CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761080Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	June 28, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761080
Product Name and Strength:	Nivestym[*] ("Filgrastim Hospira")[**] Injection *Pre-filled syringes*: 300 mcg/0.5 mL, 480 mcg/0.8 mL *Vials*: 300 mcg/mL, 480 mcg/1.6 mL
Applicant/Sponsor Name:	Hospira
FDA Received Date:	June 26, 2018
OSE RCM #:	2017-1979-2
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised carton labeling for Nivestym (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[*] Nivestym has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proprietary name Nivestym will be conditionally accepted until such time that the application is approved.
[**] In this document, we refer to the proposed biosimilar product by the descriptor "Filgrastim Hospira", which was the name Hospira used to refer to this product during development. The proper name, filgrastim-aafi, is conditionally accepted until such time that the application is approved.
[a] Garrison N. Label and Labeling Review Memorandum for Nivestym (BLA 761080). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 21. RCM No.: 2017-1979-1.

2 CONCLUSION

The revised carton labeling for Nivestym is acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) 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/

NICOLE B GARRISON
06/28/2018

HINA S MEHTA
06/28/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	June 21, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761080
Product Name and Strength:	Nivestym[*] ("Filgrastim Hospira")[**] Injection *Pre-filled syringes*: 300 mcg/0.5 mL, 480 mcg/0.8 mL *Vials*: 300 mcg/mL, 480 mcg/1.6 mL
Applicant/Sponsor Name:	Single-Ingredient and Drug-device Combination Product
FDA Received Date:	June 13, 2018
OSE RCM #:	2017-1979-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Nivestym (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[*] Nivestym has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proprietary name Nivestym will be conditionally accepted until such time that the application is approved.
[**] In this document, we refer to the proposed biosimilar product by the descriptor "Filgrastim Hospira", which was the name Hospira used to refer to this product during development. The proper name, filgrastim-aafi, is conditionally accepted until such time that the application is approved.
[a] Garrison N. Label and Labeling Review for Nivestym (BLA 761080). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 06. RCM No.: 2017-1979.

2 CONCLUSION

The revised container labels for vials and prefilled syringes in addition to the prefilled syringe carton labeling for Nivestym are acceptable from a medication error perspective. However, the revised vial carton labeling requires additional revisions to minimize the risk of the dosing errors.

3 RECOMMENDATIONS FOR HOSPIRA

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

A. Vial carton labeling
    1. Add the statement, “Discard unused portion” following “Single-Dose Vial” to minimize risk of the entire contents of the vial being given as a single dose.

9 Page(s) 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/

NICOLE B GARRISON
06/21/2018

HINA S MEHTA
06/21/2018

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:	June 18, 2018
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)** Robert Nguyen, 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 (established name):	[PF-06881893] TRADENAME (filgrastim-aafi)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761080
Applicant:	Hospira, Inc.

[1] At the time of this review, the proposed proprietary name has not been determined, and the proposed proper name, filgrastim-aafi, has been conditionally accecpted until such time that the application is approved. In this document, we refer to Hospira, Inc.'s proposed product by the descriptor "PF-06881893", which was the name Hospira Inc. used to refer to this product during development.

1 INTRODUCTION

On September 21, 2017, Hospira, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761080 for PF-06881893, a proposed biosimilar to the Reference Product, NEUPOGEN (filgrastim) injection. On December 13, 2017 the Division of Medication Error Prvention and Analysis (DMEPA) found the proprietary name (b) (4) and the nonproprietary (proper) name filgrastim-aafi conditionally acceptable; however, the Applicant withdrew the proprosed proprietary name "(b) (4)." Therefore, the proprietary name is still under consideration at this time.

The proposed indications for PF-06881893 are as follows:

- Patients with Cancer Receiving Myelsosuppressive Chemotherapy: PF-06881893is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy: PF-06881893is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia.
- Patients with Cancer Undergoing Bone Marrow Transplantation: PF-06881893is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
- Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy: PF-06881893is indicated for the mobilization of autologous hematopoetic progenitor cells into the peripheral blood for collection by leukapheresis.
- Patients with Severe Chronic Neutropenia: PF-06881893is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

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 October 11, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for PF-06881893 .

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 PF-06881893 (filgrastim-aafi) injection PPI and IFU received on September 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on May 23, 2018.
- Draft PF-06881893 (filgrastim-aafi) injection PPI and IFU received on September 21, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on May 23, 2018.
- Draft PF-06881893 (filgrastim-aafi) injection Prescribing Information (PI) received on September 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on May 23, 2018.
- Draft PF-06881893 (filgrastim-aafi) injection Prescribing Information (PI) received on September 21, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on May 23, 2018.
- Approved NEUPOGEN (filgrastim) injection comparator labeling dated September 26, 2016.

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 PPI and IFU document using the Arial font, size 10.

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 is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI are 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.

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

/s/

SHARON R MILLS
06/18/2018

ROBERT L NGUYEN
06/18/2018

LASHAWN M GRIFFITHS
06/18/2018

USE-RELATED RISK ANALYSIS, 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 6, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761080
Product Name and Strength:	Nivestym[*] ("Filgrastim Hospira")[**] Injection *Pre-filled syringes*: 300 mcg/0.5 mL, 480 mcg/0.8 mL *Vials*: 300 mcg/mL, 480 mcg/1.6 mL
Product Type:	Single-Ingredient and Drug-device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira
FDA Received Date:	September 21, 2017 and December 18, 2017
OSE RCM #:	2017-1979
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD
Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
Associate Director (Acting):	Mishale Mistry, PharmD, MPH

[*] Nivestym has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proprietary name Nivestym will be conditionally accepted until such time that the application is approved.

[**] In this document, we refer to the proposed biosimilar product by the descriptor "Filgrastim Hospira", which was the name Hospira used to refer to this product during development. The proper name, filgrastim-aafi, is conditionally accepted until such time that the application is approved.

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the updated use-error risk analysis (UERA), proposed container labels, carton labeling, and Instructions For Use (IFU) submitted by Hospira for Nivestym ("Filgrastim Hospira") Injection (BLA 761080) for areas that could lead to medication errors. DHP requested this review to inform their evaluation of the 351(k) submission for Nivestym ("Filgrastim Hospira") submitted on September 21, 2017.

1.1 REGULATORY HISTORY

US-licensed Neupogen was approved in February 1991 for the treatment of patients with cancer receiving myelosuppressive chemotherapy, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients with cancer undergoing bone marrow transplantation, patients undergoing autologous peripheral blood progenitor cell collection and therapy, patients with severe chronic neutropenia, and patients acutely exposed to myelosuppressive doses of radiation.

On September 6, 2016, an email communication was sent to Hospira in response to their request to review their summative Human Factors (HF) study protocol[a]. The Agency advised Hospira to conduct a comprehensive use-related risk analysis of the proposed "Filgrastim Hospira" prefilled syringe (PFS) to determine the necessity of a HF validation study. If the Applicant determined that an HF validation study is not needed for their product, we requested submission of their use-related risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND. On September 22, 2016, Hospira submitted a HF study protocol and what the company refers to as, "Use-Error Risk Analysis (UERA)" to validate the safe and effective use of "Filgrastim Hospira" under IND 109991.

On November 23, 2016, we evaluated the UERA and proposed HF validation study protocol submitted by the Applicant[b]. Our review of the UERA for "Filgrastim Hospira" noted that only two critical tasks and potential failures differ in comparison to US- licensed Neupogen. Those tasks and failures include premature activation of the needle guard and needle stick injury post injection. However, our review of the UERA did not identify any new use-related risk for the proposed "Filgrastim Hospira" product when compared to US-licensed Neupogen. Thus, we did not believe a HF validation study was warranted and communicated this to the Applicant. However, if the Applicant determined to proceed with the HF validation study, we reviewed the HF protocol to ensure the intended user population can understand the preparation and administration of this product. The HF validation protocol appeared generally acceptable;

[a] Information Request/Advice letter from FDA on September 6, 2016.

[b] Garrison, N. Human Factors Protocol and Use-Related Risk Analysis Review for "Filgrastim Hospira" (IND 109991). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 23. 41 p. OSE RCM No.: 2016-2177.

however, we identified several areas of concern related to the methodology and IFU. We provided recommendations to the Applicant to make additional modifications to the protocol before commencing the study.

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 Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other -Use Error Risk Analysis	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

We evaluated the proposed container label, carton labeling, Prescribing Information (PI) and, Instructions for Use (IFU) for Nivestym ("Filgrastim Hospira") injection, BLA 761080. Nivestym has the same dosing, route of administration, strength, storage requirements, environments of use, and user population as US-licensed Neupogen (BLA 103353). The Applicant is pursing all indications of US-licensed Neupogen except for the treatment of Acute Radiation Syndrome (ARS)[c]. Nivestym is supplied as a single-dose prefilled syringe (PFS) with an UltraSafe™ passive needle guard and single-dose vials. US-licensed Neupogen is supplied as a single-dose PFS with a manual needle guard and single-dose vials.

The Applicant noted that based on the Agency's feedback, a HF validation study was not conducted, but our previous recommendations were incorporated in the proposed IFU[d]. The

[c] Neupogen's indication for increased survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) is protected by orphan drug exclusivity expiring on March 30, 2022. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.

[d] Garrison, N. Human Factors Protocol and Use-Related Risk Analysis Review for "Filgrastim Hospira" (IND 109991). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 23. 41 p. OSE RCM No.: 2016-2177.

Applicant submitted the final UERA report as a part of BLA submission. The Applicant also submitted a comparison of the user tasks between Nivestym and US-licensed Neupogen. We evaluated the final UERA and user task comparison submitted by the Applicant on September 21, 2017 (see Appendix F). In the final UERA and user tasks comparison, the Applicant provided a description of essential and critical tasks required for safe and effective use of the proposed product. These tasks align to US-licensed Neupogen; with the exception that users are not required to activate the needle guard manually. The Nivestym PFS has a passive needle guard and does not require manual activation. The PFS for US-licensed Neupogen has a needle guard that requires manual activation. The Applicant indicated that this modification should reduce the occurrence of needle-stick injury. Additionally, the proposed Nivestym PFS has a (b) (4) spring mechanism that interferes with the visibility of the graduation markings on the syringe barrel at 0.1 mL and 0.2 mL. The Applicant evaluated these differences in table 1-1 within the submission titled "Critical and Essential Tasks and User Task Comparison between Neupogen and Filgrastim PFS" and determined that they should not introduce any new or unique related risks compared to US-licensed Neupogen. We reviewed these differences and concluded that they were acceptable in our previous review [e] .

3.1 PHYSICAL COMPARISON OF THE PFS COMPONENTS

We evaluated the physical comparison of the PFS components between the proposed product and reference product US-licensed Neupogen. We note the proposed Nivestym PFS plunger has a larger thumb button when compared to US-licensed Neupogen PFS. The safety device of the Nivestym PFS has a (b) (4) spring mechanism that helps trigger and activate the safety device. The spring mechanism interferes with the visibility of the graduation markings on the syringe barrel at 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of less than 0.3 mL (180 mcg) for direct administration to patients. Based on this limitation, the IFU and PI instruct users that direct administration to patients requiring less than 0.3 mL (180 mcg) is not recommended with the proposed PFS due to the potential for dosing errors. The Applicant is proposing two vial presentations that can be used in patients who require doses less than 0.3 mL (180 mcg).

Additionally, the proposed Nivestym PFS does not have a latex rubber containing needle cap, has a different color plunger rod (b) (4), and different color needle guard (b) (4) when compared to US-licensed Neupogen PFS. The Applicant evaluated these differences in table 3.2.R.6.1-1 within the submission titled "Comparison of Neupogen and PF-06881893 PFS Components" and determined that they should not introduce unique use errors

[e] Garrison, N. Human Factors Protocol and Use-Related Risk Analysis Review for "Filgrastim Hospira" (IND 109991). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 23. 41 p. OSE RCM No.: 2016-2177.

based on the UERA and user task comparison. We evaluated the submitted information and agree with the Applicant's assessment.

3.2 LABELS AND LABELING

DMEPA performed a risk assessment of the labels, labeling, prescribing information, and IFU to identify deficiencies that may lead to medication errors and determined that the proposed prescribing information is appropriate from a medication error standpoint. We note that the proposed PI and patient package insert contain language consistent with US-licensed Neupogen.

The proposed container labels and carton labeling can be improved to increase readability and prominence of the strength presentation, expiration date, barcode, dosage form, storage and usual dosage statement.

4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed PI, IFU, container labels and carton labeling identified several areas that can be improved to increase the readability and prominence of important information.

Additionally, we identified other aspects of the IFU that should be revised to add important information regarding the administration of "Filgrastim Hospira" to harmonize the "Filgrastim Hospira" IFU with the US-licensed Neupogen IFU where appropriate, to mitigate the risk of medication errors.

We provide recommendations for the Division in section 4.1 and for the Applicant in section 4.2 to be implemented prior to approval of BLA 761080.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Instructions for Use for the prefilled syringe
    1. About the Nivestym Prefilled Syringe
        a. Figure A
            i. Label the "conical base of the plunger stopper" as this term is used in partial dosing section of the IFU.
    2. What You Need For Your Injection
        a. Include an image of and list adhesive bandage because users are instructed in Step 16 that they may cover the injection site with a small adhesive bandage, if needed.
    3. Preparing the Nivestym Prefilled Syringe
        a. In Step 2 the fourth bullet, revise the statement as follows: "Do not leave the prefilled syringe in direct sunlight."
        b. Include instructions and a corresponding image(s) instructing users to check for air bubbles as a separate step after Step 9.

c. In Step 10, delete statement, [redacted] Replace with, "See Figure H, example for a dose of 0.3 mL."

d. In Figure H [redacted]

B. Prescribing Information

1. Highlights of Prescribing Information

a. Dosage and Administration

i. In the sixth bullet, revise the statement from [redacted]" to "Direct administration of less than 0.3 mL (180 mcg) using Nivestym prefilled syringe is not recommended due to potential for dosing errors."

4.2 RECOMMENDATIONS FOR HOSPIRA

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

A. All Container Labels and Carton Labeling

1. For injectable products ensure that the strength, is the primary and prominent expression on the Principal display panel (PDP). Revise the strength presentation '[redacted]' to appear as '300 mcg/mL' in accordance with USP General Chapter <7>.
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:
   DDMMMYYYY (e.g., 31JAN2013)
   MMMYYYY (e.g., JAN2013)
   YYYY-MMM-DD (e.g., 2013-JAN-31)
   YYYY-MM-DD (e.g., 2013-01-31)

B. Vial Label

1. Clarify if the numbers [redacted] are internal product codes. We recommend removing and/or relocating this number to mitigate the potential for confusion due its proximity to the lot number and expiration date.

C. Prefilled Syringe Container Label

1. The background color of the prefilled syringe labels is labeled to be [redacted] in the submission, but appear to look [redacted] making it difficult to read to the text. Please ensure the background color of the prefilled syringe labels are [redacted] so that the text is legible.
2. Clarify if the numbers [redacted] and [redacted] are internal product codes. We recommend removing and/or relocating this number to ensure there is sufficient

(b) (4) space to allow scanner to read the barcode properly in accordance with 21 CFR 201.25 (c)(1)(i).

D. Vial Carton Labeling
    1. Revise the storage statement on the side panel to read as follows: (b) (4) **at 2° to 8°C (36° to 46°F).** Do Not Freeze or Shake.**"** We recommend this to increase the prominence of this important information and minimized the risk of the storage information being overlooked.
    2. Revise the Usual dosage statement, from (b) (4) to "Usual Dosage: See prescribing information for dosage and instructions for use."
    3. Remove the redundant storage statement from the principal display panel.
    4. Relocate the statement, "The syringe plunger stopper and needle cover are not made with natural rubber latex." to the side display panel to ensure this information does not compete in prominence with important information.

E. Prefilled Syringe Carton Labeling
    1. See D.1 through D.5 and revise the syringe carton labeling accordingly.
    2. Increase the prominence of the strength presentation on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nivestym received on September 21, 2017 and December 18, 2017 from Hospira, and US-licensed Neupogen.

Table 2. Relevant Product Information for Nivestym and US-licensed Neupogen

Product Name	**Nivestym**	**US-licensed Neupogen**
Initial Approval Date	N/A	February 1991
Active Ingredient	Filgrastim-xxxx	Filgrastim
Indication	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). • Reduce the incidence and duration of sequelae of severe neutropenia, (e.g.,	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). • Reduce the incidence and duration of sequelae of severe neutropenia, (e.g.,

	fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. • For the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.	fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. • Increase survival in patients acutely exposed to myelosuppressive doses of radiation. (Hematopoietic Syndrome of Acute Radiation Syndrome). • For the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
Route of Administration	Intravenous and subcutaneous	Intravenous and subcutaneous
Dosage Form	Injection	Injection
Strength	<u>Vials</u> • Injection: 300 mcg/mL in a single-use vial • Injection: 480 mcg/1.6 mL in a single-use vial <u>Prefilled Syringes</u> • Injection: 300 mcg/0.5 mL in a single-use prefilled syringe • Injection: 480 mcg/0.8 mL in a single-use prefilled syringe	<u>Vials</u> • Injection: 300 mcg/mL in a single-use vial • Injection: 480 mcg/1.6 mL in a single-use vial <u>Prefilled Syringes</u> • Injection: 300 mcg/0.5 mL in a single-use prefilled syringe • Injection: 480 mcg/0.8 mL in a single-use prefilled syringe
Dose and Frequency	• Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy: 5 mcg/kg/day once daily • Bone Marrow Transplantation: 10 mcg/kg/day given as an	• Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy: 5 mcg/kg/day once daily • Bone Marrow Transplantation: 10 mcg/kg/day given as an

	intravenous infusion no longer than 24 hours. • Congenital Neutropenia: 6 mcg/kg/day subcutaneous injection twice per day. • Idiopathic or Cyclic Neutropenia: 5 mcg/kg/day subcutaneous injection daily. • Autologous Peripheral Blood Progenitor Cell Collection and Therapy: 10 mcg/kg/day given by subcutaneous injection. Administer Nivestym for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis.	intravenous infusion no longer than 24 hours. • Congenital Neutropenia: 6 mcg/kg/day subcutaneous injection twice per day. • Idiopathic or Cyclic Neutropenia: 5 mcg/kg/day subcutaneous injection daily. • Autologous Peripheral Blood Progenitor Cell Collection and Therapy: 10 mcg/kg/day given by subcutaneous injection. Administer Neupogen for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. • Hematopoietic Syndrome of Acute Radiation Syndrome: 10 mcg/kg as a single daily subcutaneous injection.
How Supplied	<u>Vials</u> • Single-dose, preservative-free vials containing 300 mcg/mL of filgrastim-xxxx. Dispensing packs of 10 vials. • Single-dose, preservative-free vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim-xxxx. Dispensing packs of 10 vials. <u>Prefilled Syringes</u> Single-dose, preservative-free, prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard, containing 300 mcg/0.5 mL of filgrastim-xxxx.	<u>Vials</u> • Single-dose, preservative-free vials containing 300 mcg/mL of filgrastim. Dispensing packs of 10 vials. • Single-dose, preservative-free vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim. Dispensing packs of 10 vials. <u>Prefilled Syringes</u> Single-dose, preservative-free, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe ® Needle Guard,

	• Pack of 1 prefilled syringe • Pack of 10 prefilled syringes Single-dose, preservative-free, prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard, containing 480 mcg/0.8 mL of filgrastim-xxxx. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes	containing 300 mcg/0.5 mL of filgrastim. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes Single-dose, preservative-free, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe ® Needle Guard, containing 480 mcg/0.8 mL of filgrastim. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes
Storage	Store Nivestym at 2°C to 8°C (36°F to 46°F) in the carton to protect from light. Do not leave Nivestym in direct sunlight. Avoid freezing; if frozen thaw in the refrigerator before administration. Discard Nivestym if frozen more than once. Avoid shaking. Transport via a pneumatic has not been studied.	Store Neupogen at 2°C to 8°C (36°F to 46°F) in the carton to protect from light. Do not leave Neupogen in direct sunlight. Avoid freezing; if frozen thaw in the refrigerator before administration. Discard Neupogen if frozen more than once. Avoid shaking. Transport via a pneumatic has not been studied.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 22, 2018, we searched DMEPA's previous reviews using the terms, "Filgrastim Hospira" and Nivestym. Our search identified 3 proprietary name reviews[f,g,h] and one Human Factors Protocol and Use-Related Risk Analysis Review. We confirmed that our previous recommendations were implemented or considered.

[f] Whaley, E. Proprietary Name Review for Nivestym (filgrastim hospira) IND 109991. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Jul 22. RCM No.: 2016-7400898.

[g] Garrison, N. Proprietary Name Review for Nivestym (filgrastim hospira) IND 109991. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Aug 01. RCM No.: 2016-7400898-1.

[h] Garrison, N. Proprietary Name Review for Nivestym (filgrastim hospira) IND 109991. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Dec 13. RCM No.: 2017-17678807.

APPENDIX F. USE-ERROR RISK ANALYSIS SUBMITTED ON SEPTEMBER 21, 2017

Application 761080 - Sequence 0001 - 5.3.5.4 [[Study ID]] - [[Study Title]] - human-factors - Human Factors Device Usability

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,[i] along with postmarket medication error data, we reviewed the following Nivestym labels and labeling submitted by Hospira.

- Vial Container labels received on September 21, 2017
- Syringe labels received on September 21, 2017
- Carton labeling received on September 21, 2017
- Instructions for Use received on September 21, 2017 and December 18, 2017
- Prescribing Information (Image not shown) received on September 21, 2017 and December 18, 2017

G.2 Label and Labeling Images

Vial Container labels

(b) (4)

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

9 Page(s) 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/

NICOLE B GARRISON
06/07/2018

HINA S MEHTA
06/07/2018

QUYNHNHU T NGUYEN
06/07/2018

MISHALE P MISTRY
06/08/2018

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

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

Memorandum

Date: June 7, 2018

To: Quyen Tran, PharmD, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Nivestym (filgrastim-xxxx) injection, for subcutaneous or intravenous use

BLA: 761080

In response to DHP's consult request dated October 11, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Nivestym (filgrastim-xxxx).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Quyen Tran) on May 23, 2018, and we do not have any comments.

PPI and IFUs: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFUs were sent under separate cover on June 6, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 21, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

33 Page(s) 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/

ROBERT L NGUYEN
06/07/2018

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: April 19, 2018

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

Atiqur Rahman, Ph.D.
Director
Division of Clinical Pharmacology V
Office of Clinical Pharmacology
Office of Translational Sciences

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE/OSIS

SUBJECT: Routine inspection of Quotient Sciences-Miami, Inc., Miami, FL

NOTE: The clinical portion of study C1121012 (BLA 761080) was conducted at two sites: Quotient Sciences-Miami, Miami, FL and Quotient Sciences, Jacksonville, FL. The EIR review covering inspectional findings for study C1121012 at Quotient Sciences Jacksonville was previously submitted to DARRTS on 4/12/2018.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged inspection of the clinical portion of studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012 (BLA 761080) conducted at Quotient Sciences-Miami, Inc., Miami, FL (formerly known as SeaView Research Inc.).

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After evaluating the inspectional findings, I conclude the clinical data from the audited studies are reliable. Thus, I recommend that the data from studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012 (BLA 761080) and other studies of similar design conducted at Quotient Sciences-Miami, Inc., Miami, FL be accepted for further Agency review.

Inspected Studies:

BLA 761080

Study Number: ZIN-FIL-1501
Study Title: "A randomized open-label, multiple-dose, crossover study evaluating the pharmacodynamics and pharmacokinetics of Filgrastim Hospira compared to US-approved Neupogen (Amgen) following subcutaneous administration to healthy volunteers."
Dates of conduct: March 29-June 10, 2016

Study Number: ZIN-FIL-1502
Study Title: "A randomized open-label, single-dose, crossover study evaluating the pharmacokinetics and pharmacodynamics of Filgrastim Hospira compared to US-approved Neupogen (Amgen) following subcutaneous administration to healthy volunteers."
Dates of conduct: December 18, 2015-March 1, 2016

Study Number: C1121012
Study Title: "A phase I, randomized open-label, two-period, parallel arm study to assess the immunogenicity of multiple subcutaneous doses of Filgrastim Hospira (US) or US-approved Neupogen® reference product in healthy volunteers."
Dates of conduct: October 18, 2016-January 31, 2017

Clinical site: Quotient Sciences-Miami, Inc.,
(FKA SeaView Research Inc.)
3898 NW 7th Street, Miami, FL 33126

ORA investigator Ruth Williams (OBIMO/DBIMOI) inspected Quotient Sciences-Miami, Inc., Miami, FL from November 29-December 21, 2017.

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

At the conclusion of inspection, no significant issues were observed and no Form FDA 483 was issued.

Conclusion:

Following the evaluation of inspectional findings, I conclude the clinical data from the audited studies are reliable. Therefore, I recommend that the data from studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012 (BLA 761080) be accepted for Agency review.

Based on the inspectional findings, clinical data from studies of similar design conducted at Quotient Sciences-Miami, Inc., Miami, FL between the previous inspection (May 2016) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Clinical Site:

NAI: Quotient Sciences-Miami, Inc., Miami, FL (FKA SeaView Research Inc.)
FEI#: 3005611026

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Johnson/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan

CDER/OND/DHOP/DHP/Farrell
CDER/OTS/OCP/DVP V/Rahman
CDER/ORA/BIMO/DBIMOI/Williams

Draft: GM 04/18/2018,
Edits: RCA 04/18/2018; AD 04/19/2018

ECMS:
Quotient Sciences-Miami, Inc., Miami, FL/BLA 761080

OSIS File #: BE 7674
FACTS: 11791753

Attachment 1
Studies in support of Pending Applications

Application #	Study #	Drug Name(s)	Dates of conduct
BLA 761080	ZIN-FIL-1501	Filgrastim	March 29-June 10, 2016
BLA 761080	ZIN-FIL-1502	Filgrastim	December 18, 2015-March 1, 2016
BLA 761080	C1121012	Filgrastim	October 18, 2016 - January 31, 2017

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

/s/

GAJENDIRAN MAHADEVAN
04/19/2018

RUBEN C AYALA
04/19/2018

ARINDAM DASGUPTA
04/20/2018

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: April 12, 2018

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

Atiqur Rahman, Ph.D.
Director
Division of Clinical Pharmacology V
Office of Clinical Pharmacology
Office of Translational Sciences

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE/OSIS

SUBJECT: Routine inspection of Quotient Sciences, Jacksonville, FL

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of study C1121012 (BLA 761080) conducted at Quotient Sciences, Jacksonville, FL, USA (formerly known as SeaView Research Inc.).

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

The traceability of clinical samples collected for immunogenicity testing from subjects in study C1121012 was a concern to the OCP reviewer and this issue was addressed during the inspection and no discrepancies were found. Since the

sponsor is unaware of the traceability issue, OCP should send them a request for information, if necessary.

After evaluating the inspectional findings, I conclude the clinical data from the audited study are reliable. Thus, I recommend that the data from study C1121012 and other studies of similar design conducted at Quotient Sciences, Jacksonville, FL be accepted for further Agency review.

Inspected Study:

BLA 761080

Study Number: C1121012
Study Title: "A phase I, randomized open-label, two-period, parallel arm study to assess the immunogenicity of multiple subcutaneous doses of Filgrastim Hospira (US) or US-approved Neupogen® reference product in healthy volunteers."
Dates of conduct: October 18, 2016-January 31, 2017

Clinical site: Quotient Sciences (FKA SeaView Research Inc.)
7898 Baymeadows Way
Jacksonville, FL 32256

ORA investigator Traci Armand (BIMO/DBIMOI) inspected Quotient Sciences, Jacksonville, FL from December 18-20, 2017.

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

The OCP reviewer could not find any identifying link between the clinical sample IDs and subjects IDs in the immunogenicity reports submitted to the Agency and requested audit of sample traceability for study C1121012. During the inspection, Investigator Armand audited source documents of study C1121012 for the traceability of samples collected for immunogenicity from study subjects. Although Investigator Armand found

documentation for traceability of samples collected for immunogenicity testing and subject identifications, the initial sample requisition forms did not include the randomization number for each subject (**Exhibit-1**) and the site later resubmitted these forms with correction (**Exhibit-2**). The sample traceability issue was discussed with principle investigator of site during inspection by Investigator Armand. It seems that the sponsor is unaware of the missing subject ID information and requested the FDA to send them a request for information.

At the conclusion of the inspection, Investigator Armand did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, the data audit revealed the following protocol deviations in study C1121012 associated with immunogenicity sample collections. The protocol deviations were reported to the Agency (**Exhibit-3**) and they were confirmed by Investigator Armand during the inspection. Thus, these findings have no impact on the reliability of study data.

- Subject (b) (6) met the exclusion criteria (Protocol 4.2-Exclusion Criteria; Platelet count <150,000/mL) but was included in the study

- Test article doses were not consistently administered (Protocol 5.2-Subject Compliance) to several of the study subjects because of subject noncompliance and the best examples are Subjects (b) (6) and (b) (6)

- Per protocol requirement, the vital signs were not documented for Subjects (b) (6) and (b) (6)

Conclusion:

Following the evaluation of inspectional findings, I conclude the clinical data from the audited study are reliable. Therefore, I recommend that the data from study C1121012 (BLA 761080) be accepted for Agency review.

The traceability of clinical samples collected for immunogenicity testing from subjects in study C1121012 was a concern to the OCP reviewer and this issue was addressed during the inspection and no discrepancies were found. Since the

sponsor is unaware of the traceability issue, OCP should send them a request for information, if necessary.

Based on the inspectional findings, clinical data from studies of similar design conducted by Quotient Sciences, Jacksonville, FL between the previous inspection (November 2015) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Clinical Site:
NAI: Quotient Sciences, Jacksonville, FL (FKA SeaView Research Inc.)
FEI#: 3011861600

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Johnson/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan

CDER/OND/DHOP/DHP/Farrell
CDER/OTS/OCP/DVP V/Rahman
CDER/ORA/BIMO/DBIMOI/Armand

Draft: GM 04/06/2018, 4/11/2018; 4/12/2018
Edits: RCA 4/10/2018, 4/11/2018, 4/12/2018; AD 04/11/2018

ECMS:
Quotient Sciences, Jacksonville, FL/BLA 761080

OSIS File #: BE 7674
FACTS: 11791753

Attachment 1
Studies in support of Pending Applications

Application #	Study #	Drug Name(s)	Dates of conduct
BLA 761080	C1121012	Filgrastim	October 18, 2016 - January 31, 2017

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

/s/

GAJENDIRAN MAHADEVAN
04/12/2018

RUBEN C AYALA
04/12/2018

ARINDAM DASGUPTA
04/12/2018

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

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:	April 6, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761080
Product Name and Strength:	(b) (4) (filgrastim-aafi) Injection *Vials*: 300 mcg/mL, 480 mcg/1.6 mL *Prefilled syringes*: 300 mcg/0.5 mL, 480 mcg/0.8 mL
Total Product Strength:	Vials: 300 mcg/mL Prefilled syringes: 600 mcg/mL
Product Type:	Single Ingredient Product and Drug-device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira, Inc., a Pfizer Company
OSE RCM #:	2017-2020
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Deputy Director (Acting):	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Hospira for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761080.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On September 21, 2017, Hospira submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of their product. Hospira also provided findings from an external study conducted by (b) (4) evaluating the proposed four-letter suffixes in conjunction with the nonproprietary name, for our consideration. We note that the Applicant submitted a total of ten proposed suffixes.

We reviewed Hospira's proposed suffixes in the order of preference listed by the Applicant, along with the supporting data they submitted, using the principles described in the final applicable guidance.[a]

2.1 filgrastim-aafi

Hospira's first proposed suffix -aafi, is comprised of three distinct letters (a, f, and i). Although the letters f and i are common to the core name filgrastim, we do not find that the letters readily evoke the core name in this instance as positioned in the suffix after the letters, aa. Additionally, we note that some letters in the suffix represent medical abbreviations (aa is an abbreviation for ascorbic acid, cytarabine [ara-C], and doxorubicin [Adriamycin], of each, and albuterol and ipratropium bromide [Atrovent]). We considered whether the inclusion of the letters (aa) with the suffix could be misleading or a source of confusion and errors, but we could not identify a plausible risk based on the expected use of this product or, based upon known causes of medication errors.

We also determined that the proposed suffix, –aafi, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, and does not make any misrepresentations with respect to safety or efficacy of this product. Therefore, we find the proposed suffix -aafi acceptable for this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. Per an email correspondence dated March 13, 2018, OPDP did not identify any concerns that would render this proposed suffix unacceptable.

[a] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

4. CONCLUSION

We find Hospira's proposed suffix –aafi acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to filgrastim-aafi.

4.1 COMMENTS TO THE APPLICANT

We find the nonproprietary name, filgrastim-aafi, conditionally acceptable for your proposed product. Should your 351(k) BLA be approved during this review cycle, filgrastim-aafi will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your proposal unacceptable upon our re-evaluation, we would inform you of our finding.

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

/s/

NICOLE B GARRISON
04/06/2018

DANIELLE M HARRIS
04/09/2018

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: April 2, 2018

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

FROM: Melkamu Getie-Kebtie, R.Ph., Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Amanda Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

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

SUBJECT: Surveillance inspection of (b) (4) (b) (4)

Inspection summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012 for BLA 761080 at (b) (4) (b) (4) For these studies, the antidrug antibody (ADA), isotyping, and neutralizing antibody (NAb) assays for PF-06881893 (filgrastim) were audited.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable conditions were observed during this inspection, the findings did not impact the reliability of the data from the audited studies. Thus, we recommend accepting the

audited data from ADA, isotyping, and NAb assays in studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012 for Agency review.

Inspected studies

Study No.: ZIN-FIL-1501
Study title: A randomized, open-label, multiple-dose, crossover study pharmacodynamics and pharmacokinetics of Filgrastim Hospira to US-approved Neupogen(Amgen) following subcutaneous administration to healthy volunteers
Dates of study sample analysis (ADA, isotyping, and NAb analyses): 06/27/2016 – 07/27/2016

Study No.: ZIN-FIL-1502
Study title: A randomized open-label, single-dose, crossover study evaluating the pharmacokinetics and pharmacodynamics of Filgrastim to US-approved Neupogen® (Amgen) following subcutaneous administration to healthy volunteers
Dates of study sample analysis (ADA, isotyping, and NAb analyses): 03/02/2016 – 04/01/2016

Study No.: C1121012
Study title: A Phase I, Randomized Open-Label, 2-Period, Parallel Arm Study to Assess the Immunogenicity of Multiple Subcutaneous (SC) Doses of "Filgrastim Hospira" (US) or US-Approved Neupogen Reference Product in Healthy Volunteers
Dates of study sample analysis (ADA, isotyping, and NAb analyses): 12/12/2016 – 03/29/2017

Analytical site: [redacted]

OSIS scientists Melkamu Getie-Kebtie, R.Ph., Ph.D. and Amanda Lewin, Ph.D. audited the ADA, isotyping, and NAb assays for the above studies at [redacted] from [redacted] to [redacted]

The inspection included a thorough examination of the facility, equipment, records for method validation and sample analysis, SOPs, sample shipment, handling, and storage, software audit trails, and interviews and discussions with management and staff.

At the conclusion of the inspection, we observed an objectionable condition and Form FDA 483 was issued to the analytical site. The Form FDA 483 observation (**Attachment 1**), the firm's response dated 03/21/2018 (**Attachment 2**), and our evaluation are presented below.

Form FDA 483 observation

The following observation pertains to studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012:

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Conclusion

An objectionable condition was observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional finding and the firm's response to Form FDA 483, the objectionable condition did not impact the reliability of the data from the audited studies. Therefore, for BLA 761080, we recommend accepting the data from the ADA, isotyping, and NAb assays in studies ZIN-FIL-1501, ZIN-FIL-1502, and C1121012 for further Agency review.

Classification:

VAI: (b) (4)
(b) (4)

CC:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Lewin
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au/Getie-Kebtie

Draft: MG 3/27/2018, 3/28/2018, 3/29/2018/ 3/30/2018; AL 3/27/2018, 3/29/2018
Edit: SA 3/28/2018, 3/29/2018, 3/30/2018; SC 3/30/2018; 4/2/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ [redacted]/BLA 761080 PF-06881893

OSIS file #: BE 7674
FACTS: [redacted]

Attachments

1. Form FDA 483 observation
2. [redacted] response to Form FDA 483 observation

12 Pages 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/

MELKAMU GETIE KEBTIE
04/02/2018

AMANDA E LEWIN
04/02/2018

STANLEY AU
04/02/2018
Acting Team Lead

SEONGEUN CHO
04/02/2018

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: January 18, 2017

TO: James Smith, MD
Deputy Director
Division of Metabolism and Endocrinology Products
Office of New Drugs

Ann Farrell, MD
Director
Division of Hematology Products
Office of New Drugs

Atiqur Rahman, Ph.D.
Director
Office of Clinical Pharmacology
Division of Clinical Pharmacology V

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Kara Scheibner, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

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

SUBJECT: Surveillance inspection of (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies (b) (4) (b) (4), ZIN-FIL-1502 (BLA 761080), and ZIN-FIL-1501 (BLA 761080) conducted at (b) (4)

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Significant objectionable conditions were observed during this inspection that impacted the reliability of a portion of the audited studies. However, the inspectional findings were isolated in nature and do not impact the reliability of all the data. [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4) However, data from other studies submitted to [redacted] (b) (4) BLA 761080 should be accepted for further review.

Inspected Studies:

[redacted] (b) (4)

BLA 761080

Study Number: **ZIN-FIL-1502** [redacted] (b) (4)
Study Title: "A single-center, randomized, open-label, single-dose, 2-way crossover study evaluating the PK and PD of PF-06881893 compared to US-licensed Neupogen RP in healthy subjects"
Dates of conduct: 02/19/2016 – 02/24/2016

Study Number: **ZIN-FIL-1501** [redacted] (b) (4)

Study Title: "A single-center, randomized, open-label, multiple-dose, 2-way crossover study in healthy subjects"

Dates of conduct: 04/22/2016 – 05/31/2016

Analytical site: [redacted] (b) (4)

OSIS scientists, Xiaohan Cai, Ph.D. and Kara A. Scheibner, Ph.D., audited the analytical portion of the above studies at [redacted] (b) (4) from [redacted] (b) (4) to [redacted] (b) (4)

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the conclusion of the inspection, we observed objectionable conditions and Form FDA 483 was issued to the analytical site. We also discussed several items at the closing meeting. The Form FDA 483 observation (**Attachment 1**), the firm's response dated 12/13/2017 (**Attachment 2**), and our evaluation are presented below.

[redacted] (b) (4)

(b) (4)

Conclusion:

Significant objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, there was evidence that the objectionable conditions (b) (4) (b) (4) (b) (4). However, the objectionable conditions did not impact the reliability of all the inspected studies conducted at the site and the overall performance of the site.

(b) (4) (b) (4) However, data from all other studies submitted to (b) (4) BLA 761080 should be accepted for further review. In addition, studies using similar methods conducted between this inspection (b) (4) and the end of the current Surveillance Interval should be accepted for review by the Agency without an inspection.

Xiaohan Cai, Ph.D.
Visiting Associate

Kara Scheibner, Ph.D.
Pharmacologist

Attachment 1: A copy of Form 483 issued to (b) (4)
Attachment 2: Responses received from (b) (4)
Attachment 3: Updated data tables (b) (4)

Final Classification:

VAI– (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Haidar/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Cai/Scheibner

Draft: XHC 1/8/2018; KAS 1/9/2018
Edit: YMC 1/11/2018; JAK 1/18/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/(b) (4) _PF-06881893 proposed biosimilar to Neupogen

OSIS File #: (b) (4)
BE 7674 (BLA 761080)

FACTS: (b) (4)

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

/s/

XIAOHAN CAI
01/18/2018

KARA A SCHEIBNER
01/22/2018

YOUNG M CHOI
01/22/2018

JOHN A KADAVIL
01/22/2018