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RESEARCH**

APPLICATION NUMBER:

761045Orig1s000

OTHER REVIEW(S)

USE-RELATED RISK ANALYSIS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 31, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761045
Product Name and Strength:	LA-EP2006* Ziextenzo (pegfilgrastim-bmez) 6 mg/0.6 mL
Product Type:	Drug-Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz
Submission Date:	February 27, 2019, April 3, 2019, July 18, 2019, July 26, 2019, and August 22, 2019
OSE RCM #:	2015-2000-1 and 2019-815
DMEPA Primary Reviewer:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

* LA-EP2006 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name, Ziextenzo, and the nonproprietary name, pegfilgrastim-bmez, are conditionally approved only with approval of "LA-EP2006".

1 REASON FOR REVIEW

Sandoz submitted a response to Complete Response for LA-EP2006 on February 27, 2019. This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU) for LA-EP2006 (BLA 761045) for areas of vulnerability that could lead to medication errors. In addition, we evaluated the use-related risk analysis (URRA) and comparative analyses submitted by Sandoz April 3, 2019.

1.1 PRODUCT BACKGROUND & REGULATORY HISTORY

On August 27, 2015, Sandoz submitted 351(k) BLA 761045 seeking licensure for LA-EP2006 as a biosimilar to US-licensed Neulasta. LA-EP2006 is being proposed for the indication of decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. DMEPA completed a label and labeling review for this application on June 23, 2016.^a The review included recommendations for the PI, IFU, container label, and carton labeling.

The application received a Complete Response (CR) letter on June 24, 2016^b due to clinical pharmacology and product quality issues. The CR letter stated that FDA reserved comment on the proposed labeling (including the PI and carton and container labeling) until the application is otherwise adequate. Sandoz submitted a response to the CR letter for LA-EP2006 on February 27, 2019. The assessments, conclusions, and recommendations in this review reflect new information and analyses that were not considered in the June 23, 2016 review (see Appendix H).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A

^a Whaley, E. Label and Labeling Review for LA-EP2006 BLA 761045. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 23. RCM No.: 2015-2000.

^b CR Letter: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803f1285&_afRedirect=3339187150565817

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Information Requests	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The response to complete response submission included the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU). Sandoz is pursuing only one of the indications of US-licensed Neulasta (to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia).

Based on our initial assessment of the materials submitted, we determined additional information was needed to complete our evaluation. On March 28, 2019 we sent an information request (IR), requesting the submission of a comprehensive use-related risk analysis and comparative analyses for our review. See Appendix F for complete information request communications. Our assessment of the URRAs, comparative analyses, and labeling is described in the sections that follow.

3.1 USE-RELATED RISK ASSESSMENT

We note that LA-EP2006 has the same intended users, use environments, dosing, route of administration, and storage requirements as US-licensed Neulasta (BLA 125031) for its febrile neutropenia indication.

The sponsor submitted a URRAs, which identified and evaluated the tasks involved in the use of the LA-EP2006 prefilled syringe (PFS), the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors.

We reviewed the URRAs for the proposed product. We did not identify any new or unique risks for the LA-EP2006 PFS as compared to the US-licensed Neulasta PFS, but note that users are not required to activate the needle guard manually which we view as acceptable as described below.

3.2 COMPARATIVE ANALYSES

Physical Comparison

LA-EP2006 is supplied as a single-dose, ungraduated PFS with an UltraSafe Passive™ needle guard. US-licensed Neulasta is supplied as a single-dose, ungraduated PFS with a manual needle guard and as a PFS for use with a delivery device, the OnPro kit. Both products are supplied in a carton containing one PFS. We note in the physical comparison that the LA-EP2006 PFS plunger

rod is light blue whereas the plunger rod in the US-licensed Neulasta PFS is dark blue. The LA-EP2006 PFS plunger rod is shorter (56.3 mm) and has a larger plunger head diameter (17.8 mm) as compared to the plunger rod and plunger head in the US-licensed Neulasta PFS (57.8 mm and 10 mm respectively). Additionally, LA-EP2006 PFS has a clear UltraSafe Passive needle guard while US-licensed Neulasta has a translucent blue UltraSafe Active needle guard. In this particular instance, our evaluation of the physical comparison determined the physical differences should not affect critical tasks therefore, these differences are acceptable.

Task Comparison

We note in the task comparison, that the critical tasks for LA-EP2006 align with the critical tasks for US-licensed Neulasta, with one exception that users of the US-licensed Neulasta PFS are required to activate the needle guard manually, whereas, the LA-EP2006 PFS has a passive needle guard which does not require manual activation. The passive needle guard activates automatically to cover the needle when the user releases the plunger after the injection has been given and the syringe removed from the injection site. The manual system requires an additional user step (i.e., the user slides the needle guard over the needle). We do not consider activation of the needle guard as a critical task, and therefore, we find these differences acceptable.

Labeling Comparison: Side-by-Side IFU Comparison

The LA-EP2006 IFU follows similar steps and injection technique as US-licensed Neulasta. However, we note the following differences:

- Like US-licensed Neulasta, the LA-EP2006 PFS does not have graduation marks, and therefore, doses less than 6 mg (0.6 mL) cannot be accurately measured or directly administered without manipulation of the PFS content or dose approximation. Due to the potential for dosing errors, direct administration to patients requiring doses less than 0.6 mL (6 mg) is not recommended. The Prescribing Information for US-licensed Neulasta states that the PFS is not intended for direct administration of the drug for doses less than 0.6 mL (6 mg) and we note that similar statements also appear in the proposed LA-EP2006 labeling. However, we recommend that information regarding dosing limitations of the PFS be conveyed in the IFU, which is consistent with the IFU of US-licensed Neulasta.
- The LA-EP2006 IFU does not list the buttocks as an injection site (see Figure D). The upper outer area of the buttocks is listed as an injection site for the reference product, US-licensed Neulasta. Therefore, we request that the sponsor clarifies and provides reasoning for the discrepancy between LA-EP2006 IFU and the US-licensed Neulasta.
- US-licensed Neulasta can be administered at either a 45° or 90° angle. However, Figure H in the LA-EP2006 IFU, which depicts the injection technique, shows an approximate 45° injection angle, and the text accompanying the figure does not state the injection angle. Therefore, we request that the sponsor clarifies and provides reasoning for the discrepancy between LA-EP2006 IFU and the US-licensed Neulasta. Additionally, we

recommend revising the IFU to include the injection angle that should be used to administer LA-EP2006.

- Additionally, we identified other aspects of the IFU that should be revised to add and/or relocate important information regarding the administration of LA-EP2006 to harmonize with the labeling for US-licensed Neulasta.

On July 12, 2019, we sent an IR to Sandoz to provide recommendations for the IFU (see Appendix F).

The Sponsor submitted a response to the IR and provided updated IFU on July 18, 2019 (see Appendix G). We consulted with PLT to review the IFU and provided additional recommendations in an IR sent to Sandoz on July 25, 2019 (see Appendix F). On July 26, 2019, Sandoz submitted updated labels and labeling, including an updated IFU. We had no additional comments or recommendations at that time.

Labeling Comparison: Carton and Container Labels

Our review of the comparison of the carton and container labels determined that differences identified in the comparative analysis of the carton and container labels were product-specific information (e.g., tradename and dress). As such, we find these differences acceptable.

However, from a medication error perspective, we identified several areas that may be improved to increase the readability and prominence of important information on the carton and container labels. On July 12, 2019, we sent an IR to Sandoz to provide recommendations for the container labels and carton labeling (see Appendix F).

3.3 LABELING: PRESCRIBING INFORMATION

We performed a risk assessment of the proposed PI to evaluate the potential for medication errors. In section 2.2 Administration, we note that the LA-EP2006 prefilled syringe should be allowed “to reach room temperature for a minimum of 15-30 minutes”; however, in the US-licensed Neulasta labeling, the time listed is 30 minutes (no range). Therefore, we requested the sponsor provide rationale for the difference. This request was sent in an IR to Sandoz on July 12, 2019 (see Appendix F). Sandoz submitted a response to the IR and provided updated labels and labeling (PI and PPI) on July 26, 2019 (see Appendix G).

4 CONCLUSION & RECOMMENDATIONS

Our review of the URRRA concluded that there were no new or unique risks when compared to US-licensed Neulasta. We also note that the intended user group, intended uses, and use environments for LA-EP2006 aligns with US-licensed Neulasta for the febrile neutropenia indication.

We determined that the sponsor does not need to submit a human factors validation study for our review at this time. Any changes to the URRRA would warrant further review.

Additionally, as a biosimilar, the proposed labeling for LA-EP2006 is, in relevant part, substantially the same as the labeling for US-licensed Neulasta regarding administration of doses less than 0.6 mL (6 mg). On August 22, 2019, Sandoz submitted updated labels and labeling (PI, PPI, IFU, container label, and carton labeling) to reflect FDA's "conditional acceptance" of the proprietary name "Ziextenzo" for BLA 761045 (see Appendix G). We have no additional recommendations at this time.

APPENDICES

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for LA-EP2006 that Sandoz submitted on February 27, 2019 and US-licensed Neulasta.

Table 2. Relevant Product Information for Udenyca and US-Licensed Neulasta		
Product Name	Ziextenzo	US-licensed Neulasta ^c
Initial Approval Date	N/A	January 31, 2002
Nonproprietary or Proper Name	Pegfilgrastim-bmez	Pegfilgrastim
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection	Injection
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	Cancer patients receiving myelosuppressive chemotherapy: <ul style="list-style-type: none"> • 6mg administered subcutaneously once per chemotherapy cycle. • Do not administer Ziextenzo between 14 days before and 24 hours after administration of cytotoxic chemotherapy. • Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1. 	Cancer patients receiving myelosuppressive chemotherapy: <ul style="list-style-type: none"> • 6 mg administered subcutaneously once per chemotherapy cycle. • Do not administer between 14 days before and 24 hours after cytotoxic chemotherapy. • Use weight-based dosing for pediatric patients weighing less than 45 kg, refer to Table 1.

^c Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Apr 2019. [cited 2019 Oct 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125031s198lbl.pdf

	<p>The ZIEXTENZO prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of ZIEXTENZO less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.</p> <p>Table 1. Dosing of Ziextenzo for pediatric patients weighing less than 45 kg</p> <table border="1" data-bbox="479 1207 966 1501"> <thead> <tr> <th>Body weight</th> <th>LA-EP2006 Dose</th> <th>Volume to administer</th> </tr> </thead> <tbody> <tr> <td>Less than 10kg*</td> <td>See below*</td> <td>See below*</td> </tr> <tr> <td>10-20 kg</td> <td>1.5 mg</td> <td>0.15 mL</td> </tr> <tr> <td>21-30 kg</td> <td>2.5 mg</td> <td>0.25 mL</td> </tr> <tr> <td>31-44 kg</td> <td>4 mg</td> <td>0.4 mL</td> </tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Ziextenzo</p>	Body weight	LA-EP2006 Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL	<p>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome:</p> <ul style="list-style-type: none"> Give 6 mg subcutaneously for adult victims with body weight \geq 45 kg for two doses given two weeks apart; for pediatric patients weighing less than 45 kg, use weight-based dosing. <p>The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.</p> <p>Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg</p> <table border="1" data-bbox="982 1165 1502 1459"> <thead> <tr> <th>Body weight</th> <th>Neulasta Dose</th> <th>Volume to administer</th> </tr> </thead> <tbody> <tr> <td>Less than 10kg*</td> <td>See below*</td> <td>See below*</td> </tr> <tr> <td>10-20 kg</td> <td>1.5 mg</td> <td>0.15 mL</td> </tr> <tr> <td>21-30 kg</td> <td>2.5 mg</td> <td>0.25 mL</td> </tr> <tr> <td>31-44 kg</td> <td>4 mg</td> <td>0.4 mL</td> </tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta</p>	Body weight	Neulasta Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL
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How Supplied	<p>Ziextenzo injection is a clear, colorless to slightly yellowish solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-bmez, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe Passive™ Needle Guard.</p>	<p>Neulasta is a clear, colorless, preservative-free solution available as single dose prefilled syringe with an UltraSafe® Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim as well as an OnPro kit which contains 6 mg/0.6 mL solution in a single prefilled syringe</p>																														

	Ziextenzo is provided in a dispensing pack containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 61314-866-01).	co-packaged with the on-body Injector for Neulasta.
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Store refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 8, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, 'LA-EP2006' and 'Ziextenzo'. Our search identified 1 previous label and labeling review and we considered our previous recommendations to see if they are applicable for this current review.

Reviewer	Document Title	Application	Date	RCM No.
Whaley, E.	Ziextenzo (biosimilar to Neulasta) Label and Labeling Review	BLA 761045	2016 JUN 23	2015-2000

APPENDIX C. HUMAN FACTORS

We received the following Human Factors documents submitted by Sandoz on April 3, 2019, per our March 28, 2019 information request.

Use-Related Risk Analysis

<\\cdsesub1\evsprod\bla761045\0049\m1\us\111-information-amendment\usability-risk-assessment.pdf>

Comparative Analyses

<\\cdsesub1\evsprod\bla761045\0049\m1\us\111-information-amendment\comparative-analysis.pdf>

APPENDIX F. INFORMATION REQUESTS

March 14, 2019: Request for Samples^d

We refer to your Class 2 Resubmission for BLA 761045 submitted on February 27, 2019.

We request you send three (3) intent-to-market samples (syringes), as well as associated packaging (cartons, blister) to assist in completion of our review.

Response: On April 17, 2019, we received the requested sample syringes and packaging.

March 28, 2019: Request for a URRR and Comparative Analyses

We refer to your response to complete response for BLA 761045 submitted on February 27, 2019.

We note you are proposing a 6 mg/0.6 mL single-dose prefilled syringe with UltraSafe Passive Needle Guard. However, you have not submitted a comprehensive risk analysis for your proposed product.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development).

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Submit your risk analysis and comparative analyses to the Agency for review under the BLA.

^d IR communication. <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804e3fb6>

Response: On April 3, 2019, Sandoz submitted the requested URRAs and Comparative Analyses. See Appendix C.^e

July 12, 2019: USPI, PPI, IFU, and Carton and Container Label Comments sent to Sandoz^f

On July 12, 2019, the Agency issued an information request that included the following DMEPA recommendations for the PI, IFU, carton labeling, and container label.

Prescribing Information

A. Dosage and Administration [Section 2]

1. Administration [Section 2.2]

- a. We note users are instructed to “allow the LA-EP2006 prefilled syringe to reach room temperature for a minimum of 15-30 minutes”; however, in the US-licensed Neulasta labeling, the time listed is 30 minutes (no range). Therefore, please clarify and provide rationale for the discrepancy between the LA-EP2006 PI and the US-licensed Neulasta PI.

Instructions for Use

A. Instructions for Use – General Comments

1. Overall, we recommend you incorporate all relevant information from the IFU for the reference product US-licensed Neulasta and present such information in a similar manner where appropriate.
2. In order to highlight important information and align with the with US-licensed Neulasta IFU, we recommend adding and/or revising the section headings as listed below and relocating sections of the IFU so that they appear in the following order:
 - 1) Guide to Parts (this is a new section heading)
 - 2) Storage of the LA-EP2006 Syringe
 - 3) Using the Prefilled Syringe (revised from “Important safety information”)
 - 4) Gather the supplies for the injection (revised from “Items you additionally need for your injection”)
 - 5) Preparing the LA-EP2006 prefilled syringe for use
 - 6) Prepare and clean the injection site (revised from “Subcutaneous Injection” and “The injection site”)
 - 7) How to use the LA-EP2006 prefilled syringe
 - 8) Disposal Instructions

Note that figures will need to be relabeled to accommodate the new order of information.

^e Response to IR. 2019 APR 3. [\cdsesub1\evsprod\bla761045\0049\m1\us\111-information-amendment\md-information-amendment-ir2.pdf](#)

^f IR Communication: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805047c0&_afRedirect=2400478461515238

B. Instructions for Use – Guide to Parts

1. We recommend adding “Guide to Parts” as the section heading.
2. To align with the US-licensed Neulasta IFU, we recommend deleting the current “IMPORTANT” statement and replacing it with the following statement so that it appears directly below the “Guide to Parts” heading:

Important Information: Read the Patient Information for important information you need to know about LA-EP2006 before using the Instructions for Use.
3. Consider removing the label “(b) (4)” from Figure A as this technical term may not be understood by patients and caretakers. Additionally, this term is not referenced in the remainder of the IFU.
4. To align with the US-licensed Neulasta IFU, relocate the “after use” image of the PFS (i.e., Figure E) to this section below Figure A. Figure A may serve as the “before use” image of the syringe; therefore, the current figure F may be deleted. Additionally, we recommend labeling both images as presented in the US-licensed Neulasta IFU.
5. To align with the US-licensed Neulasta IFU, we recommend adding ‘Important: The needle is covered by the gray needle cap before use’ below the image of the “before use” syringe.

C. Instructions for Use – Using the Prefilled Syringe

1. We recommend revising the section heading “(b) (4)” to read “Using the Prefilled Syringe.” We also recommend including the following statements in the order listed below to highlight important information, improve clarity, and to align with the US-licensed Neulasta IFU:
 - It is important not to try to inject yourself or someone else until you have been trained by your healthcare provider (b) (4). **Please read all the instructions before injecting. Each sealed blister contains one prefilled syringe. Each prefilled syringe contains 6 mg/0.6 mL of LA-EP2006 drug solution.**
 - Make sure that the name LA-EP2006 appears on the carton and prefilled syringe labels.
 - Check the carton and prefilled syringe labels to make sure the dose strength is 6 mg/0.6 mL.
 - You should not inject a dose of LA-EP2006 to children weighing less than 45 kg from a LA-EP2006 prefilled syringe. A dose less than 0.6 mL cannot be accurately measured using the LA-EP2006 prefilled syringe.”
 - **Do not use the LA-EP2006 prefilled syringe if the carton is opened or damaged. Do not open the outer carton until you are ready to use the LA-EP2006 prefilled syringe.**
 - The needle cap on the prefilled syringe contains natural rubber (derived from latex). Do not handle the prefilled syringe if you are allergic to latex.

- **Do not** use the LA-EP2006 prefilled syringe if the seal of the blister is broken, as it may not be safe for you to use.
- **Do not use the LA-EP2006 prefilled syringe if it has been dropped with the needle cap removed. The prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe.**
-  (b) (4).
- **Do not** shake the LA-EP2006 prefilled syringe.
- **Do not attempt to activate the LA-EP2006 prefilled syringe prior to injection.**
- Be careful not to touch the needle guard wings before use. By touching them, the needle guard may be activated too early.
- **Do not** remove the needle cap until just before you give the injection.
- The LA-EP2006 prefilled syringe cannot be re-used. Please dispose the used LA-EP2006 prefilled syringe immediately after use in a sharps container.

2. As currently presented, the “Keep LA-EP2006 and all medicines out of the reach of children” warning statement is included twice (under Important Safety Information and after Storage). We recommend deleting the first occurrence as this is duplicate information.

D. Instructions for Use – Gather the supplies for the injection

1. We recommend revising the section heading “Items you additionally need for your injection” to read “Gather the supplies for the injection”.

E. Instructions for Use – Preparing the LA-EP2006 prefilled syringe for use

1. We recommend revising the following statements and adding additional information in the order stated below to improve readability and clarity of this information:

Preparing the LA-EP2006 prefilled syringe for use



(b) (4)

DO NOT USE if:

- the liquid contains visible particles, or if the liquid is cloudy or discolored.
- it appears used or damaged.
- if the gray needle cap is missing or not securely attached.
- the expiration date printed on the label has passed.

In all cases, use a new prefilled syringe and call your healthcare provider.

F. Instructions for Use - Prepare and clean the injection site

1. We recommend deleting the “ (b) (4) ” heading and revising “The injection site” heading to read “Prepare and clean the injection site”.
2. We recommend revising the following statements and adding additional information in the order stated below to align with US-licensed Neulasta and to improve readability and clarity of this information:

Prepare and clean the injection site

- Clean the injection site with an alcohol swab. Let the skin dry.
- Do not touch this area again before injecting.

- If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
 - Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.
3. We recommend labeling Figures C and D with the appropriate injection sites to correspond with the text provided.
 4. We note Figure D and the corresponding text, does not list the upper outer area of buttocks as an injection site. The upper outer area of the buttocks is listed as an injection site if a caregiver is administering the injection for the reference product, US-licensed Neulasta. Therefore, please clarify and provide reasoning for the discrepancy between the LA-EP2006 IFU and the US-licensed Neulasta IFU.

G. Instructions for Use - How to use the LA-EP2006 prefilled syringe

1. We recommend revising statements and adding additional information to the text that accompanies Figure G improve readability and highlight important information:

Figure G

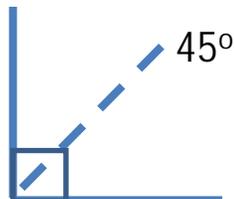


Hold the prefilled syringe by the syringe barrel. Carefully pull the needle cap straight off to remove it ~~from the ZIEXTENZO prefilled syringe~~ (see Figure G).

- Do not twist or bend the gray needle cap.
- Do not hold the prefilled syringe by the plunger rod.
-  (b) (4) (throw away) the needle cap in your household trash. You may see a drop of liquid at the end of the needle. This is normal.

2. The image used in Figure G does not match the accompanying text. The text states to “pull the needle cap straight off”, however, the image shows the needle cap is removed at an angle. Please revise the image used in Figure G to provide congruency with the text and the image. Further, we recommend adding language that instructs the user to hold the syringe barrel when removing the needle cap. As such, we recommend labeling the syringe barrel on the image.
3. Figure H shows the LA-EP2006 injection being given at an approximately 45° angle. However, US-licensed Neulasta can be administered at either a 45° or 90° angle. Therefore, please clarify and provide rationale for the discrepancy between LA-EP2006 and US-licensed Neulasta. Further, the accompanying text

does not mention at which angle the injection should be given. Therefore, revise the text to include the injection angle(s) that should be used to administer LA-EP2006. Additionally, include in the figure an additional image depicting the appropriate injection angle(s). For example:



4. The text accompanying Figure I states that [REDACTED] (b) (4) [REDACTED] " This step is not included in the US-licensed Neulasta IFU and this information was not identified as a difference in the task comparison section of the comparative analyses. Therefore, please clarify and provide rationale for the discrepancy between the LA-EP2006 PI and the US-licensed Neulasta PI.

RECOMMENDATIONS FOR SANDOZ

Container label (syringe label)

1. We note that the label contains a second perforated panel that includes the proprietary name, established name, lot number, and expiration date. Please confirm the intended use of this panel.
2. As currently presented, it is unclear whether the background color of the label is white or transparent. Please confirm the intended background color for the label.
3. Decrease the font size of the statement "Rx Only" and de-bold as this information appears more prominent than the nonproprietary name on the principal display panel.

Carton labeling (inner tray)

1. Revise the storage information statement to read "Store refrigerated at 2° to 8° C (36° to 46° F) in original carton to Protect from Light."
2. As currently presented, the location and format of the lot number and expiration date are not indicated. Please confirm the inclusion and location of these items.
 - a. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are

space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

3. Revise “Read full prescribing information before use” to read “Recommended Dosage: See prescribing information.” in accordance with 21 CFR 201.55.

Carton Labeling (outer)

1. As currently presented, the location and format of the lot number and expiration date are not indicated. Please confirm the inclusion and location of these items.
 - a. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2. As currently presented, the inclusion of a product identifier, including a 2D data matrix barcode, is not indicated. In September 2018, FDA released draft guidance, which, when finalized will represent the agency’s current thinking on the topics therein, on product identifiers required under the Drug Supply Chain Security Act.⁹ A product identifier is a standardized graphic that includes the product’s standardized numerical identifier (composed of the NDC and a unique alphanumeric serial number), lot number, and expiration date, in both human- and machine-readable formats. The product identifier data is specifically required under section 582(a)(9) of the FD&C Act to be in a “2-dimensional data matrix barcode” for packages and in a “linear or 2-dimensional data matrix barcode” for homogenous cases, which can be verified using “human-readable or machine-readable methods.” Section 582(b)(2)(A) of the FD&C Act requires manufacturers and repackagers, respectively, to “affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce”. Therefore, please confirm the inclusion and location of this information.

⁹ <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

3. We recommend removing storage information (i.e., Refrigerate. Do not freeze.) from the principal display panel as full storage information is stated on the back panel.
4. Revise the storage information statement on the back panel to read “Store refrigerated at 2° to 8° C (36° to 46° F) in original carton to Protect from Light.”
5. The net quantity “1” appears with equal prominence to the product strength (i.e., 6 mg/0.6mL) which may increase the risk of numerical confusion. Therefore, we recommend spelling out the quantity “one” and decreasing the font size so that it is in alignment with the rest of the statement “Single-dose Prefilled Syringe with needle guard.”
6. Increase the prominence of the route of administration “For Subcutaneous Use Only” to mitigate the risk of administration errors.
7. We recommend revising the preservative statement to read “Sterile solution – no preservative” to highlight this information.
8. Revise the usual dose statement, “Usual Dosage: See Prescribing Information” to read “Recommended Dosage: See prescribing information.” in accordance with 21 CFR 201.55.

Response: On July 18, 2019, Sandoz submitted updated labels and labeling (PI, IFU, PPI, container label, and carton labeling). See Appendix G.^h

^h Response to IR. 2019 JUL 18. [\cdsesub1\evsprod\bla761045\0058\m1\us\12-cover-letters\cover-letter.pdf](#)

July 25, 2019: USPI, PPI, and IFU Comments Sent to Sandozⁱ

On July 25, 2019, the Agency issued an information request that included additional DMEPA recommendations for the IFU. The following recommendations include combined comments from DMEPA and PLT.



ⁱ IR Communication. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80507e24&_afRedirect=2400380567796728

APPENDIX H. ADDENDUM TO DMEPA REVIEW DATED JUNE 23, 2016

DMEPA completed a label and labeling review on June 23, 2016, for the biologics license application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act) seeking licensure for LA-EP2006. The assessments, conclusions, and recommendations in the current review reflect new information and analyses that were not available at the time of the June 2016 review. Accordingly, this addendum is intended to update the June 2016 review based on the new information and analyses now available. This addendum is also intended to clarify certain statements in the June 23, 2016 review regarding the Pediatric Research Equity Act (PREA) that are relevant here.

In particular, DMEPA considers the information and analysis in the following materials relevant to the topics addressed in its June 23, 2016, review, and incorporates them by reference here:

- October 4, 2019, DMEPA memorandum (archived to BLA 125031). On October 4, 2019, DMEPA finalized a memorandum of a comprehensive review and analysis of medication errors associated with doses of pegfilgrastim products less than 0.6 mL (6 mg) in pediatric patients. LA-EP2006 has the same strength, dosage form, and route of administration as US-licensed Neulasta, and, like US-licensed Neulasta, would only be available in a prefilled syringe without graduation marks. Additionally, the proposed labeling for LA-EP2006, in relevant part, is substantially the same as US-licensed Neulasta's labeling, including with respect to pediatric use information and the statements that the prefilled syringe is not designed to allow for direct administration and cannot accurately measure doses less than 0.6 mL (6 mg). Therefore, if the requirements for biosimilarity are met, LA-EP2006 would be expected to be associated with the same type of dosing error and potential consequences as US-licensed Neulasta. See also October 10, 2019, Memorandum on Requirements for Pediatric Assessments Pursuant to Section 505B(b)(1) of the FD&C Act.
- Order letter to sponsor of US-licensed Neulasta. On October 10, 2019, FDA issued an order letter pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to the sponsor of US-licensed Neulasta, requiring it to submit pediatric assessments as described in section 505B(a)(2)(A) of the FD&C Act. As described in the letter, the sponsor of U.S.-licensed Neulasta is subject to a postmarketing requirement referred to as submission of pediatric assessments for Neulasta (pegfilgrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta (pegfilgrastim) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. In the letter, FDA stated it expected that a pediatric presentation – such as a vial or a pediatric-sized pre-filled syringe (with an appropriate concentration of product) – that can be used to directly and accurately deliver doses of less than 0.6 mL (6 mg) of pegfilgrastim to pediatric patients could be an "appropriate

formulation” as described in section 505B(a)(2)(A). (FDA issued similar letters to sponsors of the licensed pegfilgrastim biosimilars, Udenyca and Fulphila).

- Information request (IR) to Sandoz. An IR was sent to Sandoz on October 15, 2019, requesting its acknowledgement of a postmarketing requirement referred to as submit pediatric assessments for Ziextenzo (pegfilgrastim-bmez) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an “appropriate formulation” (presentation) that can be used to directly and accurately administer Ziextenzo (pegfilgrastim-bmez) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. DMEPA expects that fulfillment of Sandoz’s PMR would help mitigate the risk of pediatric dosing errors with LA-EP2006.

This addendum is also intended to clarify certain statements in the June 23, 2016 review regarding the Pediatric Research Equity Act (PREA) that are relevant here.

- PREA requires pediatric assessments for BLAs for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, unless the product is for an indication for which orphan designation has been granted (sections 505B(a)(1)(A) and 505B(k) of the FD&C Act). The required assessments “shall contain data, gathered using appropriate formulations for each age group for which the assessment is required” (section 505B(a)(2)(A) of the FD&C Act). FDA interprets this statutory text to include a presentation of the product that may be used to safely dose relevant pediatric patients. For additional information, see October 10, 2019, Memorandum on Requirements for Pediatric Assessments Pursuant to Section 505B(b)(1) of the FD&C Act.
- Based on FDA’s interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) and PREA, PREA requirements are applicable to proposed biosimilar products that have not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in: (1) a condition of use that has not been previously approved for the reference product; or (2) a dosage form, strength, or route of administration that differs from that of the reference product. For additional information, see FDA’s Draft Guidance for Industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Rev. 2) (Dec. 2018); when finalized, this guidance will represent the agency’s current thinking on the topics therein.

We carefully considered the June 23, 2016 review, together with the memoranda prepared subsequently, against the backdrop of the current framework for submitting pediatric assessments. We note that some of the statements and conclusions in the June 23, 2016 review are outdated. The more recent statements and conclusions based on additional data and

analyses apply here including with respect to medication errors, potential consequences, and appropriate means for addressing them.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHANIE L DEGRAW
10/31/2019 01:30:07 PM

HINA S MEHTA
10/31/2019 01:54:46 PM

QUYNHNHU T NGUYEN
11/01/2019 12:09:50 AM

MISHALE P MISTRY
11/01/2019 08:20:15 AM



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	7/1/2019		
To:	Rachel McMullen, Sr. Regulatory Health Program Manager; Laurel Menapace, Medical Officer		
Requesting Center/Office:	CDER/OHOP	Clinical Review Division:	Other
From:	David Wolloscheck, PhD OPEQ/OHT3/DHT3C		
Through (Team):	Sarah Mollo, PhD, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division): *optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: BLA 761045		
Recommendation:	Device Constituents Parts of the Combination Product are Approvable.		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (optional)
David Wolloscheck -S <small>Digitally signed by David Wolloscheck -S Date: 2019.07.01 10:50:43 -04'00'</small>	Sarah Mollo <small>Digitally signed by Sarah Mollo DN: cn=Sarah Mollo, o=FDA, ou, email=sarah.mollo@fda.hhs.gov, c=US Date: 2019.07.01 14:17:32 -04'00'</small>	

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	00010374 and 0010391
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/500t000000IDXZvAAP/view
ICC tracking #	ICC1900279
Submission Number	BLA 761045
Sponsor	Sandoz
Drug/Biologic	La-EP2006
Indications for Use	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Device Constituent	Prefilled Syringe
Related Files	ICC1500591 (Device Review), ICC1500691 (Compliance)

2. CDRH REVIEW

ICC Review Request from CDER/OHOP, Other:	Laurel Menapace, Medical Officer
Device Presentation(s) being evaluated:	Prefilled Syringe
Objective of this Memo:	Evaluation of the following changes: Updates provided by Sandoz in Sections 3.2.P and 3.2.R and review compliance of manufacturing facility to relevant sections of 21 CFR 820
Review Comments :	See Background and Scope for additional information regarding the submission and objectives of this memo.
Review Recommendation :	Approvable

Background and Scope

BLA 761045 was submitted in August 27th, 2015 and has received a CR action on June 24th, 2016. CDER has requested a device review of the original submission and a review of the device constituent parts of the combination product was conducted by John McMichael (CDRH/ODE/DAGRID/GHDB). Mr. McMichael issued a final recommendation on February 17th, 2016 that the device constituent parts are approvable. In addition, a facilities review was conducted by Crystal Lewis (CDRH/OC/DMQ/REGO), which resulted in several deficiencies to the Sponsor due to a lack of documentation to show that the manufacturer of the final finished device complied with 21 CFR 820.20, .30, .50, and .100. The CR letter issued to Sandoz did not include any CDRH related issues. The Sponsor submitted a response to the CR action on February 27th, 2019. CDER requested a CDRH consult on April 10th, 2019 to review updates to sections 3.2.P and 3.2.R, as well as the applicant's compliance status for approvability.

Since the device was previously reviewed by CDRH and found approvable for the stated indications, this memo will only evaluate the updated sections and determine whether the additional information raises concerns regarding the

ICC1900279

BLA 761045, La-EP2006, Prefilled Syringe

Sandoz

approvability of the device constituent parts of the combination product. The original device memo for this file will be attached to this document. In addition, a separate memo will review the provided information regarding the applicant's compliance to the relevant parts of 21 CFR 820.

Updates to Device Design Sections in 3.2.R

Sandoz provided a reviewer guide describing the individual changes that were made on each section in GSR 0048/1.2. Per the Sponsor, no content changes affecting the results of the activities or conclusions drawn thereof have been made. The changes made to the Device Design documentation in 3.2.R were summarized as follows:

Table 1-42 Overview of updates introduced to Module 3.2.R Technical summary device parts

Document section	Description	Reason for update
Whole module	Editorial changes	Correction of typos / errors, minor wording adjustments, restructuring of information, addition of information to improve clarity (text, figures, tables), updates of referenced documents / guidances / standards as applicable, updates of outdated information, adjustments to reflect current status of activities
Whole module	Removal of redundant information, e.g. information that is only relevant for European Union, information stated in other dossier modules (reference to those modules has been included)	Redundant information has been removed in order to condense the content of the module. However, none of these adjustments impacted the conclusions made in the previous version of the module.
Section 4.6.2	Updated information related to the shelf life of the Needle Safety Device (NSD, off-the-shelf product supplied by Becton Dickinson, BD) based on data provided by BD	The shelf life of the NSD has initially been set to four years by the manufacturer. In the meantime BD has conducted additional aging testing to support a one year shelf life extension to five years.
Section 6.7	Updated in order to include results of a Human Factors comparative analysis performed between the proposed combination product (LA-EP2006_PFS, (b) (4)) and the US-licensed reference product Neulasta	In the initial submission, Human Factors activities related to LA-EP2006_PFS_in (b) (4) consisted of evaluating and leveraging data obtained on other products already marketed in a comparable presentation (prefilled syringe with NSD), including a summative Human Factors study conducted by Novartis for another product presented in the same presentation. In order to comply with most recent FDA guidances, Sandoz additionally performed a comparative analysis between LA-EP2006_PFS_in (b) (4) and the US-licensed reference product Neulasta.

Document section	Description	Reason for update
Section 9.1	Updated to include results of additional design verification activities performed by Sandoz on level of the LA-EP2006_PFS_in (b) (4) combination product	Additional design verification activities have been performed and results have been included into the module following corresponding information requests by FDA received during the initial submission. As these data cover all relevant design verification tests for LA-EP2006_PFS_ (b) (4), generic design verification data provided by (b) (4) have been removed.
Section 13 and [Module 3.2.R Technical summary device – Attachment 1]	Newly included	Included in order to describe Sandoz' Quality Management System and the requirements applied during the development of the LA-EP2006_PFS_in (b) (4) combination product in accordance with the applicable provisions of 21 CFR Part 820.

Updated shelf-life of NSD

As stated in the original submission, Sandoz uses a 510(k) cleared needle safety device (NSD) (BD UltraSafe Passive Needle Guard, (b) (4)). The Sponsor has updated the shelf-life of the NSD from four to five years to align with the current shelf-life of the NSD per the manufacturer.

Comparative Human Factors Analysis between subject device and reference product

The Sponsor has also provided results of a Human Factors comparative analysis between the subject device and the US-licensed reference product Neulasta. In this comparative analysis, Sandoz conducted a physical comparison of the devices, as well as a comparison of the critical tasks and the labeling. The following table was provided for the physical and task comparison:

Table 6-4 Physical comparison of NG and plunger rod

Characteristic	Neulasta	LA-EP2006_PFS	(b) (4)
NG pre-activation appearance	(b) (4)		
NG post-activation appearance			
NG Length (A)	12.7 mm	12.7 mm	
NG Length (B)	62.0 mm	61.7 mm	
NG Length (C)	25.6 mm	25.4 mm	
NG color	Translucent blue	Clear	
NG mode of activation	Active – user has to activate the safety feature after injection	Passive – safety feature automatically activates at the end of stroke	
Plunger rod appearance	(b) (4)		
Plunger rod length (A)			
Plunger rod diameter (B)	10 mm	17.8 mm	
Plunger rod color	Dark blue	Light blue	

Table 6-5 Task analysis comparison of Neulasta and LA-EP2006_PFS

Tasks	Step	Neulasta	LA-EP2006_PFS_in	Difference
Store	Store at 2-8°C.	X	X	Identical task
Unpack	Bring drug to room temperature.	X	X	Identical task
	Open packaging.	X	X	Identical task
	Remove product from packaging.	X	X	Identical task
	Perform safety checks (e.g. liquid appearance).	X	X	Identical task
Prepare injection	Identify appropriate injection site.	X	X	Identical task

	Remove Rigid Needle Shield (RNS).	X	X	Identical task
Inject	Pinch skin.	X	X	Identical task
	Insert needle into skin.	X	X	Identical task
	Depress plunger until the entire solution is injected.	X	X	Identical task
	Remove syringe from injection site.	X	X	Identical task
	Manually extend the NG to protect the needle.	X	N/A	Non-identical task; LA-EP2006_PFS_in (b) (4) comes with automatic NG that covers the needle preventing injuries and can be operated one-handed
Dispose	Dispose of device and packaging according to local regulations.	X	X	Identical task

The Sponsor stated that the main difference between the devices is the automated activation of the NSD in the subject device compared to a manual activation in the US-licenses Neulasta. The labeling of the two products was compared and found to only contain minor differences mainly due to the difference in the NSD. As the NSD has already received FDA clearance, the differences between the subject and the reference device are acceptable. The additional information does not raise new concerns regarding the usability of the subject device. Hence, this is acceptable.

Updates to Design Verification Section

Sandoz has updated the design verification section to include performance requirements of the NSD set by BD. The following table with performance requirements was provided:

Table 9-1 Performance requirements and specifications utilized by BD

Essential Performance Requirement	Specification	Verification
Activation force	Spring reaction force during activation all the way through the lockout	Pass
Triggering	Correct triggering along with full activation into locked position	Pass
Compression force	Force required to override the activated locked guard to the un-activated position	Pass
Essential Performance Requirement	Specification	Verification
Separation force	Force required to separate the guard from the body when the assembled device has been activated in its locked position	Pass
Syringe Spin test	Syringe spins freely at least in one direction	Pass

The device design verification of the NSD was already reviewed as part of the 510(k) (b) (4) Sandoz reported that the tested NSDs passed the verification testing. This is acceptable.

In addition to the performance requirements of the NSD, Sandoz also provided summary design verification data of the final finished combination product. The Sponsor noted that the additional data was, per FDA recommendations, generated with the intended drug product. Sandoz included additional performance requirements that were not previously reviewed by the original device reviewer. The following table with summary information was provided:

Table 9-2 LA-EP2006_PFS (b) (4) combination product design verification testing

Test	Description	Sample size [n]	Acceptance criteria	Result
Rigid needle shield pull out force	Force required to remove the rigid needle shield from the syringe	60	(b) (4) N	PASS
Extractable volume	Amount of product expelled until the needle guard is activated	60	(b) (4) mL	PASS
Break-loose force	Force required to initiate plunger rod movement	20	(b) (4) N	PASS
Extrusion force	Force required to maintain plunger rod movement	20	(b) (4) N	PASS
Plunger activation force	Force required to activate the needle guard	60	(b) (4) N	PASS
Triggering test	Verify the activation of the device	100	All samples must pass	PASS
Compression force	Force required to override the active locked state	60	(b) (4) N	PASS
Separation force	Force required to separate the body from the guard	60	(b) (4) N	PASS
Transparent area test	Comparison of the transparent area of the NSD window and the transparent area of the syringe label	100	All samples but one must pass	PASS
Fixation hooks test	Visual verification that the fixation hooks of the NSD completely encompass the glass finger flange of the syringe body	100	All samples but one must pass	PASS
Freedom of	Visual verification to ensure	100	All samples but one	PASS

Test	Description	Sample size [n]	Acceptance criteria	Result
movement test	that the syringe can freely rotate inside the safety device		must pass	
Needle guard test	Visual verification to ensure that the needle is completely covered by the needle guard after activation	100	All samples must pass	PASS
Flag label removability	Visual verification to ensure that the flag label on the syringe can be removed from the combination product	100	All samples but one must pass	PASS

The original device review evaluated dose accuracy/extractable volume and injection force (breakloose and glide force) and found that the provided data adequately addresses the performance requirements of the device constituent parts of the combination product. The acceptance criteria for these tests remain unchanged from the original submission. Furthermore, additional verification test data was leveraged in the original submission from the respective DMF. Since, the tested devices meet all of Sandoz's specifications and the Sponsor did not report any failures, the additional information provided does not raise new concerns regarding the performance of the prefilled syringe. Hence, the updates to this section are acceptable.

Control Strategy of Combination Product

The original review mentioned that dose accuracy testing was shown to be part of the Sponsor's lot release testing. However, the additional information provided on dose accuracy states that it is simply a release specification and not part of the release testing. The Sponsor justifies this by stating that the device performed adequately during design verification testing and after shipping validation. However, verification testing and shipping studies do not account for lot-to-lot variations. The Sponsor should demonstrate that an adequate control strategy is in place to account for variations between lots. Hence, an information request will be sent to the Sponsor. See the end of this memo for details.

Additional Stability Data

Sandoz stated that the stability data in 3.2.P.8.1 was updated to include three batches from supplementary process validation from 2015 and one batch from 2016. The provided data will be evaluated to ensure that the provided data meets the predetermined acceptance criteria for the device constituent parts of the combination product.

Extractable Volume

The Sponsor provided additional data for extractable volume of 4 lots. The acceptance criterion for this test (b) (4) mL) remains unchanged from the original submission and was found adequate by the previous reviewer. The additional data provided meets the predetermined acceptance criterion and is acceptable.

Table 6-5 Results of extractable volume (mL) at intended storage condition of 5 ± 3°C

Pull Point [months] / Batch	TR-10006	7004902	7004903	7004904	7007842	7007843	7007844	7008257
0	0.6	0.6	0.6	0.6	0.63	0.62	0.63	0.62
6	0.6	0.6	0.6	0.6	n.t.	n.t.	n.t.	n.t.
12	0.6	0.6	0.6	0.6	0.62	0.62	0.62	0.62
24	0.6	0.6	0.6	0.6	0.63	0.63	0.63	*
30	n.t.	0.624	0.622	0.624	n.t.	n.t.	n.t.	*
36	0.629	0.625	0.624	0.620	0.63	0.63	0.63	*

n.t. ... not tested

* Stability study still ongoing

Note: (b) (4)

(b) (4) For the history of specifications please refer to [Module 3.2.P.5.4].

Stability data provided after accelerated aging:

Table 6-31 Results of extractable volume [mL] at accelerated storage condition of 25 ± 2 °C / 60 ± 5 % RH

Pull Point [months]	TR-10006	7004902	7004903	7004904	7007842	7007843	7007844	7008257
0	0.6	0.6	0.6	0.6	0.63	0.62	0.63	0.62
6	0.6	0.6	0.6	0.6	0.62	0.62	0.63	0.62

Note: (b) (4) For the history of specifications please refer to [Module 3.2.P.5.4].

Breakloose and gliding force

The Sponsor stated that break-loose and glide force testing is not part of release and stability specifications. This was deemed acceptable to the original reviewer of the file. Sandoz stated that the syringes comply with ISO 7864, which describes the limit of breakloose and glide force as NMT 15 N. The additional data supplied for lot 7007843 shows a slightly higher breakloose force compared to lots that were previously tested. However, the reported results still demonstrate compliance with ISO 7864 and is acceptable.

Table 6-24 Results of break-loose and gliding force [N] at intended storage condition of $5 \pm 3^{\circ}\text{C}$

Pull Point [months]	Break-loose (initial) force				Gliding (extrusion) force			
	7004902	7004903	7004904	7007843	7004902	7004903	7004904	7007843
0	2.79	2.61	2.37	3.28	2.62	2.79	2.40	2.51
5	n.t.	n.t.	n.t.	3.33 ¹⁾	n.t.	n.t.	n.t.	2.54 ¹⁾
6	n.t.	n.t.	n.t.	3.49	n.t.	n.t.	n.t.	2.71
12	n.t.	n.t.	n.t.	4.03	n.t.	n.t.	n.t.	2.81
24	n.t.	n.t.	n.t.	4.44	n.t.	n.t.	n.t.	3.11
36	3.14	3.13	3.11	3.76	2.83	2.91	2.63	2.79
min.	2.79	2.61	2.37	3.28	2.62	2.79	2.40	2.51
max.	3.14	3.13	3.11	4.44	2.83	2.91	2.63	3.11
Δ	0.35	0.52	0.74	1.16	0.21	0.12	0.23	0.60

n.t. ...not tested

¹⁾ Samples mistakenly measured after 5 months additionally to the stability program. No negative impact expected as the results are shown as an additional pull point

No additional stability data of breakloose and glide force for devices that underwent accelerated aging was provided by the Sponsor. The reported results show that the additional lots tested are within the specifications set by the Sponsor and do not raise concerns regarding the approvability of the device constituent parts of the combination product.

---END OF REVIEW---

3. APPENDIX

3.1. DOCUMENTS REVIEWED

Sequence	Module
0000	3.2.R
0048	1.2, 1.11, 3.2.R

3.2. INTERACTIVE REVIEW

	Date Sent: 5/29/2019	Date/Sequence Received: 6/5/2019
Information Request #	<p>1. You stated in 3.2.R that dose accuracy is not part of release testing of the final combination product because results from design verification and transportation validation were acceptable. Please note that design verification or a shipping test do not account for variabilities between lots. As the manufacturer of the combination product, you should demonstrate that you have an adequate control strategy in place to account for lot-to-lot variabilities. Please add dose accuracy testing to your lot release testing. Alternatively, provide information on your control strategy to ensure that the essential performance requirements of the device constituent parts of your combination product are met throughout lot-to-lot variations.</p>	
Sponsor Response	<p>1.2 Sandoz Response</p> <p>Sandoz acknowledges the question raised by the Agency and would like to provide the justification for why we consider, in accordance with the control strategy, “extractable volume” release testing (b) (4) adequate and sufficient to ensure dose accuracy from the final combination product to the patient.</p> <p>1.2.1 Dose accuracy and extractable volume</p> <p>The combination product LA-EP2006_PFS (b) (4) consists of a prefilled syringe which is assembled with the BD UltraSafe Passive™ Needle Safety Device (NSD) (b) (4). The NSD consists of the needle guard assembly and the associated plunger rod. For LA-EP2006_PFS (b) (4) the entire volume is injected by manually pushing the plunger rod down until the end of the syringe. Hence, the dosing corresponds to expelling the entire syringe content while administering LA-EP2006 (i.e. “extractable volume”). As such, the relevant test in regards to “dose accuracy” is considered to be “extractable volume”. In accordance with the control</p>	

strategy, testing of the extractable volume (b) (4) as outlined below in Section 1.2.2.

Importantly, the extractable volume of LA-EP2006_PFS (b) (4) is not affected by the NSD since the NSD gets activated only once the plunger rod has been fully pushed down (i.e. once the full content of the PFS has been emptied).

This has been confirmed by Sandoz by specifically performing tests for extractable volume on fully assembled LA-EP2006_PFS (b) (4) in the course of our design verification process. In addition, the testing of extractable volume in the course of the transport validation also confirms that combination product samples going through the validated NSD assembly process and additional mechanical stress testing in the course of the transport validation, fulfill the specification for extractable volume. This leads to the conclusion that the assembly process and the transportation of LA-EP2006_PFS (b) (4) do not impact the extractable volume. This information has been provided in [Module 3.2.R Technical summary device parts]. We have provided a summary in Table 1-1 as well.

Table 1-1 Extractable volume testing of LA-EP2006_PFS (b) (4) during design verification and transport validation

Test	Sample size	Specification	Result (mean)	Evaluation
Extractable volume: design verification	60	(b) (4)	0.62 mL ¹⁾	PASS
Extractable volume: after transport validation	5	(b) (4)	0.62 mL ²⁾	PASS

¹⁾ Result for corresponding PFS batch: 0.63 mL

²⁾ Result for corresponding PFS batch: 0.62 mL

1.2.2 Extractable volume control strategy

(b) (4)

	<p style="text-align: right;">(b) (4)</p> <p>1.2.4 Summary and conclusion With each injection of LA-EP2006_PFS (b) (4) the entire drug product volume is administered. Therefore “extractable volume” is the relevant test for “dose accuracy”. According to the control strategy, release and shelf-life specifications for extractable volume (b) (4). They account for LA-EP2006_PFS (U) (4) lot-to-lot variabilities since it was shown that the extractable volume is not impacted by neither the assembly of the NSD nor the NSD itself. Hence, Sandoz has an adequate control strategy in place to ensure that the specified volume is available for injection from LA- EP2006_PFS (b) (4)</p>
Reviewer Comments	The Sponsor has clarified that the statement that release testing is not necessary pertains to the PFS with NSD (b) (4). This is acceptable, as the Sponsor has demonstrated that the impact of the NSD on expelled volume is minimal and the stability of the NSD was assessed as part of its 510(k) submission. Hence, the response is adequate.
Response Adequate:	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	<input type="checkbox"/> Yes <input type="checkbox"/> No, See IR # Sent on Click or tap to enter a date.	



Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

CDER BLA 761045 - CDRH ICC1500591

Date: February 17, 2016

To: Rachel McMullen
Division of Hematology Products (DHP),
Office of Hematology and Oncology Products (OHOP),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: John McMichael,
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Through: CDR Alan Stevens, Acting Branch Chief,
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Please review information submitted regarding the pre-filled syringe (PFS) drug presentation. PFS information for review is located in sections 3.2.P.7 and 3.2.R-Technical Summary Device Parts. Please also comment on instructions for use of the device located in section 1.14.1.3.

Documents Reviewed: Under GSR Sequence 0000: Technical Summary Device Parts under 3.2.R, Container closure system under 3.2.P.7

The following documents were reviewed upon receiving them as attachments via Information Request:

- LA-EP2006_PFS (b) (4) URS_2 – User Requirement Specification
- LA-EP2006_PFS (b) (4) DIR_2 – Design Input Requirements
- LA-EP2006 FDF mechanical stress Version 1.0 – Transport validation report
- Report: Physicochemical characterization of LA-EP2006 DP after transport validation
- LA-EP2006_PFS (b) (4) DVERPL_2 – Design Verification Plan
- LA-EP2006_PFS DVERP1_3 – Design Verification Test Protocol
- LA-EP2006_PFS DVERR1_1 – Design Verification Test Report
- LA-EP2006_PFS CLINEV_3 – Clinical Evaluation
- AIN457_CEV_PFS in SSI (b) (4) – Secukinumab Pre-Filled Safety Syringe Clinical Evaluation Report
- EP2006_PFS_30_48 (b) (4) CLINEV_3 – Clinical Evaluation Report
- LA-EP2006_PFS (b) (4) MUEP_2 – Risk Management and Usability Engineering Plan
- LISY-1mL-LA-EP2006_HID_2 – Hazard Identification

- LA-EP2006_PFS (b) (4)_RA-AP1_2 – Application/Usability Risk Assessment
- FMEA LA-EP2006_RA-PR1_1 – Failure mode and effect analysis of the assembly and blistering process
- Response to Request for Information dated Jan. 20, 2016

CDRH Review Team:

Team Member	Role
John McMichael	Lead Reviewer – Engineering
Sarah Mollo, Ph.D.	Consultant – Biocompatibility
Steven Elliot	Consultant – Sterility

Recommendation: Device Constituent Parts of Combination Product are Approvable

I. Purpose

CDER/OND/OHOP/DHP has requested CDRH/ODE’s assistance to assess the acceptability of the PFS with needle safety device presentation of the drug product. This is an original biosimilar BLA submission.

II. Background

Sandoz has submitted an original biosimilar BLA for “LA-EP2006” (pegfilgrastim, proposed biosimilar to US-licensed Neulasta). The proposed indication is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. This application will be part of a public Oncologic Drugs Advisory Committee (ODAC) Meeting. The scope of this review covers the device component of the combination product, which includes the pre-filled syringe, its device constituent parts, and the needle safety device.

III. Device Description (information taken from Section 4 of Technical Summary Device Parts under 3.2.R in GSR)

LA-EP2006 is presented in a 1 mL long ISO prefilled syringe with a concentration of 10 mg/mL and a filling volume of 0.6 mL resulting in a strength of 6 mg/0.6 mL.

This LA-EP2006 PFS is combined with the anti-needlestick accessory BD UltraSafe Passive™ Needle Guard and a plunger rod. This BD UltraSafe Passive™ Needle Guard (b) (4) (b) (4) including the (b) (4) device and the matching plunger rod) used for LA-EP2006 PFS (b) (4) is cleared in the US under the 510(k) (b) (4) (b) (4) see Sections 4.6.2 and 14.3.



Figure 4-1 Schematic figure of the combination product

Intended Use/User Population:

The intended use for the LA-EP2006_PFS (b) (4) combination product is the safe subcutaneous application of Pegfilgrastim drug formulation for the treatment of patients with the indications listed below. The product is intended for administration by health care professionals (HCP) but also for patient self-administration of therapy as well as for administration by caregivers. In those situations in which the physician determines that the patient can safely and effectively self-administer the product, the patient should be instructed as to the proper dosage and administration. If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. For self-administration and for administration by persons assisting the patients their ability to correctly administer the drug will be assessed by the physician and the patient/caregiver has to be trained accordingly.

1. US: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

The combination product and its components are indicated for single use and the NG is indicated to aid in the protection of users from accidental sharps injuries.

The present marketing authorization application seeks licensure for all indications for which the US-licensed reference product Neulasta® is approved. Full information on the indications being applied for is provided in [Module 2.7.3].

Table 4-1 Intended user population: main characteristics

Category	Patients	Caregiver	Health Care Professional (HCP)
Age	Adults	Adults	Adults
Physical conditions	<ul style="list-style-type: none">• All stages of physical condition possible;• No physical limitation due to the disease to be treated to be expected• Needs to be judged "able to self-inject" by a HCP	<ul style="list-style-type: none">• All stages of physical condition possible;• Needs to be judged "able to inject" by a HCP	<ul style="list-style-type: none">• All stages of physical condition possible (no limitations influencing the HCP's work to be expected);
Experience with similar devices	<ul style="list-style-type: none">• First time users• Experienced users	<ul style="list-style-type: none">• First time users• Experienced users	<ul style="list-style-type: none">• Experienced users

Operational Principles

The user pulls the needle cap straight off and inserts the needle into the skin. By pressing on the plunger rod he carries out the injection. Once the plunger head is completely located between the needle guard wings and the pressure on the plunger is released, the syringe spring is automatically activated and the NG extends and covers the exposed needle.

Drug Dose Capability

LA-EP2006_PFS (b) (4) is a fixed-dose, single-use prefilled syringe providing the liquid formulation LA-EP2006 in a single dose of 6 mg.

Route of Administration/Injection Site

LA-EP2006_PFS (b) (4) is intended for the subcutaneous application of LA-EP2006. Recommended subcutaneous injection sites are the front of the thigh, lower stomach-area (abdomen) but not the area 2 inches around the navel and the upper outer arms if a caregiver or a HCP is giving the injection. Details can be found in the Instructions for Use (IFU) LA-EP2006_PFS (b) (4) IFU [Module 1.14.1.3.].

IV. Proposed Device Parts of the Combination Product (Information taken from Section 6 of Technical Summary of Device Parts under 3.2.R and Section 2 of Container closure system under 3.2.P.7)

Pre-filled Syringe:

Table 2-1 List of packaging components

Package component	Description	Drawings, specifications, quality criteria, descriptions and LoAs
Primary packaging		
Syringe barrel	1 mL, (b) (4) glass Lubrication: (b) (4)	- Technical drawing - Specification for release by the drug product manufacturer
Hypodermic needle	27 Ga x ½", (b) (4) stainless steel, conforms to AISI 304 Needle glued inside the channel tip Lubrication: (b) (4)	- Quality criteria of lubrication - Quality criteria of adhesive - Description of sterilization - LoA
Needle shield	Rubber formulation (b) (4)	- Technical drawing - Specification for release by the drug product manufacturer -LoA
Rubber stopper	(b) (4) rubber (b) (4) (b) (4)	- Technical drawing - Specification for release by the drug product manufacturer - Description of sterilization -LoA
Secondary packaging		
Rigid shield	(b) (4)	- Technical drawing
Plunger rod	(b) (4)	- Technical drawing
Medical device constituent part of the combination product		
Needle safety device	See [Module 3.2.R Technical summary device parts]	

6.1 1 mL long, glass (b) (4) syringe

The 1mL long ISO standard glass syringe used as primary packaging constituent part of the LA-EP2006_PFS (b) (4) combination product is a commercially available product from (b) (4). The syringe barrel with the needle is a single-use, sterile glass syringe barrel designed for packaging and administering medicinal products. The syringe includes a 27G ½ inch hypodermic needle with a rigid needle shield. There are no graduation marks on the PFS nor on the syringe label.

Needle Safety Device:

6.2 (b) (4) Needle Guard

The needle guard (b) (4) used as a constituent part of the LA-EP2006_PFS (b) (4) combination product belongs to the BD UltraSafe Passive™ Needle Guard (b) (4). It is intended for 1 mL long ISO standard glass syringes and is marketed by BD Medical / Safety Pharmaceutical Systems (formerly Safety Syringes Inc.). The device is composed of a guard body, spring and plunger rod, is non-sterile and for single use only.



V. CDRH Review

This review is limited in scope to the design of the device parts of the combination product and does not pertain to the LA-EP2006 drug product itself, primary container closure elements, or the manufacturing of the device constituent part.

Performance Requirements

The following is a table of the essential performance requirements as stated by the Sponsor:

Essential Performance Requirement	Requirement / Specification
Dose Accuracy (Extractable Volume)	(b) (4)
Injection Depth / Needle Length	
Extrusion Force (break loose and glide force)	
Shelf Life	36 Months

Administrative

The following table was provided by the Sponsor in reference to the Letters of Authorization granting access to information held within suppliers' master files:

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

RACHEL S MCMULLEN

02/19/2016

CDRH signed off on this ICC review memo on 2/17/16 and the Division received this on 2/19/16 from John McMichael (CDRH reviewer).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RACHEL S MCMULLEN
08/22/2019 04:47:56 PM

ICCR QUALITY SYSTEM REVIEW MEMO

Date: June 27, 2019

To: Laurel Menapace, Medical Officer, DHP/OHOP/OND, CDER, WO22, laurel.menapace@fda.hhs.gov

CC: Office of Combination Product, Combination@fda.hhs.gov
Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Rachel McMullen, DHP/OHOP/OND, CDER, WO22, Rachel.mcmullen@fda.hhs.gov

Through: CDR Nikhil Thakur, DHT3C/OHT3/OPEQ, CDRH, WO 66, Rm 2518, nikhil.thakur@fda.hhs.gov

From: David Wolloscheck, PhD, THT3C1/DHT3C/OHT3/OPEQ, CDRH, WO 66, Rm 2533, david.wolloscheck@fda.hhs.gov

Applicant/Licensure: Sandoz, Inc.
100 College Road West, Princeton, NJ 08540
3004828473

Submission (Type & Number): BLA 761045

Combination Product Name: La-EP2006

Combination Product Indications for Use: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Device Constituent (Type): Prefilled Syringe

ICCR Sharepoint Tracking Number: ICCR2019-04734

ICCR CTS Tracking Number: ICC1900294

Pre-Approval Facility Inspection: No

Documentation Review (Status): Complete

CDRH/OC Recommendation: Approvable

Instructions: Fill in fields shaded in gray or in brackets([]). Note: Brackets indicate repeated fields. Follow all instructions highlighted in gray and then delete it. In final version of this document, please make sure no text is highlighted in gray. If a section is not needed, please delete it. For example, if only one firm is involved in the manufacturing of the product, delete the second (combination product manufacturer) and third sites device constituent part manufacturer or specification developer).

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA 761045 which will require a device inspection.

PRODUCT DESCRIPTION

The device constituent parts of BLA 761045 are a prefilled syringe and a needle safety device (NSD). The device is intended to be used by healthcare professionals (HCPs) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The NSD is indicated to aid in the protection of users from accidental needle injury. The following drawing of the devices was provided in the submission:

Figure 4-1 Schematic figure of the combination product



REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the combination product, La-EP2006, in [BLA 761045](#).

Combination Product Applicant

Firm Name: Sandoz, Inc.

Address: 100 College Road West, Princeton, NJ 08540

FEI: 3004828473

Responsibility – As the applicant, Sandoz holds the primary responsibility that all manufacturing processes of the combination product are compliant with the applicable quality systems regulations. The applicant is using a drug CGMP based streamlined approach per the 2015 FDA guidance *Current Good Manufacturing Practice Requirements for Combination Products*.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted 2/22/2018 to 3/2/2018. The inspection covered drug CGMP and was classified VAI.

Inspection Recommendation:

An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Finished Combination Product Manufacturer



Responsibility – The firm is responsible for the manufacturing and packaging of the final finished combination product. Hence, it should comply with purchasing controls and CAPA. In addition, the firm is responsible for environmental monitoring and process controls.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI.

Inspection Recommendation:

An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

DOCUMENTATION REVIEW

Device Constituent Part Type: Prefilled Syringe

Device Constituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, (b) (4)

Combination Product BLA 761045 Proposed Indication for Use: To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

1. Was the last inspection of the finished combination product manufacturing site, (b) (4) OAI for drug or device observations?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	NA <input type="checkbox"/>
2. Is the device constituent a PMA or class III device?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
3. Is the final combination product meant for emergency use?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>

cGMP Risk: Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Reviewer's Note:

The combination product is used by HCP in a clinical environment and is not intended for emergency use. Furthermore, the device is a prefilled syringe, which are generally considered low risk devices unless intended for emergency use (i.e. as part of an epinephrine emergency kit). Hence, an in-depth review of the Quality Systems of the combination product manufacturer is not needed.

However, due to a transition in the review practices, a previous review of the Quality Systems (QS) documentation was conducted and deficiencies were identified. The original reviewer noted that no information was found in the file regarding the documentation requirements set out in 21 CFR 820.20, .30, .50, and .100. In sequence 48 of the BLA, Sandoz has submitted a device amendment describing the Firm's adherence to these four parts of the QS. This information is reviewed as part of this memo.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant: Sandoz, Inc.
100 College Road West, Princeton, NJ 08540
FEI: 3004828473

Finished Combination
Product Manufacturer:



No Third Manufacturing

Site :

<p>Applicable Sites</p> <p>Sandoz, Inc. <input checked="" type="checkbox"/></p> <p>(b) (4)</p>	<p>Management Responsibility, 21 CFR 820.20</p> <p>The firm provided a summary of how the firm’s management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
	<p>The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sandoz, Inc. <input checked="" type="checkbox"/></p> <p>(b) (4)</p>	<p>Design Controls, General, 21 CFR 820.30</p> <p>The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
	<p>The firm provided a copy or a summary of the plan used to design the combination product.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sandoz, Inc. <input checked="" type="checkbox"/></p> <p>(b) (4)</p>	<p>Purchasing Controls, 21 CFR 820.50</p> <p>The sponsor firm should summarize its procedure(s) for purchasing controls.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
	<p>The summary should describe the firm’s supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
	<p>The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
	<p>The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>

	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Applicable Sites Sandoz, Inc. <input checked="" type="checkbox"/>	Corrective and Preventive Action (CAPA), 21 CFR 820.100 The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
<input checked="" type="checkbox"/> (b) (4)	The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
[Site3] <input type="checkbox"/>	b. Investigation of nonconformities and their causes;	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	d. Verification or validation of the actions taken.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Applicable Sites Sandoz, Inc. <input type="checkbox"/>	Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product) If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product.	YES <input type="checkbox"/>	NO <input type="checkbox"/>
<input checked="" type="checkbox"/> (b) (4)			
None: <input checked="" type="checkbox"/>			

<p>Applicable Sites</p> <p>Sandoz, Inc. <input type="checkbox"/></p> <p>(b) (4)</p> <p>None: <input checked="" type="checkbox"/></p>	<p>Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product)</p> <p>Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.</p>	<p>YES <input type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sandoz, Inc. <input type="checkbox"/></p> <p>(b) (4)</p> <p>None: <input type="checkbox"/></p>	<p>Production and Process Controls</p> <p>The sponsor should provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.</p> <p>If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sandoz, Inc. <input type="checkbox"/></p> <p>(b) (4)</p> <p>None: <input type="checkbox"/></p>	<p>The sponsor should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.</p> <p>If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>

Applicable Sites Sandoz, Inc. <input type="checkbox"/>	The sponsor should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The firm should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
<input type="checkbox"/> (b) (4)			
None: <input type="checkbox"/>			

Reviewer’s Note:

Sandoz provided responses to the information requests in 3.2.R – Device Quality System Information – Attachment 1. The Sponsor provided documentation describing the adherence to the four QS callouts for a combination product manufacturer operating under Drug cGMPs. The information was reviewed and found to be acceptable.

No Deficiencies Identified. The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for BLA 761045 La-EP2006 is approvable from the perspective of the applicable Quality System Requirements. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

A routine surveillance inspection is recommended for the following facility to cover the device cGMP requirements:

- a.  (b) (4)

OC Decision: Approvable (Recommend approval to CDER)

Reviewer:

David Wolloscheck - Digitally signed by David
S Wolloscheck -S
Date: 2019.06.27 17:02:07 -04'00'

Branch Chief or Lead CSO:

Nikhil Thakur -S3 Digitally signed by Nikhil Thakur -S3
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Nikhil Thakur -S3,
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RACHEL S MCMULLEN
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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 26, 2019

TO: Ann T. Farrell, MD
Division Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDBE, OSIS

SUBJECT: Routine inspection of [REDACTED] (b) (4)
supporting clinical study LA-EP06-104 (BLA 761045)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an audit of Absolute Neutrophil Count (ANC) data for study LA-EP06-104 to support BLA 761045, conducted at [REDACTED] (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, ORA investigator Zerita White identified discrepancies in how ANC data were reported to the FDA.

2 Inspected Study:

BLA 761045

Study Number: LA-EP06-104

Study Title: "A randomized, double blind, crossover, three-way blinded study to compare the pharmacokinetics, pharmacodynamics, and safety of a single 6 mg subcutaneous administration of the proposed biosimilar product LA EP-2006, Neulasta US and Neulasta EU in healthy subjects"

Dates of conduct: [REDACTED]

(b) (4)

Analytical site: [REDACTED]

(b) (4)

ORA investigator Zerita White [REDACTED] inspected [REDACTED]

(b) (4)

(b) (4)

[REDACTED].

This is the first inspection of [REDACTED] at this location. The inspection was initiated to review records of Absolute Neutrophil Count (ANC) data reported in study LA-EP06-104.

(b) (4)

The clinical site generating blood samples for this portion of the study was PRA, Inc., of Lenexa, KS. During this inspection, Ms. White received documents provided by PRA to [REDACTED], to assist in examination of the ANC records. However, there was no Form FDA 482-Notice of Inspection issued to PRA.

(b) (4)

3 Inspectional Findings

During the inspection at [REDACTED] Ms. White examined calibration and preventative maintenance records on all twelve Sysmex-XN-900 units used to perform Complete Blood Count (CBC) measurements, including ANC. Ms. White randomly selected twenty subjects to reconcile ANC results with the data listings submitted to FDA.

(b) (4)

Ms. White compared the values in [REDACTED] records to the ANC results submitted to the BLA. The BLA tabulations were labeled "Reported Concentration-ng/mL" (**ATTACHMENT 1**). When Ms. White started reviewing the data, the staff at [REDACTED] informed Ms. White that this was a typographical error, and the actual units were "cells/ μ L." PRA provided an email statement that explained this error (**ATTACHMENT 2**).

(b) (4)

(b) (4)

Ms. White found no discrepancies in ANC results between [REDACTED] records and the BLA report, using the screening and enrollment log provided by PRA to [REDACTED] during the inspection (**ATTACHMENT 3**). The blood samples analyzed for ANC were labeled with the Screen ID of the enrolled subjects, instead of the randomization number. Therefore, to match the ANC results, [REDACTED] records (**ATTACHMENT 4**) had to be matched with the randomization numbers in the screening and enrollment log provided by PRA to [REDACTED] (**ATTACHMENTS 3**). For example, the Case Study Report for the subject with randomization number 3001

(b) (4)

(b) (4)

matches (b) (4) ANC results for Screen ID 3002 at PRA. We note that the protocol called for use of the randomization number only, once subjects were enrolled into the study.

This inspection audited only ANC records at (b) (4) not clinical portions of the study at PRA in Lenexa. At the conclusion of the inspection, Ms. White did not issue Form FDA 483 at (b) (4).

4. Conclusion:

After reviewing the inspectional findings at (b) (4) I conclude that ANC data for subjects at PRA in Lenexa for study LA-EP06-104 were verified. However, a typographical error was identified in the clinical study report submitted to FDA (**ATTACHMENT 1**). There were also errors in transcribing randomization numbers for (b) (4) ANC results (**ATTACHMENT 4**). I suggest that the Division of Hematology Products should invite the study sponsor to confirm records, in order to match subject identities to treatments, clinical observations, and ANC data.

VAI -

(b) (4)

cc:

OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/CDER-OSISBEQ@
fda.hhs.gov

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Li

ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XFL 06/27/2019; 07/8/2019; 07/9/2019; 07/22/2019;
7/25/2019

Edit: MFS 06/28/2019; 07/09/2019; JAK 07/17/2019; 07/25/2019;
7/26/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/

(b) (4)

OSIS File #: (b) (4) (BLA 761045)

FACTS:

(b) (4)

ATTACHMENT: 1

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 15, 2019

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Carole Broadnax, RPh, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (non-proprietary name): TRADENAME (pegfilgrastim-xxxx)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761045

Applicant: Sandoz, Inc.

¹ LA-EP2006 has been developed as a biosimilar to US-licensed pegfilgrastim. At the time of this review, the proprietary name has not yet been determined; therefore, we use TRADENAME as a placeholder until such time as it has been determined. The non-proprietary name has not been determined; therefore, we use pegfilgrastim-xxxx as a placeholder until such time as it has been determined.

1 INTRODUCTION

On February 27, 2019, Sandoz, Inc. submitted for the Agency's review a Class 2 Complete Response to the Agency's Complete Response (CR) letter issued on June 24, 2016 for their original Biologics License Application (BLA) 761045 for LA-EP2006, TRADENAME (pegfilgrastim-xxxx), a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim). On May 28, 2019, the Division of Medication Error and Prevention Analysis (DMEPA) found the proposed proprietary name Ziextenzo unacceptable. On June 21, 2019, the Applicant submitted a Request for Reconsideration of Proprietary Name. The Proprietary Name is under reconsideration by the Agency at the time of this review.

The proposed indication for LA-EP2006, TRADENAME (pegfilgrastim-xxxx) is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on May 24, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (pegfilgrastim-xxxx) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TRADENAME (pegfilgrastim-xxxx) injection PPI and IFU received on February 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 23, 2019 and July 2, 2019.
- Draft TRADENAME (pegfilgrastim-xxxx) injection Prescribing Information (PI) received on February 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on July 2, 2019.
- Approved US-licensed Neulasta (pegfilgrastim) injection labeling dated April 16, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- evaluated the PPI and IFU per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved labeling for US-licensed Neulasta where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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SUSANNAH O'DONNELL on behalf of CAROLE C BROADNAX
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LASHAWN M GRIFFITHS
07/16/2019 07:37:30 AM

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 9, 2019

TO: Patricia Keegan, MD
Division Director
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

and

Ann T. Farrell, MD
Division Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDBE, OSIS

SUBJECT: Routine inspection of Celerion Arizona, Tempe, AZ
supporting clinical studies RXDX-101-15 (NDA 212725
and NDA 212726) and LA-EP06-104 (BLA 761045)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of studies RXDX-101-15 (NDA 212725 and NDA 212726) and LA-EP06-104 (BLA 761045) conducted at Celerion Arizona, Tempe, AZ.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. However, the blinding codes for study LA-EP06-104 (BLA 761045) were not in Celerion's possession during the interval between study completion and the inspection. The final classification for Celerion Arizona, Tempe, AZ, USA is Voluntary Acton Indicated (VAI).

1.1. Recommendation

After reviewing the inspectional findings, the blinding codes for LA-EP06-104 (BLA 761045) were not in Celerion's possession after study completion. The data from study LA-EP06-104 are not reliable to support a regulatory decision, because FDA cannot confirm accurate dosing. However, the inspectional findings were isolated in nature and do not impact the reliability of data from study RXDX-101-15. Therefore, data from study RXDX-101-15 and other studies of similar design (open-label) are reliable to support a regulatory decision.

I conclude that data from the audited study RXDX-101-15 (NDA 212725 & NDA 212726) are reliable to support a regulatory decision. However, I recommend excluding data generated at Celerion for study LA-EP06-104 (BLA 761045).

2 Inspected Studies:

NDA 212725 and NDA 212726

Study Number: RXDX-101-15

Study Title: "A 2-Part, Open-Label, Randomized, 2-Period, Single-Dose Study to Assess the Relative Bioavailability of 2 Entrectinib Formulations Under Fasting Conditions and the Effect of Food on the Entrectinib F06 Formulation in Healthy Adult Male Subjects"

Dates of conduct: 02/16/2018 - 06/6/2018

BLA 761045

Study Number: LA-EP06-104

Study Title: "A randomized, double blind, crossover, three-way blinded study to compare the pharmacokinetics, pharmacodynamics, and safety of a single 6 mg subcutaneous administration of the proposed biosimilar product LA EP-2006, Neulasta US and Neulasta EU in healthy subjects"

Dates of conduct: 04/14/2017- 08/01/2018

Clinical site: Celerion Arizona
2420 West Baseline Road
Tempe, AZ
FEI#: 3009853739

ORA investigator Michelle Hines (LOS-DO) inspected Celerion Arizona, 2420 West Baseline Road Tempe, AZ from May 28 to June 5, 2019.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

Study LA-EP06-104 was designed as a double blind study. During the inspection, Ms. Hines requested access to the blinding codes to verify subject treatments. However, there were no blinding codes in Celerion's possession at that time (**Attachment 1**). It is important to note that all blinding codes were paper-based, as described in **Attachment 2**. The study did not utilize any type of Interactive Response Technology (e.g. interactive voice or web response systems) that would have maintained blinding codes and associated audit trails. Therefore, no such system was available to ORA for verifying subject treatments.

At the conclusion of the inspection, investigator Hines did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site. However, because the blinding codes for study LA-EP06-104 (BLA 761045) were not in Celerion's possession from the end of the study through the inspection, investigator Hines could not verify accuracy of dosing with the blinded products.

4. Conclusion:

After reviewing the inspectional findings at Celerion Arizona, I conclude the following:

- The data from study RXDX-101-15 are reliable. I recommend that data from study RXDX-101-15 should be accepted for further agency review.
- The data for LA-EP06-104 are NOT reliable, because FDA cannot verify accuracy of dosing with the intended products in the absence of intact blinding codes. Based on the inspectional findings, I recommend that data from study LA-EP06-104 not be accepted for further agency review. The review division may request the sponsor to submit documentation to mitigate the uncertainty of accurate dosing.

In addition, I recommend that data from other blinded studies conducted at Celerion Arizona since the previous inspection (August 2015) should not be accepted for agency

review without an inspection to authenticate the dosing records.

Final Classification:

VAI - Celerion Arizona,
Tempe, AZ
USA
FEI#: 3009853739

cc:
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Draft: XFL 06/24/2019; 7/5/2019; 7/9/2019
Edit: MFS 06/25/2019 and 07/05/2019; JAK 07/05/2019 and
07/08/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/Celerion, Tempe,
AZ, USA

OSIS File #: 8372 (NDA 212725)
8373 (NDA 212726)
7016 (BLA 761045)

FACTS: 11908319

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JOHN A KADAVIL
07/09/2019 03:02:21 PM



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 06/12/2019
To: Administrative File, **STN 761045-1-RESUB-49**
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for **LA-EP2006**
US License: 2003
Applicant: Sandoz, Inc.
Mfg Facility: Drug Substance:
Sandoz GmbH, Biochemiestrasse 10, Kundl, Austria FEI 3002806523
Lek Pharmaceuticals d.d., Kolodvorska 27, Mengeš, Slovenia FEI 3002807470
Drug Product:

(b) (4)

Product: LA-EP2006
Dosage: Injectable sterile, clear and colorless solution for subcutaneous administration. Single use pre-filled syringe containing 6 mg/0.6 mL (10 mg/mL).
Indication: Therapeutic to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia..
Due Date: 08/27/2019

RECOMMENDATION: This application is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of LA-EP2006 Drug Substance and Drug Product at the Sandoz GmbH, Lek Pharmaceuticals d.d., and (b) (4). The starting material

(b) (4)

(b) (4)
The drug substance (b) (4) is manufactured at Lek Pharmaceuticals d.d. (Mengeš, Slovenia), a subsidiary of Sandoz. LA-EP2006 Drug Product is manufactured at (b) (4) in the final

primary packaging (syringes). Sandoz GmbH releases the LA-EP2006 6 mg/0.6 mL solution for injection. In addition to the sites mentioned above in the manufacturer of LA-EP2006 6 mg/0.6 mL, Novartis Pharma AG, Lek Pharmaceuticals d.d. Ljubljana, and (b) (4) perform testing of the DS and DP. A Pre-license inspection was conducted on 03/08 – 14/2016 at Lek Pharmaceutical d.d. No FDA Form 483 was issued, and a final recommendation of acceptable (NAI) has been made. A For Cause and Pre-license inspection was conducted on (b) (4) at (b) (4). A six-item FDA Form 483 was issued, and a final recommendation of acceptable (VAI) has been made. All other related DS and DP facilities have an acceptable compliance status.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The site proposed for LA-EP2006 Drug Substance manufacture, cell banking operations, and testing is presented below in Table 1.

Table 1. Proposed Sites for LA-EP2006 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Sandoz GmbH	Biochemiestrasse 10 AT-6250 Kundl, Austria	3002806523	The EP2006 (b) (4) is manufactured and tested (according to current Good Manufacturing Practices - cGMP). Preparation of the WCB, and storage of the MCB and WCB.
Lek Pharmaceuticals d.d. (a Sandoz company)	Kolodvorska 27 SI-1234 Mengeš, Slovenia	3002807470	The LA-EP2006 drug substance (pegylated EP-2006) is manufactured by pegylation of the EP2006 (b) (4) tested and released (according to current Good Manufacturing Practices - cGMP).
		(b) (4)	DS testing.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DS testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DS testing.

Reviewer Comment 1: *The facilities for manufacture of LA-EP2006 DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

Sandoz GmbH (FEI 3002806523), EP2006 (b) (4) (unpegylated) manufacture, IPC and release testing. A comprehensive surveillance inspection conducted on 04/30/2015 for profiles BTP, CHG, CSN, CSS, CTX, POW, SPW, SVS, TCM, TTR, and CBI included evaluation of the Quality Systems, Facilities and Equipment, Production, and Laboratory Control Systems supporting production of drug substances including biologically derived drug substances, sterile powders for injection, and solid oral dosage forms. This inspection was VAI and found acceptable. Additionally, a comprehensive surveillance and Pre-approval Inspection for EP2006, BLA 125553, and BLA 125546 (Bexsero vaccine) was conducted on 09/16/2014 that covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems for Profiles CBI, CSS, CTX, SPW, SVS, and VBP. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470), LA-EP2006 drug substance manufacture by pegylation of the EP2006 (b) (4) IPC and release testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772), Drug Substance release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Substance release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

(b) (4)

This inspection was VAI and found acceptable.

- **Current Prior Approval Inspection Decisions**

BLA 761045/0. LA-EP2006 DS and DP Manufacture

Sandoz GmbH (FEI 3010479596). DIA, DMA, and OBP waived a PLI for this facility because a PLI for EP2006 was conducted on 09/16/2014, and this justification was documented in the waiver memo . A District file review was requested and the site was found acceptable based on file review.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470). DIA, DMA, and OBP conducted a joint PLI for LA-EP2006 drug substance at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772) was approved based on the facility CTL profile.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

Reviewer Comment 2: A recommendation regarding the compliance status for the DS production and testing facilities associated with the manufacture of LA-EP2006 is acceptable.

3.2.S.2.2 Overview of LA-EP2006 DS Manufacturing Operations Conducted at Sandoz GmbH and Lek Pharmaceuticals d.d.

(b) (4)

Reviewer Comment 3: The overview of EP2006 (b) (4) manufacturing operations conducted at Sandoz GmbH and LA-EP2006 DS manufacturing operations conducted at Lek Pharmaceuticals d.d. are adequately described. The EP2006 DS manufacturing operations were previously verified during the September 2014 inspection, and these operations are identical to those of the EP2006 (b) (4). The LA-EP2006 DS manufacturing operation was verified during the March 2016 inspection.

3.2.A. Appendices

3.2.A.1 Facilities and Equipment [Manufacturer – substance – Dosage Form – Product]

(b) (4)





DRUG PRODUCT FACILITIES

3.2.P Drug Product [Substance – Manufacturer]

3.2.P.2. Manufacture

3.2.P.2.1 DP Manufacturers.

The site proposed for LA-EP2006 Drug Product manufacture, cell banking operations, and testing is presented below in Table 12.

TABLE 12. Proposed Sites for LA-EP2006 DP Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
		(b) (4)	LA-EP2006 6 mg/0.6 mL DP solution for injection is manufactured, tested, and packaged.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DP Bioactivity testing.
Sandoz GmbH	Biochemiestraße 10 6336 Langkampfen Austria	3004828473	DP stability testing.
Lek Pharmaceuticals d.d.	Kolodvorska Cesta 27 Mengeš, 1234 Slovenia	3002807470	DP testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DP testing.

Reviewer Comment 23: The facilities for manufacture of LA-EP2006 DP are adequately described.

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)

Novartis Pharma AG (FEI 3002807772), Drug Product release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4)
(b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing. A comprehensive surveillance inspection conducted on 03/18/2014 for profiles CRU, CXA, and SVS included evaluation of the Quality, Production, Laboratory Control, Materials and Facility and Equipment Systems. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance Inspection was conducted on 03/16/2012 that covered the Quality, Production, Facilities & Equipment, and Laboratory Control Systems for Profiles SVS, CXA, CBI, CSN and TAM. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470), Drug Product release and stability testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Product release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

(b) (4) This inspection was VAI and found acceptable.

• **Current Prior Approval Inspection Decisions**

(b) (4)

Novartis Pharma AG (FEI 3002807772) was approved based on the facility profile and Laboratory Control Systems coverage.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing was approved based on the facility profile and Laboratory Control Systems coverage.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470). DAI, DMA, and OBP conducted a joint pre-approval inspection for LA-EP2006 drug substance (pegylated EP2006) that included Laboratory Control Systems at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

***Reviewer Comment 24:** the compliance statuses for the DP production and testing facilities associated with the manufacture of LA-EP2006 are acceptable.*

(b) (4)

CONCLUSION

Adequate descriptions were provided for the Sandoz GmbH (FEI 3002806523) and Lek Pharmaceuticals d.d. (FEI 3002807470) LA-EP2006 Drug Substance facilities, and (b) (4) LA-EP2006 Drug Product facility proposed for DS and DP manufacture. The proposed DS and DP manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Michael Shanks, Biologist, CDER/OPQ/OPF/DIA I 05/20/2016

Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA I 05/20/2016

BLA 761045-1-RESUB-49

CONCLUSION

No changes from the original submission from a Facilities Perspective and adequate descriptions were provided for the Sandoz GmbH (FEI 3002806523) and Lek Pharmaceuticals d.d. (FEI 3002807470) LA-EP2006 Drug Substance facilities, and (b) (4) LA-EP2006 Drug Product facility proposed for DS and DP manufacture. The proposed DS and DP manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Michael R.
Shanks -S

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ou=HHS, ou=FDA, ou=People,
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Date: 2019.06.12 10:11:19 -04'00'

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

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Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	BLLA 761045
Applicant	Sandoz
Proprietary Name (nonproprietary name)	Proposed Proprietary Name: ZIEXTENZO (pegfilgrastim-xxxx)
Receipt Date	02/27/19
PDUFA Goal Date (Internal Goal Date)	08/27/19
Review Classification	Response to CR; 6 month clock
Proposed Indication (or current indication if unchanged)	ZIEXTENZO is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Dosing Regimen	
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

In this review, I summarize the DHP labeling recommendations and edits in the LA-EP2006 (pegfilgrastim-xxxx; ZIEXTENZO) labeling. ZIEXTENZO (pegfilgrastim-xxxx) is a proposed biosimilar product to Neulasta (pegfilgrastim). This BLA previously received a Complete Response on 06/04/16 for product quality and clinical pharmacology issues. Sandoz has submitted their response to CR.

These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of ZIEXTENZO.

I compared the proposed labeling to the April 2019 version of the approved Neulasta labeling. I highlighted/commented on areas where there were differences and made recommendations as how to approach these differences. The edits suggested are to align with the currently approved version of the Neulasta labeling.

The following pages contain a summary of the labeling recommendations followed by the working version of the ZIEXTENZO labeling with comments by me identified by “KV##” and sequentially numbered. Given that the scientific review of the labeling is ongoing, the labeling recommendations in this review should be considered preliminary and may not represent DHP’s final recommendations for the ZIEXTENZO labeling.

Summary of Labeling Recommendations:

Highlights

Dosage Forms and Strengths:

- Removed “(b) (4)” to provide a concise summary of the USPI in Highlights. These details are also not consistent with Section 3 of the FPI.

Full Prescribing Information

Dosage and Administration:

- Section 2.2: Recommend removal of text “(the solution is clear and colorless to slightly yellowish)” as inclusion of the description within parentheses may confuse readers into believing they should not administer a solution that is clear and colorless to slightly yellowish. The usual appearance is described in Section 3.

Adverse Reactions:

- Section 6.3: Added “alveolar hemorrhage” to the list of events in the Postmarketing Experience to be consistent with recently approved Neulasta labeling (April 2019).

Use in Specific Populations:

- Section 8.1 Pregnancy: Revised formatting of “(see Data) to italics to be consistent with PLLR guidance and Neulasta USPI.

Description:

- Recommend removal of period in “E coli” to be consistent with Neulasta USPI. It is grammatically correct, but labeling should be consistent with innovator product.
- Corrected capitalization of “water for injection, USP” to “Water for Injection, USP” to be consistent with USP and the Neulasta USPI.

Text after Patient Counseling (Section 17):

- Requested that Applicant add the street address of the manufacturer. Per 21 CFR 201.1 and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling and should be located after the Patient Counseling Information section, at the end of the PI. If the product has FDA-approved patient labeling that is not a separate document from the PI, the manufacturer information should be located at the end of labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document, or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling. The street address may be omitted if it is shown in a current city directory or telephone directory.

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

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/s/

VIRGINIA E KWITKOWSKI
05/29/2019 11:13:59 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/12/2019

TO: Division of Hematology Products
Office of New Drugs

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761045

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

PRA Health Sciences, Groningen: The Office of Regulatory Affairs (ORA) inspected the site in April 2017, which falls within the surveillance interval. The inspection was conducted under the following submission: BLA 761075.

PRA Health Sciences, Salt Lake City: The Office of Regulatory Affairs (ORA) inspected the site in November 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 212038.

Celerion, Lincoln: The Office of Regulatory Affairs (ORA) inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submission:

(b) (4)

(b) (4)

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PRA Health Sciences	Clinical Chemistry Laboratory, Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands
Clinical	PRA Health Sciences	700 East 3838 South, Suite 200, Salt Lake City, UT

Facility Type	Facility Name	Facility Address
Clinical	Celerion	621 Rose Street, Lincoln, NE
Analytical	(b) (4)	

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/s/

NICOLA M FENTY-STEWART
04/12/2019 06:09:15 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 6/28/2016

To: Rachael McMullen, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Office of Prescription Drug Promotion

Through: Katie Davis, Team Leader
Office of Prescription Drug Promotion

Subject: Comments on draft labeling (Package Insert) for LA-EP2006
(pegfilgrastim)/BLA 761045

This memo is in response to your labeling consult request on October 20, 2015. DHP issued a Complete Response (CR) letter on June 24, 2016. Therefore, OPDP defers comment on the Applicant's labeling at this time. A comprehensive review of the proposed patient labeling will not be performed until after the Applicant submits an otherwise adequate application. Please send us a new consult request at such time.

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/s/

JAMES S DVORSKY
06/28/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 23, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761045
Product Name and Strength:	Ziextenzo (LA-EP2006)* Injection 6 mg/0.6 mL
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz
Submission Date:	August 27, 2015
OSE RCM #:	2015-2000
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Ziextenzo (LA-EP2006)* injection (BLA 761045) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products (DHP) requested this review to inform their evaluation of the 351(k) submission for Ziextenzo. The reference product, US-licensed Neulasta (BLA 125031), was approved in January 2002.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)#	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

#We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Ziextenzo (LA-EP2006)* injection, BLA 761045. We note that Ziextenzo has the same route of administration, strength, and storage requirements as the reference product, US-licensed Neulasta (BLA 125031). At the time when the Ziextenzo 351(k) BLA was submitted (August 27, 2015), there was no information regarding pediatric dosing in US-licensed Neulasta labeling. Since then, weight based dosing which would allow dosing of patients less than 45 kg, including pediatric patients, for the indications of decreasing the incidence of infection in patients with cancer receiving myelosuppressive chemotherapy and hematopoietic subsyndrome of acute radiation syndrome (ARS) were added to the labeling of US-licensed Neulasta. It is noted that if Sandoz can demonstrate that LA-EP2006 is biosimilar to

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US-licensed Neulasta, they can be licensed for the indication of decreasing the incidence of infection in both pediatric (because of weight-based dosing information in the reference product) and adult patients with cancer receiving myelosuppressive chemotherapy but cannot be licensed for ARS as the sponsor of US-licensed Neulasta has unexpired orphan-drug exclusivity for this indication.

Per discussion with the Division of Pediatric and Maternal Health (DPMH), Ziextenzo is subject to the Pediatric Research Equity Act (PREA) as a biosimilar product, and thus a pediatric assessment is required unless waived or deferred (see section 505B(m) of the FD&C Act). A pediatric assessment must include data gathered using an age-appropriate formulation or formulations that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the biological product is safe and effective (see section 505B(a)(2)(A) of the FD&C Act). The pediatric formulation or formulations should be capable of being accurately administered in all relevant pediatric populations.

Ziextenzo is supplied as a single-use prefilled syringe (PFS) with an UltraSafe Passive™ needle guard. The Ziextenzo PFS does not have graduation marks. US-licensed Neulasta is supplied as a single-use PFS with a manual needle guard and as a PFS for use with a delivery device, the OnPro kit. Similar to the Ziextenzo PFS, the US-licensed Neulasta PFS also does not have graduation marks, but dosing for the reference product, US-licensed Neulasta, includes pediatric doses of less than 6 mg (0.6 mL). Because the Ziextenzo's PFS, like the US-licensed Neulasta's PFS, does not have graduation marks, doses less than 6 mg (0.6 mL) cannot be accurately measured or directly administered without manipulation of the PFS content or dose approximation, both of which can lead to medication errors, as has been evidenced by postmarket reports of "lack of calibration" on the PFS as a factor that contributed to dosing errors with off label use of US-licensed Neulasta.¹

Prefilled syringes are generally designed for direct patient administration. Syringes are also among the most commonly used devices to deliver drugs, and, as a general matter, they tend to have calibrated graduation marks that allow for accurate measurement of variable amounts of fluid. Collectively, these factors will likely predispose some practitioners who are ordering, dispensing or administering a prefilled syringe not consult the label for this administration

¹ Ayres, Ebony. Label and Labeling Review for Neulasta BLA 125031/S-180. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 23. RCM No.: 2015-1012.

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aspect. Thus, there is some likelihood that practitioners will mistakenly assume that the PFS can accurately measure a variable range of doses to be directly administered to a patient.

However, labeling statements in the US-licensed Neulasta labeling clearly advise that the PFS is not designed for direct administration of the drug for doses less than 0.6mL (6 mg). Similar statements appear in the Zarxio (filgrastim-sndz) labeling approved in March 2015. These statements should reduce the risk of error in circumstances where the label is read and attended to by providers.

Thus, we determined that the issue of the PFS not being designed for direct administration of doses less than 6 mg (0.6 mL) in the current proposed Ziextenzo presentation could be addressed through modifications to Ziextenzo's proposed labeling. Specifically, we recommend that the design limitations of the PFS be conveyed as important information about the device to consider under the Dosage and Administration, Description, and How Supplied/Storage and Handling sections of the PI and within the IFU, consistent with the labeling of Zarxio and US-licensed Neulasta.

Ziextenzo, however, is subject to PREA, which requires the development of an appropriate pediatric presentation or presentations for all relevant pediatric subpopulations. While the labeling statements discussed above and in section 4 of this review mitigate the risk of medication errors in patients weighing less than 45 kg, we note that the Ziextenzo PFS is not designed to measure a variable amount of liquid that corresponds to the labeled doses.

These refinements could be made prior to approval. Alternatively, if FDA defers the pediatric assessment associated with this BLA, the development of an appropriate pediatric presentation would be done as a Post-Marketing Requirement (PMR). If these refinements are made as a PMR, the PMR should outline the need for Sandoz to develop a presentation that can be used to directly administer doses less than 6 mg (0.6 mL) and should also convey that the proposed presentations may need Human Factors studies to demonstrate that users can accurately measure the doses.

If the sponsor continues to seek approval of the current proposed presentation, the PI for Ziextenzo should be revised to include the same weight-based dosing information for patients with cancer receiving myelosuppressive chemotherapy, i.e., section 2 Dosage and Administration of the PI should be revised to include a weight-based dosing table mirroring Table 1 in the US-licensed Neulasta PI.

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The Ziextenzo IFU follows similar steps and injection technique as the reference product, US-licensed Neulasta. However, we recommend areas within the Ziextenzo IFU that differ from US-licensed Neulasta IFU be revised to be harmonized with the US-licensed Neulasta IFU. For example, US-licensed Neulasta can be administered at either a 45° or 90° angle. However, in the Ziextenzo IFU, the graphic depicting the injection technique shows an approximately 45° injection angle, and the text accompanying the graphic does not state the injection angle. Revision of this step may help to decrease the risk of confusion regarding the injection technique and will harmonize this step with the US-licensed Neulasta IFU. We also note that the Ziextenzo IFU does not list or depict the buttocks as an injection site. This aspect also differs from the reference product, US-licensed Neulasta. We recommend that this discrepancy is clarified and that the injection sites are revised, if appropriate to include the buttocks injection site. We defer to the Clinical team and Patient Labeling team to provide additional recommendations for the Ziextenzo IFU.

The carton labeling and container labeling can be improved to increase the visibility and clarity of key prescribing information, and to increase the prominence of the storage information. Our post-marketing experience also demonstrates that the net quantity (i.e., 1 prefilled syringe) may be misinterpreted as product strength (i.e., 6 mg/0.6mL) and thus, dosing errors may occur. Accordingly, the prominence of the net quantity should be reduced relative to the strength statement to decrease the risk of confusion, as recommended in the draft guidance for industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Error.² Additionally, the labeling should be updated to revise the trade name from (b) (4) to Ziextenzo. We also note the presence of a removable label on the Ziextenzo PFS, which may temporarily adhere to the syringe body and interfere with syringe visibility. In response to a March 15, 2016 Information Request from the Agency, the Sponsor stated that the purpose of the removable label is for documentation purposes and medication error prevention. We do not recommend revisions to the removable label at this time; however, we will monitor postmarketing reports for instances of medication errors or difficulties with the removable label.

We searched the FAERS database to identify medication errors with the reference product US-licensed Neulasta that may be relevant to this review. We identified fifty-six medication error cases including inappropriate schedule of administration, incorrect route of administration, and

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

improper storage (see Appendix E for a detailed description of the cases). We evaluated the Ziextenzo labels and labeling in light of the US-licensed Neulasta medication errors to ensure that information regarding the route and frequency of administration is clear and prominent, and we did not identify any needed changes. The reports of incorrect storage of US-licensed Neulasta reported US-licensed Neulasta being stored outside of refrigeration. Based on this finding, we recommend that the proposed carton labeling for Ziextenzo be revised to increase the prominence of the storage information to help mitigate the risk for incorrect storage errors.

4 CONCLUSION & RECOMMENDATIONS

Our review identified risk for medication errors in patients who weigh less than 45 kg, e.g., pediatric patients, because the U.S. Neulasta PFS and proposed Ziextenzo PFS are not designed for the direct administration of doses less than 0.6 mL (6 mg) due to lack of graduation marks. We provide specific recommendations on the proposed Ziextenzo labeling below, consistent with labeling statements for Neulasta, to mitigate this risk if the sponsor continues to seek approval of the current proposed presentation.

Because Ziextenzo is subject to PREA, however, an appropriate pediatric presentation will have to be developed. The sponsor could do this prior to approval or, if FDA defers the pediatric assessment associated with this BLA, development of an appropriate pediatric presentation will be required as a PMR.

Additionally, we identified other aspects of the labels and labeling that should be revised to add important information regarding the administration of pediatric doses if the sponsor continues to seek approval of the current proposed presentation, harmonize with the labeling for the reference product where appropriate, and to mitigate the risk of medication errors. We provide recommendations below, and we advise they are implemented prior to approval of BLA 761045.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Pediatric Presentation

- a. Ziextenzo is subject to the Pediatric Research Equity Act (PREA) as a biosimilar product. Thus, the application must include a pediatric assessment, which includes development of an appropriate pediatric presentation. The proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. The proposed pediatric presentation(s) can be developed prior to approval, or the Sponsor can request a deferral of the pediatric assessment pending development of an appropriate pediatric

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presentation. If the Sponsor chooses the latter approach, the development of an appropriate pediatric presentation will be required as a post marketing requirement (PMR).

B. Prescribing Information

- a. Update the trade name on the labeling from (b) (4) to Ziextenzo.
- b. *If the sponsor continues to seek approval of the current proposed presentation:*
Section 2 Dosage and Administration
 - i. 2.2 Administration
 1. Include the following statement in this section to inform users that Ziextenzo prefilled syringes cannot be used for the direct administration of doses less than 6 mg (0.6 mL):
 - a. The Ziextenzo prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks which are necessary to accurately measure doses of Ziextenzo less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors.
 2. We recommend including a dosing table for patients weighing less than 45 kg (see Table 1 under Section 2 of the PI for Neulasta)
- c. *If the sponsor continues to seek approval of the current proposed presentation:*
Section 11 Description
 - i. Following the sentence, “(b) (4) is supplied in 0.6 mL prefilled syringes for subcutaneous injection”, include the following statement to inform users that Ziextenzo prefilled syringes cannot be used for the direct administration of doses less than 6 mg (0.6 mL):
 1. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
- d. *If the sponsor continues to seek approval of the current proposed presentation:*
Section 16 How Supplied/Storage and Handling
 - i. Include the following statement to inform users that Ziextenzo prefilled syringes cannot be used for the direct administration of doses less than 6 mg (0.6 mL):

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

1. Ziextenzo prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe.

4.2 RECOMMENDATIONS FOR SANDOZ

We recommend the following be implemented prior to approval of this BLA 761045:

A. Carton labeling (outer)

1. Update the trade name on the labeling from (b) (4) to Ziextenzo.
2. Consider the use of boldface font to increase the prominence of “Refrigerate” on the principal display panel (PDP) to help mitigate the risk of improper storage errors.
3. Decrease the prominence of the net quantity “1” because this information appears with equal prominence to the product strength (i.e., 6 mg/0.6mL) and may increase the risk of numerical confusion.³

B. Carton labeling (inner)

1. Refer to recommendation A.1. and revise accordingly.

C. Container label (syringe label)

1. Refer to recommendation A.1. and revise accordingly.

D. Instructions for Use

1. Refer to recommendation A.1. and revise accordingly.
2. *If the sponsor continues to seek approval of the current proposed presentation:* In the first section of the IFU, include the following statement to indicate to users that Ziextenzo cannot be used to directly administer doses less than 6 mg (0.6 mL):
 - i. You should not inject a dose of Ziextenzo less than 0.6 mL (6 mg) from a Ziextenzo prefilled syringe. A dose less than 0.6 mL cannot be accurately measured using the Ziextenzo prefilled syringe.
3. Consider removing the label “ (b) (4) ” from Figure A as this technical term may not be understood by patients and caretakers. Additionally, this term is not referenced in the remainder of the IFU.

³ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

4. In Step 8, replace the term “transparent” with “clear” to mitigate the risk of confusion as patients and caretakers may not understand the term “transparent”.
5. In Step 10, revise the sentence “(b) (4)” to “Let the skin dry.” We recommend this revision to increase the clarity of this statement.
6. In Step 14, Figure J shows the Ziextenzo injection being given at an approximately 45° angle. The text in Step 14 does not mention at which angle the injection should be given. Therefore, revise the text in Step 14 to include the injection angle that should be used to administer Ziextenzo.
7. We note the IFU does not list the buttocks as an injection. The upper outer area of the buttocks is listed as an injection site for the reference product, US-licensed Neulasta. Therefore, please clarify and provide reasoning for the discrepancy between the Ziextenzo IFU and the US-licensed Neulasta IFU.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ziextenzo that Sandoz submitted on August 27, 2015, and the reference product.

Table 2. Relevant Product Information for Ziextenzo and the Listed Drug		
Product Name	Ziextenzo	Neulasta
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	LA-EP2006*	Pegylated-GCSF
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	<ul style="list-style-type: none"> - To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia - Improve survival in adult victims and pediatric victims with body weight \geq 45 kg who are at risk of developing life-threatening infections secondary to neutropenia resulting from acute exposure to radiation levels > 2 Gy.
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection, solution	Injection, solution
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	<p>Give 6 mg subcutaneously once per chemotherapy cycle.</p> <p><i>Additional dosing proposed by DHP:</i> For pediatric patients weighing less than 45 kg, use weight</p>	<p><i>Cancer patients receiving myelosuppressive chemotherapy</i></p> <ul style="list-style-type: none"> - 6 mg administered subcutaneously once per chemotherapy cycle; for pediatric patients weighing less than 45 kg, use weight

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

	based dosing (100 mcg/kg)	based dosing (100 mcg/kg) <i>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome</i> - 6 mg subcutaneously for adult victims and for pediatric victims with body weight \geq 45 kg for two doses given two weeks apart; for pediatric patients weighing less than 45 kg, use weight based dosing (100 mcg/kg)
How Supplied	Single-dose, preservative-free, prefilled syringe with an UltraSafe Passive™ Needle Guard, containing 6 mg/0.6 mL of LA-EP2006*.	- 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only - OnPro kit: 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta
Storage	Store in the refrigerator at 36°F to 46°F (2°C to 8°C) in the original pack to protect from light. Do not shake. Do not freeze. Prior to injection, Ziextenzo may be allowed to reach room temperature for a (b) (4)	Store refrigerated between 36° to 46°F (2° to 8°C) in the carton to protect from light.

*Ziextenzo has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). Since the proper name for Ziextenzo has not yet been determined, LA-EP2006 is used throughout this review in place of the nonproprietary name for this product.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 21, 2015, we searched the L:drive and AIMS using the term, Ziextenzo, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on November 30, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁴

Table 3: FAERS Search Strategy	
Date Range	FDA Received Date To: 20151101
Product	Neulasta [active ingredient] pegfilgrastim [product name]
Event (MedDRA Terms)	Contraindicated drug administered [PT] Drug administered to patient of inappropriate age [PT] Inadequate aseptic technique in use of product [PT] Medication errors [HLGT] Overdose [PT] Prescribed overdose [PT] Prescribed underdose [PT] Product adhesion issue [PT] Product compounding quality issue [PT] Product formulation issue [PT] Product label issues[HLT] Product packaging issues [HLT] Product use issue [PT] Underdose [PT]
Country	USA

Our search identified 132 cases, of which 56 described medication errors relevant for this review. Some cases described more than one type of medication error.

Inappropriate schedule of administration (n = 22)

- Twenty-two cases reported inappropriate schedule of administration of US-licensed Neulasta (FAERS Case No. 10777949, 11627136, 5766272, 5770507, 6597246, 6597285,

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

6597317, 6944160, 6944208, 6987263, 7083087, 7330371, 7885017, 7885071, 8776703, 9871756, 9871776, 8702433, 8093450, 9256070, 9256189, 9256242).

- Eleven cases described patients who accidentally received more than one dose of Neulasta during a given cycle of chemotherapy.
- Two cases described reports of two separate patients receiving doses of US-licensed Neulasta less than 24 hours after receiving chemotherapy.
- Regarding contributing factors, one case listed “something wrong with the orders” as a contributing factor. Another case listed a change in scheduling due to the holiday as a contributing factor.
- Regarding patient outcomes, two cases reported that patients experienced bone pain in response to the errors. One case reported that the inappropriate schedule of administration of US-licensed Neulasta caused an increase in tumor size. One case reported that a patient did not experience adverse events as a result of the medication error. One case reported that the patient felt ill after receiving US-licensed Neulasta earlier than scheduled. The remaining cases did not provide patient outcomes or contributing factors.

A review of Section 2 Dosage and Administration of the Prescribing Information of the reference product indicates that US-licensed Neulasta should be administered once per chemotherapy cycle and should not be administered between 14 days before and 24 hours after administration of chemotherapy. The information appears to be clearly listed. This dosing information in the Prescribing Information for Ziextenzo is identical to the reference product; as a result, we do not believe labeling revisions are not necessary at this time.

Incorrect route of administration (n = 11)

- Eleven cases (FAERS Case No. 10136263, 10777995, 11517529, 11617255, 7331621, 8393053, 8435610, 9256079, 9256118, 9256194, 9256250) described the administration of US-licensed Neulasta via an incorrect route.
 - In six of the cases, patients received or possibly received US-licensed Neulasta intramuscularly instead of subcutaneously.
 - Four cases reported patients who received US-licensed Neulasta intravenously instead of subcutaneously.
 - Six cases reported patient outcomes including decrease in neutrophil count, bone pain, chest pain, and hematoma. The remaining cases did not provide patient outcomes.
 - Contributing factors were not reported.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the route of administration is clearly listed. The route of administration information in the Prescribing Information for Ziextenzo is similar to the reference product and does not appear vulnerable to medication errors. Additionally, the proposed IFU for Ziextenzo depicts subcutaneous administration. Labeling revisions are not necessary at this time.

Incorrect storage (n = 8)

- Seven cases (FAERS Case No. 10778000, 11098586, 11457673, 3943611, 7885026, 9256234, 9690403) described incorrect storage of US-licensed Neulasta. The cases involved US-licensed Neulasta being stored outside of refrigeration. Contributing factors including leaving US-licensed Neulasta in the car, placing US-licensed Neulasta in the freezer, leaving outside (delivery), and storing outside of the refrigerator. Three of the cases reported that patients received US-licensed Neulasta that was improperly stored.
- One case (FAERS Case No. 8089474) reported possible incorrect storage of US-licensed Neulasta. The case reported that the dose of US-licensed Neulasta “did not work properly”. Per the reporter, a contributing factor is that US-licensed Neulasta may not have been stored properly during the transport along the supply line.

A review of Section 16 How Supplied/Storage and Handling of the Prescribing Information indicates that the storage information is clearly listed. Additionally, we recommend increasing the prominence of the storage information on the carton labeling to help mitigate the risk of this medication error.

Overdose (n = 4)

- Four cases (FAERS Case No. 8987095, 6944061, 6375877, 10521961) reported overdose errors.
 - o One case described a patient’s report of receipt of “a full month or four months of Neulasta in this single injection”. The patient reported fainting and abnormal WBCs. Contributing factors were not reported.
 - o One case reported that a patient received a full adult dose of US-licensed Neulasta. The reported stated that the patient should have received a dose modification due to “nadir labs”. Patient outcomes were not reported.
 - o In two cases, pediatric patients were incorrectly dispensed the entire contents of the US-licensed Neulasta PFS. One patient was administered the entire contents of the PFS and experienced elevated WBCs, decreased platelets and mild bone pain as a result of the error. The second patient was administered approximately half the contents of the PFS to achieve the intended dose of 3 mg. Per the reporter, excessive therapeutic response to dose administered indicates that a dosing error was possible.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the dosing information is clearly listed. Additionally, we note that the PI does not contain directives for dose modifications based on hematologic labs values. The dosing information in the Prescribing Information for Ziextenzo is similar to the reference product. However, we recommend that the Ziextenzo PI is updated to include the same dosing information for indications shared with the reference product US-licensed Neulasta and to inform users that Ziextenzo PFS cannot be used for the direct administration of doses less than 6 mg (0.6 mL).

Wrong technique (n = 3)

- Two cases (FAERS Case No. 8416674, 10777975) reported wrong technique in the drug usage process. Both cases described Neulasta being administered at an injection site other than those listed in the Prescribing Information. Contributing factors and patient outcomes were not reported.
- One case (FAERS Case No. 9871712) described a case in which a health care practitioner, who was administering Neulasta to a patient, "pulled back" on the US-licensed Neulasta plunger and blood appeared at the injection site. The patient's outcome was not reported.

A review of the proposed Instructions for Use for Ziextenzo indicates that the injection sites are clearly labeled and listed. We recommend changes to the IFU to increase clarity and readability and to help mitigate the risk of medication errors.

Dose omission (n = 2)

- Two cases (FAERS Case No. 6273409, 9256148) reported cases in which patients missed schedule doses of US-licensed Neulasta. The cases did not provide further details.

A review of Section 2 Dosage and Administration of the Prescribing Information indicates that the dose and frequency information is clearly listed. Label revisions are not necessary at this time.

Underdose (n = 2)

- Two cases (FAERS Case No. 11627353, 9256075) reported underdose errors. One case reported difficulty injecting the entire contents of the prefilled syringe as a contributing factor; the patient in that case did not experience adverse outcomes and returned later to receive the remainder of the dose. The remaining case did not provide contributing factors or patient outcomes.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the dosing information is clearly listed. The dosing information in the Prescribing Information for Ziextenzo is similar to the reference product. However, we recommend that the Ziextenzo PI is updated to include the same indications and dosing information as the reference product US-licensed Neulasta.

Wrong patient (n = 2)

- One case (FAERS Case No. 11627283) reported case in which a patient received a dose of Neupogen which was intended for another patient. The patient should have received US-licensed Neulasta. Contributing factors and patient outcomes were not reported.

- One case (FAERS Case No. 9256087) reported a case in which US-licensed Neulasta was administered to the wrong patient. Contributing factors and patient outcomes were not reported.

Labeling modifications are not necessary at this time.

Medication error (n = 1)

- One case (FAERS Case No. 5794099) reported a medication error involving US-licensed Neulasta. Further details were not provided.

This error did not provide details to fully interpret the case; therefore, labeling revisions are not warranted.

Wrong dose (n = 1)

- One case (FAERS Case No. 9256083) described a case in which a patient was on dose of 0.2 mL and 0.4 mL; however, the full US-licensed Neulasta prefilled syringe was dispensed. Therefore, it was unclear whether the actual doses received were accurate. The case did not report contributing factors or patient outcomes.

A review of Section 2 Dosage and Administration of the Prescribing Information for US-licensed Neulasta indicates that the dosing information is clearly listed. The dosing information in the Prescribing Information for Ziextenzo is similar to the reference product. However, we recommend that the Ziextenzo PI is updated to include the same indications and dosing information as the reference product US-licensed Neulasta. Additionally, we recommend that an improved Ziextenzo dosing device is developed to accommodate the direct administration of doses less than 6 mg (0.6 mL).

We excluded 76 cases because they described errors involving: the US-licensed Neulasta OnPro device (n = 27), name confusion with the proprietary name Neulasta (n = 21), errors not involving pegfilgrastim (n = 10), off label use (n = 6), duplicate reports (n = 3), wrong drug (n = 3), expired product errors (n = 2), unrelated literature report (n = 1), device malfunction with US-licensed Neulasta PFS (n = 1), product quality concerns with US-licensed Neulasta PFS (n = 1), and self-administration of an unprescribed product (n = 1).

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Manufacturer Control Number	FAERS Case Number	Manufacturer Control Number	FAERS Case Number	Manufacturer Control Number
6273409	US-AMGEN-KDL194291	8776703	US-AMGEN-USASP2012056682	8093450	US-AMGEN-USASP2011040854
9256148	US-AMGEN-USASP2012033729	9871756	US-AMGEN-USASP2013037619	8987095	US-AMGEN-USASP2012082547
10778000	US-AMGEN-USASP2014012826	9871776	US-AMGEN-USASP2014005309	6944061	US-AMGEN-KDL303823
11098586	US-AMGEN-USASP2015011473	7330371	US-AMGEN-KDL339668	9256070	US-AMGEN-USASP2012016639
11457673	US-AMGEN-USASP2015090215	7885017	US-AMGEN-KDL400721	9256189	US-AMGEN-USASP2012064963
3943611	US035894	7885071	US-AMGEN-KDL432148	9256242	US-AMGEN-USASP2012065128
7885026	US-AMGEN-KDL412600	8702433	Not reported	6375877	Not reported
8089474	US-AMGEN-USASP2011040381	7083087	US-AMGEN-QUU359140	11627353	US-AMGEN-USASP2015095835
9256234	US-AMGEN-USASP2012057800	10136263	US-AMGEN-USASP2014029976	9256075	US-AMGEN-USASP2012013258
9690403	US-AMGEN-USASP2013080410	10777995	US-AMGEN-USASP2014017176	11627283	US-AMGEN-USASP2015046989
10777949	US-AMGEN-USASP2014022803	11517529	US-AMGEN-USASP2015094289	9256087	US-AMGEN-USASP2012023927
11627136	US-AMGEN-USASP2014081624	11617255	US-AMGEN-USASP2015104232	8416674	US-AMGEN-USASP2012010237
5766272	US-AMGEN-US121053	7331621	US-AMGEN-KDL384006	10777975	US-AMGEN-USASP2014050259
5770507	US-AMGEN-US122453	8393053	US-AMGEN-USASP2012007495	10521961	Not reported
6597246	US-AMGEN-US212163	8435610	US-AMGEN-USASP2012012561	9256083	US-AMGEN-USASP2012023514
6597285	US-AMGEN-US232664	9256079	US-AMGEN-USASP2012022135	9871712	US-AMGEN-USASP2013010108
6597317	US-AMGEN-US221947	9256118	US-AMGEN-USASP2012049496		
6944160	US-AMGEN-KDL286632	9256194	US-AMGEN-USASP2012067109		
6944208	US-AMGEN-KDL277614	9256250	US-AMGEN-USASP2012082836		

6987263	US-AMGEN- QUU344715	5794099	US100455		
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E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁵ along with postmarket medication error data, we reviewed the following Ziextenzo labels and labeling submitted by Sandoz on August 27, 2015.

- Container label (syringe)
- Carton labeling (inner)
- Carton labeling (outer)
- Prescribing Information (not pictured)
- Instructions for Use (not pictured)

G.2 Label and Labeling Images

- Container label (syringe)



- Carton labeling (inner)

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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

/s/

EBONY A WHALEY
06/23/2016

LUBNA A MERCHANT
06/23/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 9, 2016

TO: Ann Farrell, M.D.
Director
Office of Hematology and Oncology Products (OHOP)
Division of Hematology Products (DHP)
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Review of EIR for Parexel International GmbH, Berlin, Germany covering BLA 761045 for LA-EP2006 (pegfilgrastim) sponsored by Sandoz, Inc.

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of Pharmacokinetic/ Pharmacodynamic study LA-EP06-101 at Parexel International GmbH, Berlin, Germany. No significant deficiencies were observed and no Form FDA 483 was issued. The final classification is No Action Indicated (NAI).

After review of the inspectional findings, I recommend that the data from the clinical portion of study LA-EP06-101 be accepted for further agency review.

Study Number: LA-EP06-101
Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US-registered) after single

dose subcutaneous application in healthy subjects"

Study Dates: June 24 - December 28, 2010

Clinical Site: Parexel International GmbH
Early Phase Clinical Unit
Spandauer Damm 130, D-14050
Berlin, Germany

The inspection of the clinical portion of study LA-EP06-101 was conducted by ORA investigator Marc A. Jackson at Parexel International GmbH, Berlin, Germany from March 7-11, 2016. The inspection included a review of the Independent Ethics Committee (IEC) approval process and correspondence, informed consent process, randomization and blinding, adverse events (AEs), concomitant medications, study sample processing and storage, test and reference article accountability, dispensation and storage, employee training, and SOPs. No significant discrepancies were observed and no Form FDA 483 was issued at the conclusion of the inspection. Reserve samples were collected and sent to CDER-DPA, St. Louis, MO.

This review is based on the draft Establishment Inspection Report (EIR). Upon receipt and review of the final endorsed EIR by OSIS, this review will be amended if the findings in the endorsed EIR warrant a change in the recommendations.

Recommendations:

Following review of the draft EIR, the data from the clinical portion of the audited study were found to be reliable. Thus, this reviewer recommends that the data from study LA-EP06-101 be accepted for further agency review.

Srinivas R. Chennamaneni, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical Site

**NAI: Parexel International GmbH, Early Phase Clinical Unit,
Berlin, Germany**

FEI: 3008483972

CC:

OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Chennamaneni
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Stanley
OND/OHOP/DHP/Farrell/McMullen
ORAHQ/BIMO/Bukowczyk/Jackson

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Parexel International GmbH, Early Phase Clinical Unit,
Berlin, Germany/BLA 761045_LA-EP2006 (pegfilgrastim), 10 mg/mL

Draft: SRC 5/30/2016

Edit: GB 6/6/2016; CB 6/7/2016

OSI: **BE7016**

FACTS: 11600978

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

/s/

SRINIVAS RAO N CHENNAMANENI
06/09/2016

CHARLES R BONAPACE
06/09/2016

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 5/24/2016

From: Michael Shanks, OPQ/OPF/DIA
Patrick Lynch, Ph.D., OBP/DBRRII
Bo Chi, Ph.D., DMA/MABIV

To: BLA File, STN 761045/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of LA-EP2006 DS at the Sandoz GmbH facility in Kundl, Austria.

Applicant: Sandoz, Inc.

Facility: Sandoz GmbH
Biochemiestrasse 10
AT-6250 Kundl
Austria
FEI 3002806523

Product: LA-EP2006

Dosage: Injectable sterile, clear, and colorless solution for subcutaneous administration. Single use pre-filled syringe containing 6 mg/0.6 mL (10 mg/mL).

Indication: Therapeutic to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

Waiver Recommendation

BLA STN 761045/0 proposes manufacture of EP2006 [REDACTED] (b) (4) [REDACTED] at Sandoz GmbH, Kundl, Austria (FEI 3002806523), the pegylation of [REDACTED] (b) (4) LA-EP2006 DS at Lek Pharmaceuticals d.d., Mengeš, Slovenia (FEI 3002807470), and LA-EP2006 DP at [REDACTED] (b) (4) [REDACTED]. The proposed EP2006 [REDACTED] (b) (4) manufacturing process, up to (b) (4) [REDACTED] step, is identical to that of the EP2006 DS previously approved under BLA 125553 manufactured at Sandoz GmbH, Kundl, Austria.

The most recent inspection of the Sandoz GmbH was a comprehensive surveillance inspection conducted on 04/20-30/2015 for profiles BTP, CHG, CSN, CSS, CTX, POW, SPW, SVS, TCM, TTR, and CBI included evaluation of the Quality Systems, Facilities

and Equipment, Production, and Laboratory Control Systems supporting production of drug substances including biologically derived drug substances, sterile powders for injection, and solid oral dosage forms. This inspection was VAI and found acceptable. Additionally, a comprehensive surveillance and Pre-approval Inspection for **EP2006**, (**BLA 125553**) and Bexsero vaccine (BLA 125546) was conducted on 09/08-09/16/2014 and covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems for Profiles CBI, CSS, CTX, SPW, SVS, and VBP. This inspection was VAI and the facility was found to be compliant with CGMPs. .

Based on the compliance history of the firm, the current CGMP status, and the fact that Sandoz GmbH has been licensed to manufacture **EP2006 DS** (BLA 125553), and other biological products using similar manufacturing processes, it is recommended that the pre-license inspection of the Sandoz GmbH DS manufacturing facility in Kundl, Austria (FEI 3002806523) be waived for BLA 761045/0 (action date 06/26/2016).

Summary

BLA STN 761045/0 proposes manufacture of EP2006 (b) (4) at Sandoz GmbH, Kundl, Austria (FEI 3002806523), the pegylation of EP2006 (b) (4) (b) (4) DS at Lek Pharmaceuticals d.d., Mengeš, Slovenia (FEI 3002807470), and LA-EP2006 DP at (b) (4). This waiver recommendation is in regard to EP2006 (b) (4) manufacture at Sandoz GmbH.

Facility and Process Information



Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

The firm is registered as a human and veterinary drugs, and medical device manufacturer. Sandoz GmbH Kundl, Austria (Module 3) is currently licensed for manufacture EP2006 drug substance under BLA STN 125553/0. The last surveillance inspection on March 2016 covered 36 products and included a PLI to support the approval of BLA STN 761042/0 for Brelsina. The inspection prior to the most recent was conducted by ORA (PR/SEA-DO and PRL W) and CDER (BMAB/OC and DTP/OBP) from 9/8/2014 to 9/16/2014 covering the manufacture of EP2006 drug substance (and associated testing operations) under FDA application BLA STN 125553/0.

2. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

Previous inspections have encompassed profile classes BTP, CBI, CFS, CRU, CSN, CSS, CHG, CTL, CTX, POW, SPW, SVS, TCM, TTR and VBP, and in all cases have resulted in an acceptable NAI or VAI status.

- 3.



As noted in the response to Question 1, Sandoz GmbH Kundl, Austria (Module 3) is currently approved for manufacture of EP2006 drug substance under BLA STN 125553.

4. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The proposed manufacturing scheme for EP2006  is identical to the currently approved manufacturing process for EP2006 drug substance under BLA STN 125553.

Signed:

Michael R. Shanks, OPF/DIABRI Reviewer _____ DATE _____

Patrick Lynch, Ph.D., OBP/DBRRII Reviewer _____ DATE _____

Bo Chi, Ph.D., DMA/MABIV Reviewer _____ DATE _____

Christopher Downey, Ph.D., OBP/DBRRII ATL _____ DATE _____

Patricia Hughes, Ph.D., DMA/MABIV Branch Chief _____ DATE _____

Zhihao (Peter) Qiu, Ph.D., OPF/DIABRI, Branch Chief _____ DATE _____

David Frucht, MD, DBRR II/OPB, Director _____ DATE _____



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 05/19/2016
To: Administrative File, STN 761045
From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for **LA-EP2006**
US License: **2003**
Applicant: Sandoz, Inc.
Mfg Facility: Drug Substance:
Sandoz GmbH, Biochemiestrasse 10, Kundl, Austria FEI 3002806523
Lek Pharmaceuticals d.d., Kolodvorska 27, Mengeš, Slovenia FEI 3002807470
Drug Product:

[Redacted] (b) (4)

Product:
Dosage: Injectable sterile, clear and colorless solution for subcutaneous administration. Single use pre-filled syringe containing 6 mg/0.6 mL (10 mg/mL).
Indication: Therapeutic to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia..
Due Date: 06/26/2016

RECOMMENDATION: This application is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of LA-EP2006 Drug Substance and Drug Product at the Sandoz GmbH, Lek Pharmaceuticals d.d., and [Redacted] (b) (4). The starting material for the production is [Redacted] (b) (4).

The PAI at Sandoz GmbH for this application was waived. The drug substance process consisting of pegylation [Redacted] (b) (4) LA-EP2006 DS is manufactured at Lek Pharmaceuticals d.d. (Mengeš, Slovenia), a subsidiary of Sandoz. LA-EP2006 Drug Product is manufactured at the final fill finish site [Redacted] (b) (4) in the final

primary packaging (syringes). Sandoz GmbH releases the LA-EP2006 6 mg/0.6 mL solution for injection. In addition to the sites mentioned above in the manufacturer of LA-EP2006 6 mg/0.6 mL, Novartis Pharma AG, Lek Pharmaceuticals d.d. (b) (4) perform testing of the DS and DP. A Pre-license inspection was conducted on 03/08 – 14/2016 at Lek Pharmaceutical d.d. No FDA Form 483 was issued, and a final recommendation of acceptable (NAI) has been made. A For Cause and Pre-license inspection was conducted on (b) (4) at (b) (4). A six-item FDA Form 483 was issued, and a final recommendation of acceptable (VAI) has been made. All other related DS and DP facilities have an acceptable compliance status.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The site proposed for LA-EP2006 Drug Substance manufacture, cell banking operations, and testing is presented below in Table 1.

Table 1. Proposed Sites for LA-EP2006 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Sandoz GmbH	Biochemiestrasse 10 AT-6250 Kundl, Austria	3002806523	The EP2006 (b) (4) is manufactured and tested (according to current Good Manufacturing Practices - cGMP). Preparation of the WCB, and storage of the MCB and WCB.
Lek Pharmaceuticals d.d. (a Sandoz company)	Kolodvorska 27 SI-1234 Mengeš, Slovenia	3002807470	The LA-EP2006 drug substance (pegylated EP-2006) is manufactured by pegylation of the EP2006 (b) (4) tested and released (according to current Good Manufacturing Practices - cGMP). (b) (4) DS testing.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DS testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DS testing.

Reviewer Comment 1: *The facilities for manufacture of LA-EP2006 DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

Sandoz GmbH (FEI 3002806523), EP2006 (b) (4) (unpegylated) manufacture, IPC and release testing. A comprehensive surveillance inspection conducted on 04/30/2015 for profiles BTP, CHG, CSN, CSS, CTX, POW, SPW, SVS, TCM, TTR, and CBI included evaluation of the Quality Systems, Facilities and Equipment, Production, and Laboratory Control Systems supporting production of drug substances including biologically derived drug substances, sterile powders for injection, and solid oral dosage forms. This inspection was VAI and found acceptable. Additionally, a comprehensive surveillance and Pre-approval Inspection for EP2006, BLA 125553, and BLA 125546 (Bexsero vaccine) was conducted on 09/16/2014 that covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Systems for Profiles CBI, CSS, CTX, SPW, SVS, and VBP. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470), LA-EP2006 drug substance manufacture by pegylation of the EP2006 (b) (4) IPC and release testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772), Drug Substance release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products: (b) (4) Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Substance release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

This inspection was VAI and found acceptable.

- **Current Prior Approval Inspection Decisions**

BLA 761045/0. LA-EP2006 DS and DP Manufacture

Sandoz GmbH (FEI 3010479596). DIA, DMA, and OBP waived a PLI for this facility because a PLI for EP2006 was conducted on 09/16/2014, and this justification was documented in the waiver memo . A District file review was requested and the site was found acceptable based on file review.

Lek Pharmaceuticals d.d. (a Sandoz company), Mengeš, Slovenia, (FEI 3002807470). DIA, DMA, and OBP conducted a joint PLI for LA-EP2006 drug substance at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

(b) (4)

Novartis Pharma AG (FEI 3002807772) was approved based on the facility CTL profile.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

Reviewer Comment 2: A recommendation regarding the compliance status for the DS production and testing facilities associated with the manufacture of LA-EP2006 is acceptable.

3.2.S.2.2 Overview of LA-EP2006 DS Manufacturing Operations Conducted at Sandoz GmbH and Lek Pharmaceuticals d.d.

(b) (4)

3.2.A. Appendices

3.2.A.1 Facilities and Equipment [Manufacturer – substance – Dosage Form – Product]

3.2.A.1 Sandoz GmbH Facility

➤ **2.1.1-2 Sandoz Manufacturing Facility**

(b) (4)



DRUG PRODUCT FACILITIES

3.2.P Drug Product [Substance – Manufacturer]

3.2.P.2. Manufacture

3.2.P.2.1 DP Manufacturers.

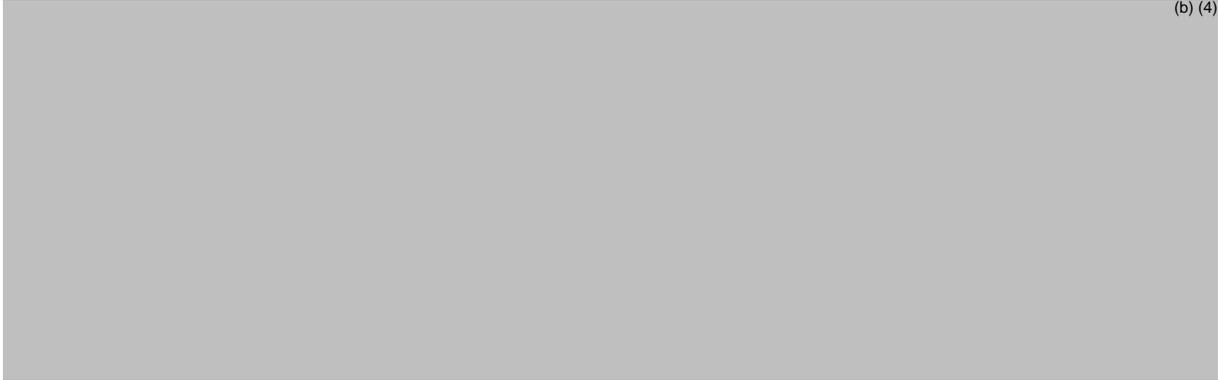
The site proposed for LA-EP2006 Drug Product manufacture, cell banking operations, and testing is presented below in Table 12.

TABLE 12. Proposed Sites for LA-EP2006 DP Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
			(b) (4) LA-EP2006 6 mg/0.6 mL DP solution for injection is manufactured, tested, and packaged.
Novartis Pharma AG	Lichtstrasse 35 4056 Basel Switzerland	3002807772	DP Bioactivity testing.
Sandoz GmbH	Biochemiestraße 10 6336 Langkampfen Austria	3004828473	DP stability testing.
Lek Pharmaceuticals d.d.	Kolodvorska Cesta 27 Mengeš, 1234 Slovenia	3002807470	DP testing.
Lek Pharmaceuticals d.d.	Verovskova 57 SI-1526 Ljubljana Slovenia	3002807460	DP testing.

Reviewer Comment 23: The facilities for manufacture of LA-EP2006 DP are adequately described.

- **Prior Inspection History for DS Manufacturing and Testing Sites**



Novartis Pharma AG (FEI 3002807772), Drug Product release and stability testing. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval of BLA125553/000 EP2006 conducted on 01/14/2015 covered both Quality and Laboratory Systems. This inspection was NAI and found acceptable. A surveillance and pre-approval inspection of the bio analytics lab focusing on bioassays performed in support of the preapproval products:  (b) (4)  Cosentyx, BLA 125504, was conducted on 12/05/2013 covering the Quality and the Laboratory Systems. This inspection was NAI and found acceptable.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing. A comprehensive surveillance inspection conducted on 03/18/2014 for profiles CRU, CXA, and SVS included evaluation of the Quality, Production, Laboratory Control, Materials and Facility and Equipment Systems. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance Inspection was conducted on 03/16/2012 that covered the Quality, Production, Facilities & Equipment, and Laboratory Control Systems for Profiles SVS, CXA, CBI, CSN and TAM. This inspection was VAI and found as acceptable.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470), Drug Product release and stability testing. A comprehensive surveillance inspection conducted on 09/18/2015 for profile CFN covered the Quality System, Facilities and Equipment System, Production System, and Laboratory Control System. This inspection was NAI and found acceptable. Additionally, a comprehensive surveillance inspection conducted on 10/19/2012 for profiles CSN and CFN and covered the Quality System, Materials System, Facilities and Equipment System, Production System and Laboratory Control System. This inspection was NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460), Drug Product release and stability testing. An abbreviated surveillance and follow-up coverage inspection on 06/30/2015 covered the Quality and Production Systems. Additionally, there have been two Field Alert Reports (FARs) submitted involving environmental monitoring excursions and a media fill failure. Both investigations were reviewed during this inspection and appeared adequate. This inspection was VAI and found acceptable.  (b) (4)



 This inspection was VAI and found acceptable.

• **Current Prior Approval Inspection Decisions**

(b) (4)

Novartis Pharma AG (FEI 3002807772) was approved based on the facility profile and Laboratory Control Systems coverage.

Sandoz GmbH (FEI 3004828473), Drug Product stability testing was approved based on the facility profile and Laboratory Control Systems coverage.

Lek Pharmaceuticals d.d., Mengeš (FEI 3002807470). DAI, DMA, and OBP conducted a joint pre-approval inspection for LA-EP2006 drug substance (pegylated EP2006) that included Laboratory Control Systems at this facility on 03/14/2016. The inspection was classified NAI and found acceptable.

Lek Pharmaceuticals d.d, Ljubljana, Slovenia (FEI 3002807460) was approved based on the facility CTL profile.

Reviewer Comment 24: *the compliance statuses for the DP production and testing facilities associated with the manufacture of LA-EP2006 are acceptable.*

(b) (4)

CONCLUSION

Adequate descriptions were provided for the Sandoz GmbH (FEI 3002806523) and Lek Pharmaceuticals d.d. (FEI 3002807470) LA-EP2006 Drug Substance facilities, and the (b) (4) LA-EP2006 Drug Product facility proposed for DS and DP manufacture. The proposed DS and DP manufacturing and testing sites are recommended for approval from a facilities assessment standpoint.

Michael R. Shanks -S
Digitally signed by Michael R. Shanks -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200140831
7, cn=Michael R. Shanks -S
Date: 2016.05.20 14:20:09 -04'00'

Michael Shanks
Biologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S
Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Zhihao Qiu -S,
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Date: 2016.05.20 14:31:45 -04'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: May 18, 2016

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): Ziextenzo (pegfilgrastim)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761045

Applicant: Sandoz Inc.

1 INTRODUCTION

On August 27, 2015, Sandoz Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761045 for Ziextenzo (pegfilgrastim) injection under Section 351(k) of the Public Health Service Act. With this application Sandoz Inc. seeks approval for Ziextenzo (pegfilgrastim) injection as a biosimilar product to approved BLA 125031 for Neulasta (pegfilgrastim). The Applicant seeks approval for the same indication for which the referenced product Neulasta (pegfilgrastim) is approved: to decrease the incidence of infection as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

On November 4, 2015, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Ziextenzo (pegfilgrastim) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for Ziextenzo (pegfilgrastim) injection.

2 CONCLUSIONS

Due to outstanding deficiencies, DHP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

NATHAN P CAULK
05/18/2016

BARBARA A FULLER
05/18/2016

LASHAWN M GRIFFITHS
05/19/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 28, 2016

TO: Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: Inspection of [REDACTED] (b) (4)
[REDACTED] (LA-EP2006
[pegfilgrastim], a biosimilar to Neulasta®), sponsored
by Sandoz Inc.

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of pharmacodynamic (PD) portions of the following clinical study conducted by [REDACTED] (b) (4)
[REDACTED]

Based upon the results of the inspection, we recommend that ANC and CD34+ PD data from study LA-EP06-101 be accepted for further Agency review.

Study Number: LA-EP06-101 ([REDACTED] (b) (4) report N-A-OTH-11-028)
Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US- registered) after single dose subcutaneous application in healthy subjects"

Study Dates: June 24, 2010 through December 28, 2010

Inspection of pharmacodynamic data from this study was conducted by OSIS/DGDBE Pharmacologist Kara A. Scheibner at [REDACTED] (b) (4)

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with [REDACTED] (b) (4) management and staff. Following inspection of the study, Form FDA-483 was not issued.

Note that separate review memos covering inspections at other sites are finalized in DARRTS.

Conclusion: Based on review of the establishment inspection report, we recommend that ANC and CD34+ data from study LA-EP06-101 be accepted for further agency review.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Final

[REDACTED] (b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Scheibner

OTS/OSI/DNDBE/Bonapace/Dasgupta

Draft: KAS 04/26/16

Edits: MFS 04/26/2016; JC 4/27/2016

OSI File#: [REDACTED] (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/[REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

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/s/

KARA A SCHEIBNER
04/29/2016

SEONGEUN CHO
04/29/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 28, 2016

TO: Ann Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: Inspection of [REDACTED] (b) (4)
[REDACTED] covering BLA 761045 (LA-EP2006
[pegfilgrastim], a biosimilar to Neulasta®), sponsored
by Sandoz Inc.

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of **Pharmacokinetic (PK) portions** of the following clinical studies conducted by [REDACTED] (b) (4)

Based upon the results of the inspection, we recommend that **PK data** from studies LA-EP06-101 and LA-EP06-302 be accepted for further review. However, we could not exclude the possibility of interferences from hemolytic and/or lipemic matrix on the ability to accurately quantitate pegfilgrastim concentrations. The OCP reviewer should consider potential impacts of hemolysis and lipemia on accurate measurement of pegfilgrastim.

Study Number: LA-EP06-101 [REDACTED] (b) (4) report N-A-OTH-11-028)

Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US- registered) after single dose subcutaneous application in healthy subjects"

Study Dates: June 24, 2010 through December 28, 2010

Study Number: LA-EP06-302 ((b) (4) report N-A-OTH-12-027)

Study Title: "Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta®"

Study Dates: March 5, 2012 through December 4, 2013

Inspection of the pharmacokinetic data from these studies was conducted by OSIS/DGDBE Pharmacologist Kara A. Scheibner at

(b) (4)

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with (b) (4) management and staff.

Following the inspection, Form FDA-483 was issued (Included in Firm's response; **Attachment 1**). Additional minor observations were discussed throughout the inspection, and at the inspection close-out meeting. We received a written response to the FDA-483 observations from (b) (4) on February 4, 2016 (**Attachment 1**). The FDA-483 observations, (b) (4) and our evaluation of the observations and responses follow.

(b) (4)

(b) (4)

Conclusion: Based on the observations above, and (b) (4) response, this reviewer recommends that **Pharmacokinetic data** from studies LA-EP06-101 ((b) (4) report N-A-OTH-11-028) and LA-EP06-302 ((b) (4) report N-A-OTH-12-027) be accepted for further agency review. However, based on available data, a lack of

matrix interference on the analysis of pegfilgrastim could not be assured. This reviewer recommends that the OCP reviewer consider the potential impact of hemolytic and lipemic matrix interference on the ability to accurately quantitate pegfilgrastim concentration.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Final

[Redacted] (b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Scheibner

OTS/OSI/DNDBE/Bonapace/Dasgupta

Draft: KAS 03/01/16

Edits: MFS 03/01/2016; JC 4/27/2016

OSI: File#: BE7016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ [Redacted] (b) (4)

FACTS: [Redacted] (b) (4)

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/s/

KARA A SCHEIBNER
04/29/2016

SEONGEUN CHO
04/29/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 26, 2016

TO: Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

and

Hasan A. Irier, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: Inspection of [REDACTED] (b) (4) covering
BLA 761045 (LA-EP2006 [pegfilgrastim], a Biosimilar to
Neulasta®), sponsored by Sandoz Inc.

Summary:

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of anti-drug antibody (ADA) and neutralizing antibody (NAb) portions of the following clinical studies conducted by [REDACTED] (b) (4)

Based upon the results of the inspection, we recommend that results from ADA screening and confirmatory assay be accepted,

but recommend reanalysis of results using a less stringent cut point (99 %). In addition, we recommend that titer data be carefully considered, because of the firm's current practices of repeat analysis and data reporting during the titer assays.

Study Number: LA-EP06-101
Study Title: "Pharmacokinetic and pharmacodynamic comparison of LA-EP2006 with the reference product Neulasta® (EU- and US- registered) after single dose subcutaneous application in healthy subjects"
Study Dates: ADA analysis: 12/1/10 through 2/22/11; NAb analysis: 2/21/11 through 2/25/11

Study Number: LA-EP06-301
Study Title: "A randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating efficacy and safety of LA-EP2006 and Neulasta® (EU-licensed) in breast cancer patients treated with myelosuppressive chemotherapy"
Study Dates: ADA analysis: 8/26/13 through 5/14/14; NAb analysis: 3/26/15 through 4/2/15

Study Number: LA-EP06-302
Study Title: "Pivotal study in breast cancer patients investigating efficacy and safety of LA-EP2006 and Neulasta®"
Study Dates: ADA analysis: 12/18/13 through 2/10/14; NAb analysis: 2/20/15 through 4/23/15

Inspection of the immunogenicity data from these studies was conducted by OSIS/DGDBE Pharmacologists Kara A. Scheibner and Hasan A. Irier at (b) (4) from

(b) (4)

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with (b) (4) management and staff.

Following inspection of the studies, Form FDA-483 was issued (**Attachment 1**). Additional minor observations were discussed throughout the inspection and at the inspection close-out meeting. We received a written response to the FDA-483 observations from (b) (4) on February 11, 2016 (**Attachment 2**). The Form FDA-483 observations, (b) (4) response, and our evaluation of the observations and responses follow.

Please note that this review is for observations related **specifically to BLA 761045**. Some of the observations (e.g., 1a, 1b, 1c) included in the Form FDA-483 applied to studies in BLA 761042, which were reviewed in a separate memo that was finalized on 02/08/2016 under BLA 761042.

OBSERVATIONS

(b) (4)

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(b) (4)

Conclusion: Based on the observations above, and (b) (4) response, we recommend the following:

1. We recommend accepting ADA data from screening and confirmatory assays in studies LA-EP06-301 and LA-EP06-302 for further agency review. However, given that the confirmatory cut points used for LA-EP2006, EP2006, and PEG were at 99.9%, we recommend the data be reassessed using a 99% confidence level. This reanalysis may result in additional confirmed positive samples, and thus, the impact on overall study outcome should be assessed.
2. We recommend that the results of ADA titer analysis from studies LA-EP06-301 and LA-EP06-302 be scrutinized carefully by the Review Division. Due to the concerns described above on repeat analysis and data reporting, we cannot ensure that the final reported results accurately represent ADA levels present in study samples.
3. Please note that due to time constraints, the inspection did not cover a thorough review of validation and study data for NAb analysis.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Hasan A. Irier, Ph.D.
DGDBE, OSIS

Final

(b) (4)

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

OTS/OSIS/DGDBE/Cho/Skelly/Choi/Scheibner

OTS/OSI/DNDBE/Bonapace/Dasgupta

Draft: KAS 04/26/16

Edits: MFS 4/26/2016; JC 4/28/2016

OSI: File#: (b) (4)

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/ (b) (4)

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CLINICAL INSPECTION SUMMARY ADDENDUM

Date	April 21, 2016
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief
To	Patricia Dinndorf M.D., Clinical Reviewer Albert Deisseroth, M.D., Ph.D., M.S., Clinical Team Leader Rachel McMullen, M.P.H., M.H.A., Regulatory Project Manager
BLA	761045
Applicant	U.S. Biopharmaceuticals Sandoz, Inc., a Novartis Company
Drug	Pegfilgrastim (LA-EP2006), (biosimilar product to approved Neulasta®)
NME	Yes (Priority Application)
Therapeutic Classification	Biosimilar-351k application
Proposed Indication	Febrile neutropenia
Consultation Request Date	November 12, 2015
Summary Goal Date	May 1, 2016
Action Goal Date	June 26, 2016
PDUFA Date	June 26, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For BLA 761045, four clinical sites (Drs. Mehta, Motan, Nagarkar, and Ratnavelu) were selected for audit and inspection. The contract research organization (CRO) (b) (4) was also inspected.

The preliminary classification for the inspections of Drs. Nagarkar and Ratnavelu, and the CRO, (b) (4) is No Action Indicated (NAI) based on communications with the field investigator. The final classification for the inspection of Dr. Mehta is Voluntary Action Indicated (VAI). The study data derived from these clinical sites and CRO are considered reliable in support of the requested indication.

The preliminary classification of the inspection of Dr. Motan's site is Official Action Indicated (OAI). The findings at Dr. Motan's site regarding predated ECGs and some medical visit records is unlikely to have a significant impact on evaluation of the primary efficacy endpoint or safety assessment, since there is no evidence that patients appeared to have been harmed. However, final regulatory classification of inspection findings is pending review of the inspection report and evidence collected by OSI.

Based on results of the clinical investigators and the contract research organization (CRO) (b) (4) inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the indication.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. BACKGROUND

Both filgrastim and pegfilgrastim are granulocyte colony stimulating factors (G-CSFs) that act on hematopoietic cells by binding to specific cell surface receptors. Post-binding, these G-CSFs stimulate proliferation, differentiation, and end cell functional activation. Pegfilgrastim is marketed in the US and European Union (EU) by Amgen Inc. (Neulasta®), and is indicated to reduce the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes).

Two clinical trials (LA-EP06-301 and LA-EP06-302) were submitted in support of the applicant's BLA. Four foreign clinical sites were selected for audit, since domestic data were insufficient. These sites were selected based upon geographic location (countries outside the U.S. with potentially different standards of care) and enrollment numbers.

Study LA-EP06-301

Study 301 was a randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating efficacy and safety of LA-EP2006 (pegfilgrastim) and EU-authorized Neulasta. Patients with histologically proven breast cancer, who had an indication for neoadjuvant or adjuvant treatment with docetaxel, doxorubicin, and cyclophosphamide ["TAC"] chemotherapy were included in the study. The primary efficacy endpoint of this study was the mean duration of severe neutropenia (DSN) during Cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an absolute neutrophil count less than $0.5 \times 10^9/L$.

This study was conducted from June 28, 2012 (first patient, first visit) through February 11, 2014 (6-month safety follow-up, last patient last visit). The study was conducted in six countries: Russia, Ukraine, Romania, India, Brazil, and Mexico. Three hundred seventy three (373) patients were screened and 316 were randomized.

Based on the sponsor's analysis, LA-EP2006 was demonstrated to be equivalent and non-inferior to Neulasta in terms of DSN. The mean DSN in Cycle 1 was 0.75 days in patients treated with LA-EP2006 and 0.83 days in patients treated with Neulasta. DSN ranged from 0 to 3 days (LA-EP2006) and from 0 to 4 days (Neulasta), respectively (Full Analysis Set (FAS set)).

Study LA-EP06-302

Study 302 was also a randomized, double-blind, parallel-group, multi-center Phase 3 comparative study investigating the efficacy and safety of LA-EP2006 (pegfilgrastim) and EU-authorized Neulasta. Patients with histologically proven breast cancer, who had an indication for neoadjuvant

or adjuvant treatment with docetaxel, doxorubicin, cyclophosphamide (TAC) chemotherapy were included in the study. The primary efficacy endpoint of this study was the mean duration of severe neutropenia (DSN) during Cycle 1 of chemotherapy, defined as the number of consecutive days in which a patient had an absolute neutrophil count less than $0.5 \times 10^9/L$.

This study was conducted from March 5, 2012 (first patient, first visit) through December 4, 2013 (last patient, last visit). The study was conducted in eight countries: Argentina, Chile, India, Malaysia, Puerto Rico, Russia, Spain, and the US. Three hundred fifty two (352) patients were screened and 308 were randomized.

Based on the sponsor's analysis, LA-EP2006 was demonstrated to be equivalent and non-inferior to Neulasta in terms of DSN. Overall, the mean DSN was slightly longer in patients allocated to LA-EP2006 (FAS, 1.36 ± 1.133 days) than in patients allocated to Neulasta (FAS, 1.19 ± 0.984 days). Maximum DSN was also higher in patients allocated to LA-EP2006 (FAS, 6.0 days) than in patients allocated to Neulasta (FAS, 4.0 days).

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Ajay Mehta, M.D. Central India Cancer Research Institute, 11 Shankar Nagar, West High Court Road, Nagpur 440010, Maharashtra, India	Site #901 Protocol LA-EP2006-301 Subjects (See below) 15 Screened 14 Enrolled	February 22-26, 2016	Pending: Preliminary VAI
Doina Elena Ganea Motan, M.D., Ph.D. Spitalul Judetean de Urgenta "Sf. Ioan Cel Nou" Bdul. Nr. 21 Suceava, Jud. Suceava, 720237, Romania	Site #404 Protocol LA-EP2006-301 Subjects (See below) 14 Screened 10 Enrolled	February 22-25, 2016	Pending: Preliminary OAI
Rajnish Nagarkar, M.D. Curie Manavata Cancer Centre Nashik Maharashtra, 422004 India	Site #905 Protocol LA-EP2006-302 Subjects (See below) 7 Screened 6 Enrolled	March 14 - 18, 2016	Pending: Preliminary NAI
Kananathan Ratnavelu, M.D. NCI Hospital, 71800 Nilai, Negeri Sembilan Darul Khusus Malaysia	Site #404 Protocol LA-EP2006-302 Subjects (See below) 11 Screened 8 Enrolled	February 29 - March 4, 2016	Pending: Preliminary NAI

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
(b) (4)	CRO for: Protocol LA-EP2006-301 Subjects =316 Protocol LA-EP2006-302 Subjects =308	February 29 - March 3, 2016	Pending: Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. Dr. Ajay Mehta, M.D./Study Protocol LA-EP2006- 301/Site #901

Maharashtra, India

The inspection was conducted from February 22 to 26, 2016. A total of 15 subjects were screened and 14 enrolled. Twelve patients completed the study; two study subjects died, thus, these were early terminations from the study. An audit of 14 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the conclusion of the inspection.

Specifically, five subjects (one episode each in Cycle #5 for Subjects 9, 11, 13, and 14, and two episodes in Cycles #5 and #6 for Subject 15) received recombinant human G-CSF products (commercial product/incorrect study drug) that were not allowed during the course of the study according to section 6.6.7 of the protocol.

Reviewer comments:

These findings were not considered critical, and were previously reported to the BLA. Further, Dr. Mehta explained in his response that the study drug product intended for administration had undergone a temperature excursion outside the allotted threshold and commercial product was administered to a limited number of subjects in later cycles.

Dr. Mehta's response to the List of Inspectional Observations on March 11, 2016 was considered adequate.

Notwithstanding the above isolated regulatory deficiency, data submitted by this clinical site appear acceptable in support of this specific indication.

2. Doina Elena Ganea Motan, M.D., Ph.D./ Study Protocol LA-EP2006- 301/Site #901
Suceava, Romania

The inspection was conducted from February 22 to 25, 2016. A total of 14 subjects were screened and 11 enrolled. Ten patients completed the study; one study subject withdrew consent after enrollment. An audit of 11 enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. There were protocol deficiencies related to ECGs. The protocol required that "the following test and/or data collection must be performed on Day 21 (\pm 3days) of Cycle 6," but this was not done for all subjects.

A Form FDA 483 (Inspectional Observations) was issued at the conclusion of the inspection and observations have been discussed with DHP.

Specifically, nine of 24 ECGs at the site were noted to have the headers containing date and time removed and hand written dates added. For four of the subjects' ECGs (Subjects (b) (6)) records in the site's cardiology department indicated that the ECGs had been performed on different dates (end of study) than the handwritten date (end of treatment) present on the ECG tracing indicated.

Reviewer comments:

During the inspection, the ORA investigator confirmed that these four subjects had ECGs performed at the institution's Department of Cardiology on the end of study visit day. Dr. Motan's response indicates that these ECGs had been predated by site staff who did not understand good clinical practice documentation practices. Additionally, Dr. Motan indicated that medical records of six subjects (including four subjects who also had pre-dated ECGs) had similarly been predated. Site staff was retrained on proper documentation and GCP procedures and the records were corrected appropriately to indicate the date procedures had actually been performed. The clinical investigator indicated that the site had a poor understanding of appropriate GCP

documentation practices and had predated these subjects' source documents. The findings related to predated ECGs are unlikely to have a significant impact on evaluation of the primary efficacy endpoint. No cardiac adverse events were reported for subjects enrolled at this site.

OSI is reviewing the inspection report and evaluating evidence included with the report. The inspectional observations noted above are based on communication with the field investigator, preliminary review of the EIR and Form FDA 483, and the clinical investigator's written response to the 483. The date documentation violations reported at this site are unlikely to impact assessment of the primary efficacy endpoint, and based upon review of adverse events data reported for this site, also no impact on subject safety from a cardiac standpoint. A clinical inspection summary addendum will be generated if conclusions change significantly upon receipt of the Establishment Inspection Report (EIR).

3. Rajnish Nagarkar, M.D./ Study Protocol LA-EP2006- 302/Site #905
Maharashtra, India

The inspection was conducted from March 14 to 18, 2016. A total of seven subjects were screened and six enrolled. Six subjects completed the study. An audit of seven screened subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Kananathan Ratnavelu, M.D./ Study Protocol LA-EP2006- 302/Site #404
Malaysia

The inspection was conducted from February 29 to March 4, 2016. A total of 11 subjects were screened and 8 enrolled. Seven patients completed the study; one study subject withdrew from the study after enrollment. An audit of 8 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR-CRO

(b) (4)

The inspection was conducted from (b) (4). This CRO inspection was needed to ensure that there were no monitoring concerns for this biosimilar application. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors; review of controls and security of electronic systems; and data collection and handling procedures; adequacy of monitoring and corrective actions taken by the sponsor/monitor for the studies; clinical site study personnel training in GCP, and memorandum documents and reporting updates to clinical site investigators regarding serious unexpected adverse events.

In general, this site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued at the end of the CRO inspection. No monitoring problems were found during the CRO inspection. Data submitted by this CRO appear acceptable in support of the requested indication.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
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CC:

Central Doc. Rm.

Review Division /Division Director/Anne Farrell

Review Division /Medical Team Leader/Albert Deisseroth

Review Division/Medical Officer/Patricia Dinndorf

Review Division /Project Manager/Raquel McMullen

Review Division/MO/Anthony Orenca

OSI/Office Director/David Burrow (Acting)

OSI/DCCE/ Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson

OSI/DCCE/GCP Reviewer/Anthony Orenca

OSI/ GCP Program Analyst/Yolanda Patague

OSI/Database PM/Dana Walters

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/s/

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04/21/2016

JANICE K POHLMAN
04/21/2016

KASSA AYALEW
04/21/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic Device Branch (REGO)

Date: February 9, 2016

To: Patrick Lynch, CDER/OBP/DBRRII
Patrick.Lynch@fda.hhs.gov

Chris Downey, CDER/OBP/DBRRII
Christopher.Downey@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Rachel McMullen

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

Viky Verna -S

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Date: 2016.03.11 12:13:02 -0500

From: Crystal Lewis, REGO, DMQ, OC, CDRH

Applicant: Sandoz, Incorporated
100 College Road West
Princeton, NJ 08540
FEI#

Application # BLA761045

Consult # ICC#1500691

Product Name: LA-EP2006 (pegfilgrastim, proposed biosimilar to US-licensed Neulasta)

Pre-Approval Inspection: No

Documentation Review: Additional Information Required

Final Recommendation: **DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA761045.

PRODUCT DESCRIPTION

LA-EP2006 is indicated for use with patients who have been diagnosed with non-myeloid malignancies who are receiving myelosuppressive anti-cancer drugs. The drug's proposed

indication is to decrease the incidence of infection that is associated with febrile neutropenia. The LA-EP2006 drug product is marketed as a single use combination product that consists of a pre-filled syringe and a needle safety device.

REGULATORY HISTORY

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:



Responsibility – The firm is responsible for the final assembly and packaging for the final combination product.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection conducted on [redacted] (b) (4) The inspection covered drug GMP policies and was classified VAI.

Inspection Recommendation:

(1) An inspection is not required because:

- The firm has received a drug inspection which covered GMP requirements within the last two years. The inspection was acceptable therefore a preapproval inspection is not required.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

The firm’s documentation for Management Control was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm’s documentation for Design Control was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm’s documentation for Purchasing Controls was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm's documentation for CAPA was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING**Production and Process Controls**

The firm's documentation for Production and Process Controls were not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.70.

Production Flow

The firm's documentation for Production Flow was not found.

Acceptance Activities

The firm's documentation for Acceptance Activities was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.80(b),(c),(d).

Documentation Review Recommendation**Deficiencies to be conveyed to the applicant**

The following deficiencies have been identified while doing the documentation review of application LA-EP2006 (pegfilgrastim, proposed biosimilar to US-licensed Neulasta), BLA761045, in reference to applicable 21 CFR 820 regulations and (or) manufacturing of the finished combination product:

1. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.30, Design Controls. Specifically, your firm did not describe its design control system which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Your firm should also provide a copy or a summary of the plan used to design the combination product. Your firm should explain how it implemented the plan for the combination product project.
2. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.20, Management Controls. Specifically, the submission did not include information addressing which firm has ultimate responsibility for the overall combination product. The submission did not include a description of the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements). Please provide a description of your procedures for Management Controls.
3. The information provided by your firm has inadequately addressed the requirements of 21

CFR 820.50, purchasing controls. The submission did not specify the controls applicable to your firm's suppliers. This would include any contract design, service or contract manufacturers for the combination product under review. Please provide a description of your procedures for Management Controls. Please explain how your firm will ensure that changes made by contractors/suppliers will not affect the final combination product.

4. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.100, Corrective and Preventive Action (CAPA) System. Your firm did not provide any details or a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System. Please provide a description of your CAPA system and explain how it will ensure identification existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of nonconformance; and, verification or validation of the actions. Please explain how the CAPA system will communicate between facilities involved in the manufacturing of the combination product.

5. Please describe your procedures for receiving or incoming acceptance activities. The procedure(s) should include the extent the supplier has demonstrated a capability to provide products and services to meet your firm's specifications.

6. Please provide a summary of its procedures for final acceptance activities. These procedures should include specific release criteria such as sterilization and quarantine for finished combination products.

7. The information provided by your firm did not describe its production and process controls. Please provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product occurs, and how such conditions could affect the combination product.

8. The information provided did not describe the production flow for the combination product. Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

RECOMMENDATION

The approvability of application LA-EP2006 (pegfilgrastim, proposed biosimilar to US-licensed Neulasta) BLA761045 should be delayed for the following reasons:

- (1) Deficiencies were identified during the (1) documentation review. Additional information from the firm is needed to complete the documentation review.

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Lewis -S

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Crystal Lewis

Prepared: CLewis: 02/09/16
Reviewed: VVerna:2/16/16; 3/11/16

CTS No.: ICC150691
BLA761045

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

Firm to be inspected:

Firm Name

Address

FEI:

CDRH recommends the inspection under the applicable Medical Device Regulations of Firm Name, located in City, Country (FEI # 12345).

OPTIONS:

(1) A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

(2) A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the Combination product name (Application number).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

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REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Reviewer Name

Title,

Branch

Division

Office of Compliance, WO66 RM XXXX

Phone: 301-796-XXXX

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Branch Chief Name

Chief

Branch Name

Division

Office of Compliance, WO66 RM XXXX

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THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/s/

RACHEL S MCMULLEN

03/23/2016

CDRH signed off on this ICC review memo on 3/11/16 and the Division received this on 3/11/16 from Crystal Lewis (CDRH OC reviewer).