronic submission – eCTD**

Sandoz intends to submit the initial application in electronic form using the eCTD format according to current FDA requirements. In the following the applicant would like to take the chance to point out Sandoz' position and strategy on eCTD.

The applicant will provide a "reviewer's guide" as appendix to the cover letter with the initial submission containing information on the content, hyperlinking strategy, naming conventions, legacy documents, literature references, metadata etc., in order to facilitate a smooth and convenient review of the application for the Agency.

Because Sandoz pursues a global development, it proposes to provide all documentation in A4 format while guaranteeing that the page layout is compatible with letter format. In other words, all documents will be suitable for printing on letter format paper as well as A4 format paper. Page margins follow the specifications in the guideline (PDF Portable Document Format (PDF) Specifications).

### **Question 1:**

#### **Annotated table of contents**

Sandoz intends to submit an electronic CTD dossier as required by the FDA. In the briefing package submitted together with this meeting request, a table of contents of the dossier is provided as Table 13-1. A brief description of all documents is included into this table of contents.

Does the Agency agree that the proposed documents as described are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required, which have to be included in the eCTD dossier for an application under section 351(k) of the Public Health Service Act?

**FDA Response:**

**No, we do not agree that your proposal is adequate. Please see the responses to the remaining questions for information on additional documents and information that should be included in your planned eCTD submission.**

**Question 2:**

**Scanned PDFs – OCR**

Some existing documents such as literature references or CRF's are not available in a searchable format (i.e. not created from a readable source or OCR).

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

**FDA Response:**

**Yes, we agree.**

**Question 3:**

**Hyperlinking**

Sandoz intends to use efficient inter-document hyperlinking between individual dossier documents, besides adequate intra-document hyperlinking. This will facilitate a quick and convenient review. Hyperlinking is planned within Modules 2 and 3 and from Module 2 to the respective sections in Modules 3, 4, and 5. It is not planned to hyperlink documents within Modules 4 and 5 or across Modules 3, 4 and 5 to keep the number of hyperlinks to a reasonable amount.

Does the Agency agree with the proposed hyperlinking strategy?

**FDA Response:**

**No, we do not agree. Please provide hyperlinks within Module 5.**

**2.1 CMC**

**Question 4:**

Does the Agency agree that the CMC data package is sufficient to permit review of the registration application?

**FDA Response:**

**No, we do not agree. We have insufficient information to determine if the CMC data package is sufficient to permit meaningful review of the BLA. Furthermore, you stated that you intend to include "only selected information of the data packages" in the CTD (page 27). We advise that the CMC data and information expected for review of the proposed biosimilar product should be included in the BLA.**

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

- 1. The “final” analytical similarity assessment strategy, as outlined in the response to our information request dated November 1, 2013, intended to demonstrate that EP2006 is analytically “highly similar” to the reference product, US-licensed Neupogen, and to support an analytical bridge between EP2006, US-licensed Neupogen and the EU-approved filgrastim product (marketed in the EU as “Neupogen”) is based on limited data. We have identified deficiencies including limited product characterization (e.g. lack of tests to evaluate product strength and disulfide bond integrity, and insufficient orthogonal methods for characterization of aggregates and higher order structure) and limited number of lots of EP2006, US-licensed Neupogen and the EU-approved filgrastim product analyzed. We note that the data may not be sufficient to support a demonstration of “highly similar” or to build an adequate scientific bridge.**

**In your response to the information request, you state that you “compare your biosimilar products to the reference product throughout the development process on many more lots over time”. The comparative analytical data generated during development may be considered to support analytical similarity provided the analytical characterization of the products is robust, sufficient lots of EP2006, US-licensed Neupogen and the EU-approved filgrastim product were evaluated, and the EP2006 material used in the assessment includes EP2006 product manufactured by the clinical process and by the proposed commercial process for which you seek approval.**

- 2. We note that you have made changes to the manufacture of EP2006 drug substance and drug product (e.g. scale and site of manufacture), and plan to submit comparability data in your BLA submission. Please be aware that in addition to demonstrating comparability between the pre-change and post-change drug substance (DS) and drug product (DP), analytical similarity of EP2006 manufactured by the clinical processes (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at Lek Pharmaceuticals d.d., Slovenia and IDT Biologika GmbH, Germany) and proposed commercial product (i.e. DS manufactured at Sandoz GmbH Kundl, (b) (4) and DP manufactured at GP Grenzach Produktions GmbH, Germany) needs to be demonstrated to US-licensed Neupogen.**
- 3. You plan to submit analytical data comparing EP2006, US-licensed Neupogen and the EU-approved filgrastim product to demonstrate analytical similarity of your product to the reference product, US-licensed Neupogen, and to establish an analytical bridge between EP2006, US-licensed Neupogen, and the EU-approved filgrastim product. In your BLA submission, clearly specify the data you intend to use to demonstrate analytical similarity and the data intended to establish the analytical bridge between your product, the reference product, and the EU-approved filgrastim product. For the analytical bridge, we expect all three comparisons (EP2006 to US-licensed Neupogen, EP2006 to the EU-approved filgrastim product, and the EU-approved filgrastim product to US-approved Neupogen) to meet the pre-specified acceptance criteria for similarity. Additionally, specify whether the analytical similarity assessment was**

**conducted with EP2006 lots manufactured by the clinical and proposed commercial processes.**

**With respect to organization of the CMC data package, address the following in the BLA submission:**

**1. Module 3 should also include the following data:**

- i. You propose to provide “Executed Batch Records” upon request. This is not acceptable. Executed batch records should be provided in the BLA submission.**
- ii. You plan to provide analytical method validation reports for non-compendial methods in Module 3 section 3.2.S.4.3. These reports along with method validation protocols should be located in the regional section (3.2.R)**
- iii. Table 13-1 does not specify whether analytical comparability and analytical similarity protocols will be provided. Provide analytical comparability and analytical similarity protocols in separate 3.2.R modules.**
- iv. Functional assays, including mechanism of action, should be provided and a justification that EP2006 has the same mechanism(s) of action as US-licensed Neupogen needs to be included in your BLA submission. 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.**

**2. In addition, include the following additional information in the relevant CTD sections.**

<b>CTD section</b>	<b>Comment</b>
<b>1.1.2 FDA form 356h</b>	<b>Indicate if the manufacturing and testing sites are ready for inspection.</b>
<b>1.3 Administrative information</b>	<b>A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections. Environmental Assessment or a request for categorical exclusion</b>
<b>2 Common Technical document summaries</b>	<b>Summaries of “Executed Batch Records” and summaries of “Analytical Comparability and Analytical Similarity protocols”</b>
<b>3.2.S.2.5 Process validation and/or evaluation</b>	<ul style="list-style-type: none"> <li><b>• Three successful consecutive [REDACTED] (b) (4) [REDACTED] hold time validation runs at manufacturing scale from microbiology perspective.</b></li> </ul>

	<ul style="list-style-type: none"> <li>• <b>Information</b> [redacted] (b) (4) including microbiology data</li> <li>• <b>Data summaries of shipping validation studies</b></li> </ul>
<b>3.2.S.4.3 Validation of analytical procedures</b>	<b>Qualification reports for bioburden and endotoxin tests.</b>
<b>3.2.P.3.5 Process validation and/or evaluation</b>	<ul style="list-style-type: none"> <li>• [redacted] (b) (4) retention study report [redacted] (b) (4)</li> </ul> <p>[redacted] (b) (4)</p> <ul style="list-style-type: none"> <li>• <b>Hold time validation at scale from microbiology perspective</b></li> </ul> <p>[redacted] (b) (4)</p> <ul style="list-style-type: none"> <li>• <b>Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs,</b></li> <li>• <b>A description of the routine environmental monitoring program</b></li> <li>• <b>Shipping validation data, including container closure integrity data</b></li> </ul>
<b>3.2.P.5.3 Validation of analytical procedures</b>	<b>Qualification of bioburden, endotoxin, and sterility tests.</b> <b>Results of rabbit pyrogen test using three drug product lots.</b>
<b>3.2.P.8.2 Post-approval Stability Protocol and Commitment</b>	<b>Container closure integrity test</b> [redacted] (b) (4) <b>on the stability program.</b>
<b>3.2.A Appendices</b>	<b>Information about other products manufactured in the facilities and strategies to prevent contamination and cross-contamination should also be described in this section.</b>

**Question 5:**

Does the Agency concur with Sandoz' proposal to provide the detailed summary reports for biosimilarity studies with the originators as well as the comparability studies performed for quality changes during development as separate 3.2.R modules?

**FDA Response:**

**Your proposal to provide analytical similarity reports and analytical comparability reports as separate 3.2.R. modules is acceptable. However, full analytical similarity, and analytical comparability reports should be provided. Please refer to comment 3 in the response to question 1 above regarding the content of the analytical similarity and analytical bridge data.**

**Question 6:**

Does the Agency concur with Sandoz' proposal to include more detailed information on the process characterization as separate 3.2.R module(s) (e.g. detailed description of methodology and specific examples from process characterization studies)?

**FDA Response:**

**Yes, we concur.**

**Question 7:**

Sandoz will provide information on several supportive clinical studies (see also Clinical Question 5). These studies were conducted using (b) (4) which is different from the product Sandoz is seeking approval for (b) (4)

Does the Agency agree with Sandoz's proposal that inclusion of CMC data on (b) (4) used in supportive clinical studies is not needed?

**FDA Response:**

**No, we do not concur. The purpose of the "supportive clinical studies" is not clear from the information provided in your meeting package. Therefore, it is unclear whether the associated CMC data are required in the BLA. In the event the "supportive clinical data" generated with the different (b) (4) material are required to support your 351(k) application, sufficient CMC data should be provided to establish the relationship between such (b) (4) material and the EP2006 product for which you seek approval.**

**Question 8:**

The product concerned is considered a combination product composed of the drug and two device components, in particular a pre-filled syringe and a needle safety guard (b) (4). Sandoz proposes to submit information on the pre-filled syringe and the needle safety guard, and their respective interfaces in a summary document in section 3.2.R of the eCTD. To avoid redundant information, appropriate hyperlinks to Module 3.2.P documents will be set and the respective information will not be repeated in Module 3.2.R. As requested during the pre-IND

meeting (see pre-IND meeting minutes dated 28 October 2010), Sandoz will provide objective evidence that the device components can be handled safely and effectively by the intended user groups consisting of patients, healthcare professionals, and caregivers. The summary report that Sandoz intends to provide is based on a simulated use handling study conducted by Novartis Pharma AG for a combination product composed of the identical device components (i.e. pre-filled syringe, needle safety guard) and comparable instructions for use regarding the Novartis product. This study revealed that all intended user groups can safely and effectively handle the device. Although the patient population differs between the Novartis product and EP2006 it can be safely assumed that the device components also suits EP2006 users, because they don't have any special needs from a human factors perspective that is caused by the disease (e.g. such as patients suffering from rheumatoid arthritis (RA)).

Does the Agency concur that the outlined approach to address the requirements for the presented combination product EP2006 is acceptable?

**FDA Response:**

**You stated that that you will provide a summary from a simulated use study that was conducted with a Novartis product. In addition, you stated that the device components (pre-filled syringe and needle safety guard) are identical to the Novartis product. However, it appears that the patient population differs between the Novartis product and EP2006. Different patient population indicates different intended user group. A key component of human factors/usability validation testing is that users who are representative of actual users be used for the testing.**

**At this time, we cannot determine whether your approach is acceptable without information that provides a comprehensive analysis of the intended users for your product and how they are comparable to the users of the Novartis product, and without a comprehensive use-related risks analysis on the use of your product. This risk analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.**

**You should submit these detailed analyses for review. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.**

### 2.3 Pharmacology/Toxicology

**Question 9:**

Does the Agency agree that the pharmacology and toxicology package summarized in Table 12-1 is sufficient to permit assessment of biosimilarity at the nonclinical level and the review of the respective sections of proposed biosimilar BLA dossier?

**FDA Response:**

**Yes. The pharmacology and toxicology package is acceptable for BLA filing. However, a final determination of biosimilarity will be made during the BLA review based on the totality of the evidence submitted.**

**Question 10:**

Does the Agency agree that for licensure of EP2006 as a biosimilar product to Neupogen under 351(k) of the Public Health Service Act, the pharmacology and toxicology information can be submitted as study reports in PDF format, without providing additional electronic, individual animal data listings?

**FDA Response:**

**You may submit the data in the PDF format; however, all data including individual animal data should be submitted to the BLA.**

### 2.4 Clinical

**Question 11:**

Does the Agency agree that the clinical data package is sufficient to permit assessment of biosimilarity at the clinical level and the review of the respective sections of the proposed biosimilar BLA dossier?

**FDA Response:**

**The proposed clinical package presented in the meeting package may not be adequate to support a demonstration of biosimilarity. We have the following concerns:**

- **We note that study EP06-109 only compared a single 10 µg/kg SC dose PK of EP2006 with US-licensed Neupogen. For a PK similarity assessment for a G-CSF product, we strongly recommend that the selected dose (or doses) be in the linear ascending part of the dose-response curve (i.e., lower than 10 µg/kg which is on the plateau of the dose-response curve) and should be justified. In 2010, we recommended that you study both the 5 µg/kg and 10 µg/kg doses. As stated in the draft guidance for industry Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act (p. 7) –as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of**

**the proposed biosimilar product directly with the U.S.-licensed reference product. The draft guidance for industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product also explains that when the administered dose is on the plateau of a dose-response curve, the clinical trial will not be sensitive in detecting differences between the two products (see lines 749-750).**

- **With regard to study EP06-109, for PD sampling for CD34+ in peripheral blood to be adequate, you should characterize the AUC of CD34+ and CD34max following at least five daily doses. If the CD34+ data to support the mobilization indication is limited to single dose evaluation as is described in the meeting packet, you should provide a justification supporting the adequacy of the data in the BLA submission.**
- **As described in the draft guidance for industry on Biosimilars — Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, a sponsor may seek to use data derived from clinical studies comparing a proposed product with a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed to provide adequate scientific justification for this approach would likely include a clinical PK and/or PD study conducted with the U.S. licensed reference product. The adequacy of this scientific justification and bridge to the US-licensed reference product would be a review issue. In addition, a sponsor may submit publicly available information regarding the non-U.S.-licensed product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.**

**We note that a 3-way clinical PK and/or PD bridging study has not been conducted for this development program. Therefore, based on the information contained in the meeting package, we assume that you intend to scientifically justify the relevance of the comparative data obtained using the EU-approved filgrastim product to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge. As outlined in the response to Question 4, we note that the analytical data you intend to submit may not be sufficient to build an adequate scientific bridge. The analytical bridge should include direct physicochemical comparison of all 3 products, US-licensed Neupogen to EP2006, the EU-approved filgrastim product to EP2006, and the EU-approved filgrastim product to US-licensed Neupogen, and all three comparisons should meet the pre-specified acceptance criteria for analytical similarity.**

**Assuming you intend to establish an acceptable bridge to the U.S.-licensed reference product through an “analytical-only” bridge, you will need to provide a justification in your BLA as to the adequacy of the “analytical-only bridge” and why a 3-way clinical PK/PD comparison is not necessary to bridge data from your four PK/PD**

**studies that utilized EU-approved filgrastim as the comparator. The absence of a 3-way bridging PK/PD study will be a review issue. However, if you cannot build an adequate scientific bridge to your four PK/PD studies that utilized EU-approved filgrastim as the comparator, based on the issues described in the first 2 bullets of the response to Question 11, the clinical data generated in study EP06-109 may not be sufficient to support a demonstration of biosimilarity of EP2006 to US-licensed Neupogen.**

**Based on the concerns identified regarding the adequacy of the analytical data to build a sufficient scientific bridge, we strongly encourage you to complete a single dose, three-way clinical PK bridging study, using an appropriate dose level, comparing US-licensed Neupogen, EU-approved filgrastim, and EP2006.**

**We note that the utility of data from the single arm study (EP06-301) in patients with breast cancer is limited due to the reliance on a historical control.**

**Question 12:**

To address Pediatric Research Equity Act (PREA), Sandoz plans to submit a pediatric assessment consisting of scientific rationale and justification for extrapolation to treatment in pediatric patients. Since the underlying mechanism of action of the reference product Neupogen® is identical for all indications it is approved for, Sandoz considers it justified to extrapolate the clinical data from phase III studies and the biosimilarity of EP2006 demonstrated by totality of the overall package to all other remaining indications for which the reference product Neupogen® is approved for.

Does the Agency agree with this approach to address Pediatric Research Equity Act?

**FDA Response:**

**Yes, we agree with your approach in principle. The adequacy of this approach will be a review issue. However, we note that your justification for extrapolation for purposes of demonstrating biosimilarity should focus on extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) in the context of your biosimilar development program rather than extrapolation of efficacy (but not safety or dosing) from adult populations to pediatric populations.**

**Question 13: Day-120 safety update**

Sandoz will provide the interim safety reports of the European post-approval studies EP06-401, EP06-402, and EP06-501 during the day-120 safety update if not included in the initial application. Further, if new safety findings regarding the widely used product class of filgrastim-containing drugs are available for Sandoz, either from public available source or Sandoz data, it will be reported.

Does FDA agree with this proposal?

**FDA Response:**

**Yes, we agree.**

**Question 14: Format of study data/analysis programs**

Data analyses were performed using SAS® Software. Sandoz intends to provide the Agency with all collected/derived data in CDISC SDTM-format, along with annotated CRFs (please find a sample CRF in Appendix 3 – Case Report Form), and a document including data set descriptions as well as variable descriptions (define.pdf). Data will be provided as SAS transport files (XPT files). All analyses of Sandoz will be built on the provided SDTMs.

Since the studies were originally analyzed based on non-CDISC data, the original SAS programs do not relate to the datasets submitted. Therefore, Sandoz does not intend to provide any SAS programs at the time of filing. The adaptation and validation of these programs is ongoing and specific programs will be provided upon request.

Does the Agency concur with Sandoz' that the data format and the potential to provide SAS programs upon request, is adequate to support the submission, filing, and review of Sandoz' proposed biosimilar BLA for EP2006?

**FDA Response:**

- **We concur with your data format.**
- **Please provide a Statistical Analysis Dataset, in SAS transport format to our Electronic Document Room (EDR). This dataset shall have one record only per subject and need to include at least following information:**
  - **Demographic variables**
  - **Baseline characteristics**
  - **Population flags**
  - **Efficacy outcomes (primary, secondary, etc.)**
  - **Covariates and subgroup variables**
  - **Subject disposition variables**
- **The define.pdf file should contain the descriptions of variable names on data sets. All derived variables should be clearly defined so that these variables can be traced to variables in the raw datasets. Please also include the programs that were used to derive the dataset.**

**Question 15: Data to be included and summarized**

The clinical overview (Section 2.5) and the summaries (2.7.3 and 2.7.4) in Module 2 of the dossier will primarily be based on the results of five phase 1 studies (EP06-101, EP06-102, EP06-103, EP06-105, and EP06-109) conducted in healthy volunteers and one single-arm phase 3 (EP06-301) study in breast cancer patients. In addition, efficacy and safety results of the comparative Phase 3 trial (EP06-302) in breast cancer patients using vials and interim efficacy and safety data of study EP06-501 in healthy donors will be included as supportive data.

Due to the differences in the application route, frequency, and dose, Sandoz proposes to present the phase 1 study results side-by-side without any integrated analyses.

Based on the completely different setting in the phase 3 study as compared to the healthy volunteer studies and to the stem cell mobilization study and given that the supportive study EP06-302 uses a different presentation, no pooled analyses will be performed across these studies. In particular, Sandoz proposes not to include specific ISE and ISS documents in the file, but to assess and discuss the overall efficacy and safety profile in the clinical summary sections.

The four phase 1 studies conducted in Japan are considered only supportive and the results will not be included in the Module 2, however the study reports will be provided in Section 5.3 of the dossier.

Does the Agency concur with this approach?

**FDA Response:**

**Yes, we agree.**

**As noted in the response to Question 7, in the event the data from the studies conducted in Japan are necessary to support your 351(k) application, sufficient data should be provided to establish the relationship between the material used in the studies and the EP2006 product for which you seek approval.**

## **2.5 Labeling**

**Question 16:**

Does the Agency agree that the biosimilar prescribing information for EP2006 should be essentially the same as the prescribing information of the US reference listed biologic Neupogen®?

**FDA Response:**

**Your proposed approach to draft proposed labeling is a reasonable starting point for submission of your proposed 351(k) BLA. Submit your draft proposed labeling for EP2006 in the PLR format. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your 351(k) BLA.**

## **2.6 Additional Comments**

**Statistics**

The proposed no imputation for missing data is not acceptable. Sensitivity analyses, including an appropriate method of imputation, should be performed to account for the limitation of the data and to examine the potential impact of any missing data. Too much missing data undermine the reliability and confidence of the results. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.

**Product Quality Microbiology**

All facilities should be registered with FDA at the time of the 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 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:

- 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 (b) (4) 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).
- (b) (4)
- Bioburden and endotoxin data obtained (b) (4) of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- (b) (4)

The CMC Drug Product section of the 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”.

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

- (b) (4) retention study (b) (4).
- (b) (4)
- (b) (4). Hold times should be validated at manufacturing scale.
- (b) (4)

- 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.

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 for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed [REDACTED] (b) (4) for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed [REDACTED] (b) (4), as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610(b).
- The effect of hold time on endotoxin recovery should be assessed [REDACTED] (b) (4)

### **Immunogenicity**

Table 13-1 does not specify the location of the validation reports for immunogenicity assays used to evaluate human sera samples and the immunogenicity data. Provide validation reports for immunogenicity assays in section 5.3.1. “Reports of Biopharmaceutical Studies” under 5.3.1.4 “Reports of Bioanalytical Methods for Human Studies”. The immunogenicity data should be included under Section 2.7. “Clinical Summary” and a synopsis in section 2.5. “Clinical Overview”.

### **Regulatory**

1. You describe the strength of your proposed product and the reference product in your Briefing Book as 30 MU/0.5mL and 48 MU/0.8 mL for the prefilled syringe. It is unclear why you have chosen different units of measure (“MU” or “Mio. Units”) than appear in the approved product labeling for US-licensed Neupogen, the reference product, which describes the strength of the product in mcg/mL. As stated in FDA’s draft guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the BPCI Act, the total content of drug substance and concentration of drug substance generally should be expressed using the same measure as the reference product (see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm2598>

[09.htm#Q12](#)). Revise all references to the strength of your proposed product and the reference product accordingly.

2. You state that the applicant will provide a “reviewer’s guide” as appendix to the cover letter with the initial submission containing information on, among other things, naming conventions. Please note that your 351(k) BLA submission should clearly describe whether the comparator used in each study is the US-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature throughout your 351(k) BLA submission that clearly differentiates these products. A single explanation in the reviewer’s guide will not be adequate. Furthermore, we note that statements such as “Using Neupogen as reference product at every stage in development...” (Briefing Book, page 16) are misleading and erroneous, and require correction.

### **3.0 PREA PEDIATRIC STUDY PLAN**

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(n) 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 the submission of your planned 351(k) BLA; see additional comments below regarding expected review timelines.

Section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 505B(e) of the FD&C Act to set forth a process for reaching agreement between applicants and FDA on initial PSPs. This provision of FDASIA has an effective date of January 5, 2013. Section 505B(e)(2)(A) of the FD&C Act as amended by FDASIA provides that applicants should submit an initial PSP no later than 60 calendar days after the date of the end-of-Phase 2 meeting, or at another time agreed upon by FDA and the applicant. As required by FDASIA, FDA has issued guidance on PSP requirements, including timing of PSP submission. Refer to Guidance for Industry 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>

Sections 505B(e)(2)(C) and 505B(e)(3) 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); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. 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.

#### **4.0 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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