CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761039Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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ADDENDUM TO PEDIATRIC REVIEW

From:	Erica Radden, M.D., Medical Officer Division of Pediatric and Maternal Health (DPMH), Office of New Drugs (OND) Office of Drug Evaluation IV (ODE IV)
Through:	John J. Alexander, M.D., M.P. H., Deputy Director DPMH, OND, ODE IV
To:	Division of Hematology Products (DHP)
Drug:	CHS-1701/Udenyca (proposed biosimilar to US-licensed Neulasta [pegfilgrastim])
Formulation:	6 mg/0.6 mL solution in a single use prefilled syringe administered by subcutaneous injection.
Therapeutic Class:	Leukocyte growth factor
Application Number:	BLA 761039 (IND 115573)
Applicant:	Coherus Biosciences, Inc.
Subject:	Labeling Review Addendum
Proposed 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.

Consult Request: DHP consulted DPMH to provide recommendations for pediatric use information in labeling and assist in preparation for the Pediatric Review Committee (PeRC) meeting.

Materials Reviewed:

- Division of Pediatric Maternal Health (DPMH) consult request
- Agreed upon initial Pediatric Study Plan (iPSP) for CHS-1701, IND 115573 (July 23, 2015) and Amended iPSP (September 12, 2016)
- Current Neulasta (pegfilgrastim) labeling (June 18, 2018) per Drugs@FDA
- Prior DPMH review for CHS-1701 (IND 115573) dated August 30, 2016 and (BLA 761039) dated June 9, 2017
- Sponsor's proposed labeling for CHS-1701 (May 3, 2018)

Consult and Regulatory Background:

On May 3, 2018, Coherus Biosciences, Inc. resubmitted their BLA for CHS-1701/Udenyca, a proposed biosimilar to US-licensed Neulasta (pegfilgrastim) following a Complete Response (CR) due to immunogenicity, product quality and microbiology issues. (See the prior DPMH review for BLA 761039 for further background information and discussion of the pediatric assessment.) The applicant has not submitted any new pediatric data. Additionally, their proposed pediatric plan to extrapolate pediatric data from the reference product, Neulasta, based on the biosimilar development program and to defer the submission of an age-appropriate presentation to fulfill PREA is also unchanged. DPMH was consulted to provide pediatric labeling recommendations for this review cycle and assist in preparation for the Pediatric Review Committee (PeRC).

DPMH Review of Pediatric Use Labeling

This DPMH-Pediatric team labeling review will specifically focus on edits to 8.4 (Pediatric Use). The following recommendations are based on labeling discussions between DHP and DPMH. Additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text.

Applicant's Proposed Labeling:

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of pegfilgrastim (b) (4) have been established in pediatric patients. No overall differences in safety were identified between adult and

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pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma *[see Clinical Pharmacology (11~~2~~.3) and Clinical Studies (13~~4~~.1)]*.

DPMH Comments: In accordance with 21 CFR 201.57(c)(9)(iv)(C) and (D) and the Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice, DPMH has generally recommended that the Section 8.4 use statement describing that safety and effectiveness has been established for the proposed product include the product's proprietary name (i.e., Udenyca). However, for this biosimilar product, DPMH acknowledges the concern that use of the proprietary name in this statement could imply that the data used to support the statements in Section 8.4 were obtained from studies conducted with Udenyca rather than the reference product. Labeling for another approved pegfilgrastim biosimilar uses the proper name, pegfilgrastim, in the Section 8.4 use statement. While DPMH would prefer to include the proprietary name in the pediatric use statement, because we do not object to either "Udenyca" or "pegfilgrastim" here, we defer to DHP to determine which product name is appropriate in this instance, particularly given similar language in the labeling for another pegfilgrastim biosimilar.

Conclusion:

DPMH agrees with the final pediatric plan proposed by Coherus to extrapolate pediatric data from the reference product, US-licensed Neulasta, based on the biosimilar development program and to defer the submission of an age-appropriate presentation to fulfill PREA. The PeRC also concurred with the pediatric plan for this product on October 3, 2018.

DPMH reviewed the applicant's draft labeling, and participated in the team internal meetings from June to October 2018. DPMH provided labeling recommendations for the pediatric population per 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

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/s/

ERICA D RADDEN
11/01/2018

JOHN J ALEXANDER
11/01/2018

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:	October 30, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761039
Product Name and Strength:	Udenyca (pegfilgrastim-cbqv) Injection 6 mg/0.6 mL
Applicant/Sponsor Name:	Coherus Biosciences, Inc.
FDA Received Date:	October 26, 2018
OSE RCM #:	2018-920-1
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 Udenyca (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] A teleconference was held with the Applicant on October 24, 2018 providing advice on the format for product identifiers on the carton labeling. In addition, we provided advice to the Applicant on October 15, 2018 to use consistent color of the graphic logo throughout the labeling.

2 CONCLUSION

The revised container label and carton labeling for Udenyca are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Garrison N. Label and Labeling Review for Udenyca (BLA 761039). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 06. RCM No.: 2018-920.

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/s/

NICOLE B GARRISON
10/30/2018

HINA S MEHTA
10/31/2018

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

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

Memorandum

Date: October 24, 2018

To: Jennifer Lee, 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 UDENCYA™ (pegfilgrastim-cbqv) injection, for subcutaneous use

BLA: 761039

In response to DHP's consult request dated May 15, 2018, 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 Udencya (pegfilgrastim-cbqv).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Jennifer Lee) on September 17, 2018 and we do not have any comments.

PPI/IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on October 24, 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 August 30, 2018, 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.

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/s/

ROBERT L NGUYEN
10/24/2018

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:	October 24, 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):	UDENYCA (pegfilgrastim-cbqv)[1]
Dosage Form and Route:	injection, for subcutaneous injection
Application Type/Number:	BLA 761039
Applicant:	Coherus Biosciences, Inc.

[1] The proprosed proprietary name, UDENYCA and the nonproprietary (proper) name, pegfilgrastim-cbqv are conditionally acceptable, until such time as the application is approved.

1 INTRODUCTION

On May 3, 2018, Coherus Biosciences, Inc. submitted for the Agency's review a class 2 resubmission of their proposed Biologics License Application (BLA) 761039 for UDENYCA (pegfilgrastim-cbqv), a proposed biosimilar to NEULASTA (pefilgrastim) (BLA 125031), in response to an Agency Complete Response Letter dated June 9, 2017. The proposed indication for UDENYCA (pegfilgrastim-cbqv) 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 15, 2018 and May 3, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for UDENYCA (pegfilgrastim-cbqv) injection.

2 MATERIAL REVIEWED

- Draft UDENYCA (pegfilgrastim-cbqv) injection PPI received by DMPP and OPDP on May 3, 2018.
- Draft UDENYCA (pegfilgrastim-cbqv) injection IFU received by DMPP and OPDP on May 3, 2018, and August 27, 2018, revised by the review division throughout the review cycle and received on September 17, 2018.
- Draft UDENYCA (pegfilgrastim-cbqv) injection Prescribing Information (PI) received by DMPP and OPDP on May 3, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on September 17, 2018.
- NEULASTA (pegfilgrastim) injection Reference Product labeling dated April 28, 2018.
- FULPHILA (pegfilgrastim-jmdb) injection approved Biosimilar to NEULASTA (pegfilgrastim) injection labeling dated June 4, 2018.

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.

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
- ensured that the PPI and IFU meet 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 comparator labeling 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 is 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/

SHARON R MILLS
10/24/2018

ROBERT L NGUYEN
10/24/2018

LASHAWN M GRIFFITHS
10/24/2018

U.S. FOOD & DRUG ADMINISTRATION

MEMO TO THE RECORD
BLA 761039

DATE:	October 9, 2018
FROM:	CDR Keith Marin, MS, MBA, Nurse Reviewer
OFFICE/DIVISION/BRANCH:	ODE/DAGRID/GHDB, WO 66, 2604
DEVICE NAME:	Udenyca, pegfilgrastim-xxxx (biosimilar) prefilled syringe
SPONSOR:	Coherus
CONTACT:	Joslyn Brunelle, Biologist Office of Biotechnology Products (OBP) Division of Biotechnology Review & Research IV Center for Drug Evaluation and Research (CDER)

LEAD REVIEW NOTE: The sponsor confirmed on June 18, 2018 that the device has not been modified from the previous approval configuration. As a result, our prior review still stands and no additional information is needed at this time.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Keith G. Marin -S Digitally signed by Keith G. Marin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=0011250397 Date: 2018.10.09 12:56:44 -04'00'
Branch Chief Sign-Off	Alan M. Stevens -S

RISK ASSESSMENT RESPONSE, 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:	September 6, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761039
Product Name and Strength:	Udenyca[*] ("CHS-1701")[**] Injection 6 mg/0.6 mL
Product Type:	Drug-Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Coherus Biosciences, Inc.
Submission Date:	August 9, 2016, May 3, 2018 and May 11, 2018
OSE RCM #:	2018-920
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

[*] Udenyca has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name Udenyca is only conditionally accepted until final approval of CHS-1701.

[**] The proposed nonproprietary name for Udenyca has not yet been conditionally accepted. We therefore continue to refer to the proposed product as "CHS-1701" throughout this review in place of the nonproprietary name for this product.

Reference ID: 4316918

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU) for Udenyca ("CHS-1701") injection (BLA 761039) for areas of vulnerability that could lead to medication errors. In addition, we evaluated revisions to the Application Failure Mode Effects Analysis (aFMEA) submitted by Coherus on August 9, 2016. After revisions of the FMEA, Coherus provided justification that a Human Factors Study is not needed. The Division of Hematology Products (DHP) requested this review to inform their evaluation of the 351(k) class 2 re-submission for Udenyca ("CHS-1701") ("CHS-1701") injection.

1.1 REGULATORY HISTORY

In January 2002, US- licensed Neulasta was 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. In 2015, US-licensed Neulasta was approved to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

In a December 2015 BPD Type 3 Meeting with Coherus Biosciences, DMEPA recommended that the sponsor perform a comprehensive use-related risk analysis of the proposed prefilled syringe to determine if a human factors study was needed.[a]

On April 7, 2016, Coherus Biosciences submitted what the company refers to as its "Application Failure Modes and Effect Analysis" (aFMEA) to the IND. In our review dated June 6, 2016, we noted that the aFMEA did not include an assessment of the measurement and administration of pediatric doses.[b] We also noted at the time that the Sponsor's aFMEA did not include the same intended users as US-licensed Neulasta; (b) (4) US-licensed Neulasta is labeled for use by HCPs, patients, and caregivers. Therefore, the FMEA should be revised to evaluate all intended user groups.[c] Therefore, we recommended that the sponsor conduct a Human Factors (HF) validation study to include lay users (such as patients and caregivers) to demonstrate that all intended users can use the proposed product safely and effectively and demonstrate that intended users can accurately measure and administer Udenyca at doses less than 6 mg (0.6 mL). Our recommendations were communicated to the sponsor on June 3, 2016.

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[a] Memorandum of Meeting Minutes for CHS-1701 (IND 115573). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Hematology and Oncology Products, Division of Hematology Products (US); 2015 DEC 16. 70 p.

[b] Whaley, E. Use-Related Risk Analysis Memorandum for CHS-1701 (IND 115573). 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 JUN 06. 14 p. OSE RCM No.: 2015-2425.

[c] Guidance for Industry: Applying Human Factors and Usability Engineering to Medical Devices. 2016. Available from http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

In preliminary questions sent to the Agency for an August 2016 BPD Type 4 meeting[d], the Sponsor concluded that a HF validation study was not necessary and requested Agency concurrence. We recommended that the sponsor revise the aFMEA to include all intended users and then determine if a HF validation study is needed. If the Sponsor determined that a HF validation study was not needed, then we recommended that they submit their justification to the Agency for review and concurrence. During the meeting discussion, the Sponsor informed the Agency that they updated the aFMEA to include all intended users and will submit the revised aFMEA with their justification to the BLA. We note the Sponsor has submitted an updated pediatric plan on April 14, 2017 in which they plan to defer development of their pediatric presentation through 2021.

The application received a Complete Response (CR) letter on June 9, 2017 due to immunogenicity, product quality, and microbiology issues. The CR letter explained that FDA reserved comment on the proposed labeling (including the PI and carton and container labeling) until the application is otherwise adequate. Coherus Biosciences submitted a response to the CR letter for Udenyca ("CHS-1701") BLA 761039 on May 3, 2018. The information conveyed in the BLA resubmission does not impact our earlier assessments, conclusions, and recommendations.

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	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

[d] Memorandum of Meeting Minutes for CHS-1701 (IND 115573). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Hematology and Oncology Products, Division of Hematology Products (US); 2016 AUG 25. 59 p.

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Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**

*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

Coherus Biosciences re-submitted their 351(k) application for Udenyca ("CHS-1701"). We evaluated the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, Instructions for Use (IFU), and revised aFMEA for Udenyca ("CHS-1701") injection, BLA 761039. Udenyca has the same dosing, route of administration, strength, and storage requirements as US-licensed Neulasta (BLA 125031). The Sponsor 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), as the Sponsor of US-licensed Neulasta has an unexpired orphan-drug exclusivity for the treatment of Acute Radiation Syndrome (ARS). Udenyca is supplied as a single-dose, ungraduated prefilled syringe (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.

Differences Identified in Failure Mode Effects Analysis and Labeling

Within the revised aFMEA, the Sponsor provided a description of key operating steps that are considered critical tasks. These critical tasks align with the critical tasks of US-licensed Neulasta, with one exception that users of US-licensed Neulasta are required to activate the needle guard manually, whereas, the Udenyca PFS has a passive needle guard and does not require manual activation. We note that users of the Udenyca PFS must slowly remove their thumb from the plunger to automatically retract the needle and secure it inside the syringe body whereas users must manually pull the blue safety needle guard for US-licensed Neulasta. Therefore, in our review of the revised aFMEA, we note that premature activation of the needle guard is not listed as a potential failure, which differs compared to US-licensed Neulasta because the needle is activated automatically after releasing pressure from the plunger on the PFS. Additionally, we note that the Sponsor revised the aFMEA to include all intended users (e.g., patients, caregivers, and healthcare professionals) and pediatric doses. We do not consider activation of the needle guard as a critical task, and therefore, we find these differences acceptable.

The Udenyca IFU follows similar steps and injection technique as US-licensed Neulasta. However, we note there is a step of stabilizing the PFS after inserting the needle in the pinched skin, which is not present in the US-licensed Neulasta IFU. For example, US-licensed Neulasta provides instructions on using the prefilled syringe after the guide to parts. The instructions inform users not to give the injection unless they or their caregivers have received training from

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a healthcare provider. Additional information listed under using the prefilled syringe also informs users not to inject a dose of US-licensed Neulasta to children weighing less than 45 kg from a Neulasta PFS. However, this information is omitted from the Udenyca IFU. Revision of the Udenyca IFU to include important administration information may help to reduce the risk of administration errors and will harmonize this information with the US-licensed Neulasta IFU. We have recommendations in section 4.1 below for areas within the Udenyca IFU that differ from US-licensed Neulasta IFU be revised to be harmonized with the US-licensed Neulasta IFU. We also note that the Udenyca IFU does not list or depict the outer area of the upper arm as an injection site, but lists the back of the arms as an injection site. This aspect also differs from, US-licensed Neulasta. We have a recommendation in section 4.1 below to clarify the injection site discrepancy and to revise the injection sites if appropriate to include the outer area of the upper arm injection site. We defer to the Clinical team and Patient Labeling team to provide additional recommendations for the Udenyca IFU.

Similarities in PFS and labeling

Like US-licensed Neulasta, the Udenyca 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. Direct administration to patients requiring doses less than 0.6 mL (6 mg) is not recommended due to the potential of dosing errors. The Prescribing Information for US-licensed Neulasta clearly states that the PFS is not intended for direct administration of the drug for doses less than 0.6 mL (6 mg). We note that similar statements also appear in the proposed Udenyca labeling, which should reduce the risk of error in situations where healthcare providers read the product labeling. However, we have recommendations in section 4.1 below that information regarding dosing limitations of the PFS be conveyed in the IFU, which is consistent with the labeling of US-licensed Neulasta.

4 CONCLUSION & RECOMMENDATIONS

Our review of the aFMEA concluded that there were no new or unique risks when compared to US-licensed Neulasta and we note that the intended user group, intended uses, and use environments for Udenyca aligns with US-licensed Neulasta.

Our review of the carton labeling and container labels identified several areas that can be improved to increase the readability and prominence of important information. We note that the labels and labeling contains the term, "(b) (4)"; which is not consistent with the draft guidance[e]; we defer to the Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term on labels and labeling. We determined that the proposed PI, container labels, and carton labeling, is vulnerable to confusion that can lead to medication errors. Additionally, we identified other aspects of the IFU that should be revised to add

[e] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

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important information regarding the administration of Udenyca to harmonize with US-licensed Neulasta labeling where appropriate.

We conclude that the Sponsor has adequately considered the risks associated with the proposed Udenyca prefilled syringe and we agree that a human factors validation study is not needed at this time. Any changes to the aFMEA would warrant further review.

We provide recommendations in Sections 4.1 and 4.2 below and advise they are implemented prior to approval of BLA 761039.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Instructions for Use

1. In the first section of the IFU, relocate the before use and after use images (b) (4) Entitle the section, "Guide to Parts".
2. Below "Guide to Parts", include the following statement:
   Important (b) (4)
   Read the Patient Information for important information you need to know about Udenyca before using the Instructions for Use.
3. Storage Information
   a. Add the statement, "Keep out of the reach of children" to mitigate the risk of administration errors.
4. Revise the section titled, (b) (4)" to "Using the Prefilled Syringe".

   a. Include the following statements to bring clarity to this important information:
      i. "**It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider**." We recommend this to mitigate the risk of administration errors.
      ii. Make sure that the name Udenyca appears on the carton and prefilled syringe label.
      iii. You should not inject a dose of Udenyca to children weighing less than 45 kg from a Udenyca prefilled syringe. A dose less than 0.6 mL cannot be accurately measured using the Udenyca prefilled syringe.
      iv. Check the carton and prefilled syringe label to make sure the dose strength is 6 mg/0.6 mL.
      v. Do not use the prefilled syringe if the carton is open or damaged.

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vi. Revise the statement, "[redacted]" to "Do not use the syringe if it has been dropped [redacted] The prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe."

vii. Do not attempt to activate the [redacted] prior to injection.

5. Prepare Injection
   a. Inspect the Syringe and [redacted]
      i. Include the following statements to bring clarity to this important information:

         Do not use the prefilled syringe if the [redacted] needle cap is missing or not securely attached.

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

      ii. Label the inspection window of the syringe on image in Figure [redacted]
6. Select and clean injection site
   a. We note the IFU does not list the outer area of the upper arm as an injection site. The outer area of the upper arm is listed as an injection site for US-licensed Neulasta. Therefore, please clarify and provide reasoning for the discrepancy between the Udenyca IFU and US-licensed Neulasta IFU.
   b. Revise and include the following statements to bring clarity to this important information:
      i. Section 5A
         a. "[redacted]" to "[redacted] upper arm (only if someone else is giving you the injection)"
         b. "[redacted]" to "Upper outer area of buttocks (only if someone else is giving you the injection)"
      ii. Labeled images in Figure 8
         a. "Back of [redacted] "Upper arms"
         b. [redacted]" to "Upper outer [redacted] buttocks"
      iii. Section 5B,
         a. Do not touch this area again before injecting.
         b. 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.
7. Inject the dose
   a. The image used in Figure [redacted] does not match the accompanying text. The text states to pull the needle cap straight off, however, the image shows [redacted]. Please revise the image used in

Reference ID: 4316918

Figure (b) (4) We recommend this to provide congruency with the text and the image.

b. Revise the statement, (b) (4)" to "Do not (b) (4) the syringe. Dispose of (throw away) the (b) (4) needle cap in your household trash."

4.2 RECOMMENDATIONS FOR COHERUS

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

A. All Container Labels and Carton Labeling
   1. For this product, ensure that the strength, expressed as total protein content per total volume, is the primary and prominent expression on Principal display panel (PDP). See USP General Chapters <7> Labeling. Revise the strength presentation to appear as 6 mg/0.6 mL. This comment includes when presenting the strength in white lettering with a green background color.
   2. If space permits, consider adding the dosage form "Injection" to appear below the proper name as follows:

      Udenyca
      (pegfilgrastim-xxxx)
      Injection
      6 mg/0.6 mL
   3. The drug barcode is often used as an additional verification before drug administration in the hospital setting; there it is an important safety feature that should be part of the label whenever possible. Therefore, we require you add the product's linear barcode to each individual package as required per 21 CFR 201.25(c)(2) and 21 CFR 610.67.
   4. As currently presented, the container label and carton labeling use the package type term, "(b) (4)"; however, the Prescribing Information uses the package type term, "single-dose". Revise the container label and carton labeling to "single-dose" to be consistent throughout the labeling.
   5. Revise the font color (b) (4) to a darker font to afford adequate legibility of the text.

B. Container label (syringe label)
   1. Include the route of administration "For subcutaneous use" to appear above the package type term.
   2. Decrease the font of the statement "Rx Only" as this information appears more prominent than the nonproprietary name on the PDP.

C. Carton labeling (outer)
   1. Revise and relocate the usual dose statement, "(b) (4)" to read "Dosage- See prescribing information for dosage and instructions for use" on the side or back panel in accordance with 21 CFR 201.55.

Reference ID: 4316918

2. Revise the storage information from "[redacted] (b) (4)" to "Store refrigerated at 2° to 8°C (36° to 46°F) in the original carton to protect from light. Do Not Freeze. Do Not Shake.".
3. Decrease the prominence of the graphic preceding the proprietary name in accordance with 21 CFR 201.10(a). As currently presented, the graphic could be misinterpreted for the letter, "O" and appears to be included as a part of the proprietary name.
4. Relocate the statement, "Not made with Natural Rubber Latex." to the side display panel to ensure this information does not compete in prominence with important information.

D. Carton labeling (inner tray)
1. See C.2 through C.3 and revise the inner carton labeling accordingly.
2. The route of administration appears twice on the inner tray carton labeling. Remove the duplicate statement that appears below the storage information to improve readability and increase white space. Additionally, consider increasing the prominence of the route of administration on the left side of the PDP to mitigate the risk of administration errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Udenyca that Coherus submitted on May 3, 2018 and May 11, 2018 and US-licensed Neulasta.

Table 2. Relevant Product Information for Udenyca and US-Licensed Neulasta

Product Name	**Udenyca**	**US-licensed Neulasta**
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	Pegfilgrastim-xxxx	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	Give 6mg subcutaneously once per chemotherapy cycle. Pediatric patients weighing less than 45 kg: Body weight / Udenyca Dose / Volume to administer Less than 10kg* / See below* / See below*	*Cancer patients receiving myelosuppressive chemotherapy* • Give 6mg subcutaneously once per chemotherapy cycle. *Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome* • Give 6 mg subcutaneously for adult victims with body weight≥ 45 kg for two doses given (b) (4) weeks apart; for pediatric

Reference ID: 4316918

<table>
<tr>
<td></td>
<td>
<table>
<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>
</table>
*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Udenyca
</td>
<td>
patients weighing less than 45 kg, use weight based dosing.
Dosing of Neulasta for pediatric patients
<table>
<tr><td>Body weight</td><td>Neulasta Dose</td><td>Volume to administer</td></tr>
<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>
</table>
*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta
</td>
</tr>
<tr>
<td>How Supplied</td>
<td>Single dose, preservative free, prefilled syringe with an UltraSafe Passive™ Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim-xxxx.</td>
<td>Single dose prefilled syringe with an UltraSafe® Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim.
OnPro kit: 6 mg/0.6 mL solution in a single prefilled syringe copackaged with the Onbody Injector for Neulasta.</td>
</tr>
<tr>
<td>Storage</td>
<td>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.</td>
<td>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.</td>
</tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 20, 2018, we searched the L:drive and AIMS using the terms, Udenyca to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two proprietary name reviews[f,g] and one nonproprietary name suffix memorandum[h].

[f] Whaley, E. Proprietary Name Review for Udenyca (IND 115573). 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); 2015 MAR 09. Panorama No. 2015-1877840.

[g] Garrison, N. Proprietary Name Review for Udenyca (BLA 761039) 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 OCT 06. Panorama No. 2016-9553701.

[h] Garrison, N. Nonproprietary Name Suffix Memorandum for Udenyca (BLA 761039) 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); 2017 MAR 08. Panorama No. 2016-1833.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

NICOLE B GARRISON
09/06/2018

HINA S MEHTA
09/06/2018

QUYNHNHU T NGUYEN
09/10/2018

MISHALE P MISTRY
09/11/2018

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: August 3, 2018

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

FROM: Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seong H. Jang, Ph.D.
Acting Deputy Director
DGDBE, OSIS

SUBJECT: Inspection of (b) (4)
Analytical Site supporting BLA 761039

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of portions of studies CHS-1701-05 and CHS-1701-04 (BLA 761039) conducted at (b) (4)

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

After reviewing the inspectional findings, I conclude that data from the audited studies are reliable. Thus, I recommend that data from studies CHS-1701-05 and CHS-1701-04, and other studies using similar methods, should be accepted for further Agency review.

Inspected Studies:

BLA 761039
Study Number: **CHS-1701-05**
Study Title: "A Randomized, Single-Blind, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Bioequivalence of CHS-1701

(Coherus Pegfilgrastim) with Neulasta® in Healthy Subjects"

Dates of sample analyses: NAb assays 12/14/2017 - 1/13/2018

Study Number: **CHS-1701-04**
Study Title: "A Randomized, Double-Blind, Two-period, Parallel-arm Study to Assess the Immunogenicity of Two Subcutaneous Doses of CHS-1701 (Coherus Pegfilgrastim) with Two Subcutaneous Doses of Neulasta® in Healthy Subjects"

Dates of sample analyses: NAb assays 1/29/2018 - 2/17/2018
Ab titer assays 2/8/2018 - 2/13/2018

Non-Responsive

[redacted]

OSIS scientist Michael F. Skelly audited analytical portions of the above studies at [redacted] (b) (4) from [redacted] (b) (4) to [redacted] (b) (4).

[redacted]

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

The sponsor arranged assays for G-CSF-specific neutralizing antibodies (NAb) and titer (Ab titer) of G-CSF-specific binding antibodies, in certain samples found positive at another contract laboratory with assays for PEG-filgrastim-specific assays. The sponsor communicated DHP's recommendations to [redacted] (b) (4) for method validations and bioanalytical conduct,

Reference ID: 4302331

following a Complete Response Letter (June 9, 2017) and a Type 2 Meeting (November 29, 2017).

At the conclusion of the inspection, I did not observe any objectionable conditions and I did not issue Form FDA 483 to the bioanalytical site.

Conclusion:

After reviewing the inspectional findings, I conclude that data from the audited studies are reliable. Therefore, I recommend accepting (b) (4) data from studies CHS-1701-05 and CHS-1701-04 (BLA 761039) for further review.

Based on the inspectional findings, any immunogenicity, pharmacodynamic, and biomarker studies using similar methods and conducted between the previous bioanalytical inspection ((b) (4) , by ORA only, on behalf of CBER) and the end of the current surveillance interval should be accepted for review by the Agency, without an inspection.

Michael F. Skelly, Ph.D.
Lead Pharmacologist

Final Classification:

NAI (b) (4)

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

Draft: 7/31/2018
Edits: SA 7/31/2018, 8/2/2018; SHJ 8/3/2018

ECMS: (b) (4)

OSIS File #: (b) (4)

FACTS: (b) (4)

Reference ID: 4302331

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/

MICHAEL F SKELLY
08/03/2018

STANLEY AU
08/03/2018
Team Lead

SEONG H JANG
08/06/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)
Division of Manufacturing and Quality (DMQ)

ICCR QUALITY SYSTEM REVIEW MEMO

Date:	June 19, 2018
To:	Joslyn Brunelle, CDER/OND/ OPQ/OBP/DBRRIV, WO71 RM2214, Tel: 240-402-9235, E-mail: Joslyn.Brunelle@fda.hhs.gov
CC:	Office of Combination Product, Combination@fda.hhs.gov CDER/OPQ/OPF, Juandria.Williams@fda.hhs.gov
Through:	Booth Shanika, Branch Chief, REGO/DMQ/OC, CDRH, WO 66, Rm 3618, shanika.booth@fda.hhs.gov
From:	Corbin, Louis, REGO/DMQ/OC, CDRH, WO66, Rm 3456, E-mail: louis.corbin@fda.hhs.gov
Applicant/Licensure:	Coherus BioSciences, Inc 333 Twin Dolphin Drive Redwood City CA 94065 FEI: 3019682611
Submission (Type & Number):	BLA 761039
Combination Product Name:	Udenyca, pegfilgrastim-xxxx (biosimilar) Pre-filled Syringe, Solution for Injection, 6 mg / 0.6 mL
Combination Product Indications for Use:	Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia
Device Constituent (Type):	Prefilled Syringe
ICCR Sharepoint Tracking Number:	ICCR2018-02904
ICCR CTS Tracking	ICC1800409

Number:

Pre-Approval Facility Inspection:	No, Post-Approval and/or Routine Surveillance Inspections Requested
Documentation Review (Status):	**Response Adequate**
CDRH/OC Recommendation:	**Approvable**

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA 761039 which will require a device inspection.

BACKGROUND

This is a follow-up review following complete response to information request by the firm to CDER. A Quality Systems review of the initial submission, ICC1600756, was completed on January 26, 2017, with the following CDRH Office of Compliance Recommendation:

1. UDENYCA™, BLA 761039 IR information –Adequate. No Deficiencies remaining.
2. BLA 761039 - Approvable
3. Pre-approval inspection recommended.

The current review establishes that no significant QS requirement changes were made by the firm since the initial review, and that the recommended site inspections were completed and adequate.

PRODUCT DESCRIPTION

The medical devices constituent part of the combination product is an UltraSafe (b) (4) ™ Passive Needle Guard cleared by CDRH under the 510(k) pathway (K (b) (4)). Each syringe is inserted into a passive needle guard to protect health care staff from inadvertent needle sticks. The UltraSafe (b) (4) ™ passive needle guard system functions with a plunger rod designed specifically for the UltraSafe (b) (4) ™ system. The passive needle guard and plunger rods are described in Section 3.2.P.7.3 of the submission. The rigid needle shield supplied as a unit with the syringe is described in Section 3.2.P.7.2 of the submission.

The PFS is a manually-operated, single-use, disposable system. The primary container closure system includes a syringe needle safety device, which may reduce the potential

occurrence of accidental needle-sticks to healthcare professionals and patients after administration and during disposal of a used prefilled syringe.

The intended use of the Udenyca is 'Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia'.

Figure 1: **UDENYCA Primary Packaging System**

(b) (4)

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the combination product, Udenyca, pegfilgrastim-xxxx (biosimilar) Pre-filled Syringe, Solution for Injection, 6 mg / 0.6 mL, in BLA 761039.

Combination Product Applicant

Firm Name: Coherus BioSciences, Inc,
Address: 333 Twin Dolphin Drive, Redwood City, CA 94065
FEI: 3019682611

Responsibility – BLA Holder

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 3/13/2017 to 3/16/2017 . The inspection covered medical device QS and was classified NAI.

Inspection Recommendation:

An inspection is not required because a recent medical device inspection of the firm was acceptable.

Finished Combination Product Manufacturer

Firm Name: (b) (4)

FEI: (b) (4)

Responsibility – Combination product manufacturing, labeling and packaging

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 NAI.

Inspection Recommendation:
A post-approval inspection is recommedded because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed.

Device Constituent Part Manufacturer

Firm Name: (b) (4)

FEI: (b) (4)

Responsibility – (b) (4) for ULTRASAFE (b) (4) PASSIVE NEEDLE GUARD (finished device) used in BLA761039.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:
A post-approval or routine inspection is recommended because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm a recent medical device inspection of the firm has not been performed.

Note: (b) (4)

A post-approval or routine inspection is recommended for (b) (4)), the device constituent part manufacturer, who is manufacturing finished general use syringes or other products that are 510(k) products or CDRH approved products. This site has not been FDA inspected since 2011.

DOCUMENTATION REVIEW

Device Consituent Part Type: Prefilled Syringe
Device Consituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD
Device Consituent Part Clearance Type : 510(K)
Device Consituent Part Clearance Number: (b) (4)
Combination Product BLA 761039 Proposed Indication for Use: Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anticancer 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 ☐	NO ☒	NA ☐
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3. Is the final combination product meant for emergency use?	YES ☐	NO ☒	UNK ☐
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☒	NO ☐	UNK ☐
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 ☐	NO ☒	UNK ☐
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 ☒	NO ☐	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

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.

This is a follow-up review following complete response to information request by the firm to CDER. A Quality Systems review of the initial submission, ICC1600756, was completed on January 26, 2017, with the following CDRH Office of Compliance Recommendation:
1. UDENYCATM, BLA 761039 IR information –Adequate. No Deficiencies remaining.
2. BLA 761039 - Approvable
3. Pre-approval inspection recommended.

On June 14th, 2018, the firm confirmed that there had been no significant changes made to their QS since the last QS review completed by CDRH for BLA 761039 on January 26, 2017. In particular, the firm confirmed that no changes were made to following QS requirements; Management Responsibility (21 CFR 820.20), Design Control, General (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and Corrective and Preventive Action (21 CFR 820.100).

A medical device QS inspection was conducted at the applicant, Coherus BioSciences, Inc., between 03/13 -03/16, 2017, and was classified NAI. A cGMP inspection was conducted at the final combination product manufacturer, (b) (4) , and was classified NAI.

Therefore a full review is not warranted given the low risk nature of the device, the previous QS documentation review that was deemed adequate, and the adequate compliance history for both the applicant and final combination product manufacturer.

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.

Documentation Review Recommendation:

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 761039 Udenyca, pegfilgrastim-xxxx (biosimilar) Pre-filled Syringe, Solution for Injection, 6 mg / 0.6 mL 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.

For a complete documentation review of the application for compliance with the Quality System Requirements please see ICC1600756 (ICCR2016-00261).

A post-approval or routine inspection is recommended for the following facilities:

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

OC Decision: **Approvable (Recommend approval to CDER)**

Reviewer: Louis R. Corbin -S3
Digitally signed by Louis R. Corbin -S3
Date: 2018.06.20 11:39:27 -04'00'

Branch Chief or Lead CSO: Jamie Kamon-brancazio -S
Digitally signed by Jamie Kamon-brancazio -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001568505, cn=Jamie Kamon-brancazio -S
Date: 2018.07.25 14:57:29 -04'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

Through: John J. Alexander, M.D., M.P. H., Deputy Director
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

To: Division of Hematology Products (DHP)

Drug: CHS-1701/Udenyca (proposed biosimilar to Neulasta [pegfilgrastim])

Application Number: BLA 761039 (IND 115573)

Sponsor: Coherus Biosciences, Inc.

Proposed Indications: 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.

Proposed Dosage Form & Route of Administration: 6 mg/0.6 mL solution in a single use prefilled syringe administered by subcutaneous injection.

Proposed Dosing Regimen: 6 mg administered subcutaneously once per chemotherapy cycle.

Consult Request: DHP requests assistance in review of the efficacy supplement, participation in the labeling discussions, and preparation for the Pediatric Review Committee (PeRC) meeting.

Materials Reviewed:

- Division of Pediatric Maternal Health (DPMH) consult request
- Agreed upon initial Pediatric Study Plan (iPSP) for CHS-1701, IND 115573 (July 23, 2015) and Amended iPSP (September 12, 2016)
- Current Neulasta (pegfilgrastim) labeling (April 28, 2016) per Drugs@FDA
- Prior DPMH review for CHS-1701 (IND 115573) dated August 30, 2016
- Sponsor's proposed labeling for CHS-1701 (September 9, 2016)

Consult and Regulatory Background:

On August 9, 2016, Coherus Biosciences, Inc. submitted a BLA for CHS-1701 under the 351(k) pathway as a proposed biosimilar to Neulasta (pegfilgrastim). Neulasta (pegfilgrastim) is a leukocyte growth factor licensed by Amgen, Inc. and was first approved in 2002. Pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.[1]

Neulasta has the following indications:

- 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.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome or ARS)

Neulasta was granted orphan exclusivity for this indication and as such, Coherus cannot seek licensure of CHS-1701 for that indication until the orphan exclusivity expires. Therefore, Coherus only plans to seek approval for the febrile neutropenia indication.

DHP requested DPMH assistance in review of the efficacy supplement; providing labeling recommendations for pregnancy, lactation and pediatric use; and preparing for the Pediatric Review Committee (PeRC) meeting.

[1] Current Neulasta (pegfilgrastim) labeling (April 28, 2016)

Reference ID: 4109744

Pediatric Assessment:

Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(m) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred. The Agency confirmed agreement with the agreed initial Pediatric Study Plan (iPSP) on July 23, 2015. However, at the time of submission, the approach to address PREA was still under discussion in the Agency. (See the prior DPMH consult review for CHS-1701, IND 115573 dated January 14, 2016 for further discussion on the pediatric development plan.) Accordingly, in the iPSP, Coherus proposed to demonstrate biosimilarity to Neulasta (pegfilgrastim) and defer studies in patients birth to 17 years of age while the recommended approach to address PREA was being determined.

In a meeting held on August 8, 2016, Coherus was given the following advice:

> "Since you intend to seek licensure for the "neutropenia" indication in adults for which US-licensed Neulasta was previously licensed, you must address PREA. You may fulfill PREA requirements by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating pediatric information from the reference product to CHS-1701."
>
> "As stated above, CHS-1701 is subject to PREA. Therefore, your application must include a pediatric assessment, which includes the 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 you can request a deferral of the pediatric assessment pending development of an appropriate pediatric presentation. If you choose the latter approach, the development of an appropriate pediatric presentation will be required as a post marketing requirement (PMR)."

Although the agreed iPSP was included in the initial BLA submission, the applicant agreed to provide an updated plan based on the above advice within 30 days of submission.

Accordingly, Coherus submitted a proposed amended iPSP to IND 115573 on September 9, 2016 and to BLA 761039 on October 26, 2016 in which they provided scientific

Reference ID: 4109744

justification to support biosimilar extrapolation (b) (4) [redacted]. The following advice was provided to the sponsor on March 13, 2017 regarding their pediatric study plan:

> Under PREA, you are required to provide a pediatric assessment which includes the development of an appropriate pediatric presentation. The development of a prefilled syringe with graduated markings to allow dosing to patients <45 kg would be appropriate. The pediatric presentation(s) can be developed prior to approval, or you can request a deferral of the pediatric assessment pending development of an appropriate pediatric presentation. If you choose the latter approach, the development of an appropriate pediatric presentation will be required as a post marketing requirement (PMR) and provide a timeline for the development of your pediatric presentation. The proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. Please update your plan to address PREA, and revise sections 1.9.4.5 and 1.9.4.7.

Ultimately, the applicant provided an updated pediatric plan on April 14, 2017 (b) (4) [redacted] They also propose to defer development of their pediatric presentation through 2021.

Conclusion:

DPMH agrees with the final pediatric plan proposed by Coherus to extrapolate pediatric data from the reference product, Neulasta, based on the biosimilar development program and to defer the submission of an age-appropriate presentation to fulfill PREA. DHP has determined that CHS-1701 will receive a Complete Response (CR) due to immunogenicity, product quality and microbiology issues, and labeling discussions will resume once a response is submitted.

DPMH participated in the internal meetings from September 2016 to May 2017. DPMH also provided comments on the Advice Letter to Coherus. Our input is reflected in the written comments in the Advice Letter dated March 13, 2017.

Reference ID: 4109744

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

/s/

ERICA D RADDEN
06/09/2017

JOHN J ALEXANDER
06/09/2017

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, 2017

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

FROM: Makini K. Cobourne-Duval, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

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

SUBJECT: Review of EIRs covering BLA 761039 for clinical inspections conducted at the following facilities:

- Spaulding Clinical Research, LLC, West Bend, WI
- Wisconsin Diagnostic Laboratories, Milwaukee, WI
- WCCT Global, LLC, Cypress, CA
- Medpace Clinical Pharmacology Unit, Cincinnati, OH
- Medpace Reference Laboratories, Cincinnati, OH
- Vince & Associates Clinical Research Inc., Overland Park, KS
- ICON Early Phase Services, San Antonio, TX

Inspection Summary

Inspections of the clinical and the absolute neutrophil count (ANC) data from study CHS 1701-05 and the clinical data from study CHS 1701-04 for BLA 761039 (proposed biosimilar to pegfilgrastim) were conducted at multiple sites by ORA investigators as indicated the table below. Based on the information in the EIRs, this reviewer recommends accepting the clinical and ANC data from study CHS-1701-05 and the clinical data from study CHS-1701-04 for further Agency (FDA) review, with the exception of the following data:

1) Study CHS-1701-04 from Vince and Associates
2) Study CHS-1701-05 - selected subjects from Spaulding Clinical Research and Wisconsin Diagnostic Laboratories

Inspected Studies

Sponsor: Coherus BioSciences, Redwood Shores, CA

Study	Medication	Analysis	Study Site	ORA Investigator	Recommendation
CHS-1701-05	CHS-1701 (pegfilgrastim)	CLINICAL	Spaulding Clinical Research, West Bend, WI	Denise Burosh	Partially Acceptable
			WCCT Global, LLC, Cypress, CA	Yvonne LaCour	Acceptable
			Medpace Clinical Pharmacology Unit, Cincinnati, OH	Marcia Worley	Acceptable
			ICON Early Phase Services, San Antonio, TX	Joel Martinez	Acceptable
		ABSOLUTE NEUTROPHIL COUNT	Wisconsin Diagnostic Laboratories, Milwaukee, WI	Corey Reno	Partially Acceptable
			Medpace Reference Laboratories, Cincinnati, OH	Marcia Worley	Acceptable
			ICON Early Phase Services, San Antonio, TX	Joel Martinez	Acceptable
CHS-1701-04	CHS-1701 (pegfilgrastim-(b) (4))	CLINICAL	Spaulding Clinical Research, West Bend, WI	Denise Burosh	Partially Acceptable
			Medpace Clinical Pharmacology Unit, Cincinnati, OH	Marcia Worley	Acceptable
			ICON Early Phase Services, San Antonio, TX	Joel Martinez	Acceptable
			Vince & Associates Clinical Research Inc., Overland Park, KS	Lori Gioia	Not Acceptable

Study Number: CHS-1701-05

Study Title: "A Randomized, Single-Blind, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Bioequivalence of CHS-1701 (Coherus Pegfilgrastim) with Neulasta® in Healthy Subjects."

Study Dates: 01/12/2016 (Study Initiation Date) through 06/21/2016 (Study Completion Date)

Study Number: CHS-1701-04

Study Title: "A Randomized, Double-blind, Two-period, Parallel-arm Study to Assess the Immunogenicity of Subcutaneous Doses of CHS-1701 (Pegfilgrastim-[redacted] with Two Subcutaneous Doses of Neulasta® in He Subjects." (b) (4)

Study Dates: 04/20/2015 (Study Initiation Date) through 12/18/2015 (Study Completion Date)

Note: For the sites discussed below, the information covers both studies with the exception of WCCT Global and Vince & Associates. The inspection at WCCT Global covered only study CHS-1701-05. The inspection at Vince & Associates covered only study CHS-1701-04.

CLINICAL

ORA investigators Burosh, Gioia, LaCour, Martinez, and Worley audited the clinical portions of studies CHS-1701-05 and CHS-1701-04 as indicated for the sites listed in the table above during January 2017 through March 2017. The items the investigators reviewed at each site included randomization, blinding, adverse events, subject data, and records related to the IRB.

For **WCCT Global, LLC** and **ICON Early Phase Services,** there were no discussion items or Form FDA-483s issued at the close of the inspections.

The following observations were recorded in the EIRs for the **Spaulding, Medpace,** and **Vince & Associates** sites:

1) **Spaulding Clinical Research, LLC**
   A one item Form FDA-483 and three discussion items were issued to Spaulding Clinical Research, LLC at the close of inspection.

Form FDA 483 observations, Firm's Response to Form 483 observations, and OSIS Assessment

Form FDA-483 Observation

An investigation was not conducted in accordance with the signed statement of investigator, signed agreement with the sponsor, and investigational plan.

Specifically,

A) During the conduct of Coherus study #CHS-1701-05 your firm allowed subjects (# (b) (6)) with clinically significant laboratory results to be retested at the time of screening and determination of eligibility. The protocol does not allow for retesting of subjects with clinically significant laboratory results and the subjects should have been determined to be ineligible.

B) During the conduct of Coherus study #CHS-1701-05 your firm allowed subject # (b) (6) with clinically significant laboratory Hematocrit and Hemoglobin results to be retested at Day -1, Period 3. The protocol does not allow for retesting of subjects with clinically significant laboratory results and the subjects should have been determined to be ineligible to continue in the study.

C) During the conduct of Coherus study #CHS-1701-04 subject # (b) (6) had a clinically significant ALT laboratory result of 129 u/L (normal range 8-41 u/L) at Day 13 visit, during period one. This clinically significant laboratory result was not reported by your firm as an adverse event which is required by protocol section 6.3.4 (v.3.0, 08May2015).

Firm's Response to Form FDA 483 Observation

Observations A&B:

The firm's use of the term "clinically significant" was only intended to indicate a medically significant lab result that should be recorded as an adverse event. The firm states that in the future, the "clinically significant" term will be used to indicate a lab result value that is truly medically significant and likely requires some level of medical follow-up. According to the firm's response, the other values that are outside of acceptable protocol ranges, but are not considered medically significant will be defined as "not clinically significant/not acceptable".

Observation C:

In the transition of the study from one coordinator to another, the clinically significant lab result, which was reported to the initial coordinator, was not communicated to

next coordinator due to an oversight. However the oversight was discovered several weeks later during data reconciliation, added to the protocol deviation log. The firm stated that they reported the AE to the sponsor and will be implementing a transition plan to ensure proper communication between project coordinators. The firm also states that they are reviewing their process to ensure clinically significant results are properly documented and acted upon.

OSIS Assessment

- *Observations A&B:*
  OSIS recommends excluding the aforementioned subjects (# (b) (6) for observation A and # (b) (6) for observation B) in study CHS-1701-05 because they did not meet the eligibility requirements for study CHS-1701-05.

- *Observation C:*
  OSIS recommends that the review division evaluate the clinical significance of the laboratory abnormality (elevated ALT) for the subject # (b) (6) in study CHS-1701-04.

Other Issues Discussed in the EIR

A) Two of the freezers used for storage of the PK samples did not have current calibration. These two freezers were last calibrated on 10/27/15 and the calibration sticker on the side states calibration was due 10/2016. Final shipment of the study samples was in July 2016; however they are using these freezers for current study sample storage.

B) The need for the improvement of the documentation regarding what study drugs remained at the end of the study and a list of what was returned to the sponsor.

C) The need for the improvement of drug accountability records to show total inventory when dosing occurs and when returned to inventory.

OSIS Assessment

- Issue A:
  Given that studies CHS-1701-05 and CHS-1701-04 were completed prior to 10/2016, this observation would not affect the reliability of the data for the audited studies.

- Issue B:
  This observation would not affect the reliability of the data.

- Issue C:
  Given the fact that there are no apparent dosing discrepancies for studies CHS-1701-05 and CHS-1701-04, based on the dosing records, this observation would not affect the reliability of the data.

2) Medpace Clinical Pharmacology Unit

No Form FDA-483 was issued to Medpace at the close of inspection. However, there were two discussion items for this site.

Issues Discussed in the EIR

A) A protocol deviation affecting study CHS-1701-04 in which specimen collection did not follow the site's SOP and resulted in the need to re-collect the specimen 2 hours late

B) Documentation issues:
- Study CHS-1701-04
  - o incomplete information regarding the history of a potential latex allergy (Subject (b) (6)
  - o failure to obtain the signature of a study pharmacist who left employment during the course of the study
- Study CHS-1701-05
  - o one subject (Subject (b) (6)) who had a missing signature on one of the two places on the informed consent form
  - o delayed documentation of study training for protocol amendments (Amendment 3)

OSIS Assessment

- Issue A:
  Due to the fact that study CHS-1701-04 is an immunogenicity study, the timing of blood draw for this study is less critical compared to that for a pharmacokinetic study. Therefore, it is OSIS's assessment that the fact the specimens were collected 2 hours late would not affect the reliability of the data.
  The review division should be aware that according to the EIR, this observation affects subjects in group 2, not group 1 as indicated in Listing 16.2.2.1.
- Issue B:
  Based on reviewing the information in the EIR for studies CHS-1701-05 and CHS-1701-04, this reviewer concludes that the documentation issues mentioned above would not affect the reliability of the data for either study.

3) **Vince & Associates Clinical Research Inc.**
This EIR review covers two inspections conducted at this site: 1) a for-cause inspection in December 2016 for the clinical investigator, and 2) a surveillance inspection in January 2017 for the site.

- ***December 2016 Inspection:*** At the close of this for-cause inspection, a Form FDA-483 was issued to the investigator for failing to conduct the study according to the investigational plan.

Form FDA 483 observations, Firm's Response to Form 483 observations, and OSIS Assessment

Form FDA 483 observation
An investigation was not conducted in accordance with the investigational plan.

Specifically, for study CHS-1701-04 titled "A Randomized, Double-Blind, 2-Period Parallel-Arm Study to Assess the Immunogenicity of 2 subcutaneous doses of CHS-1701 (Coherus Pegfilgrastim) and 2 subcutaneous doses of Neulasta in Healthy Subjects", 33 out of 35 subjects were dosed incorrectly in study period 2. These subjects should've received the same study drug in period 2 as in period 1, but received the opposite study drug instead.

Firm's response to Form FDA 483 observation
The firm stated that the error was discovered by the unblinded Clinical Research Associate during a routine monitoring visit. According to the EIR, the investigator stated that he was blinded and was not aware of the dosing error until he was informed by the pharmacist. The error was discovered while the study was ongoing by the monitor. The firm reported to have conducted a formal investigation and developed and implemented preventative steps.

OSIS Assessment
This observation will have a significant impact on the reliability of the data due to the fact that the protocol was not carried out according to the investigational plan attributed to the dosing error. This dosing error affected a majority of the subjects for this study at this site and therefore all of the data from the Vince & Associates site for study CHS 1701-04 should be excluded.

Other Issues Discussed in the EIR

There was an issue with unblinding the wrong subject ((b) (6); randomization #(b) (6)) due to a SAE instead of the intended subject ((b) (6); randomization #(b) (6)).

OSIS Assessment

While there was an issue with unblinding the wrong subject, the correct subject was recorded in the SAE listing. Given that unblinding was limited to a single subject, the impact on the integrity of the study is not likely significant.

- ***January 2017 Inspection:*** At the close of the inspection for Vince & Associates Clinical Research Inc., no Form FDA-483 was issued. However, there was one discussion item noted in the EIR.

  Issues Discussed in the EIR

  The need for the improvement of documentation to completely record corrections and ensure the clarity of reasons why the corrections were made. It was noted in the EIR that there were several instances where corrections were made and it could not be determined why. There was also one adverse event not reported. The missing AE was a toothache (Subject (b) (6)).

  OSIS Assessment

  This observation impacts the reliability of the data for this study due to the fact that there are several instances corrections without explanation of why these corrections were made.

  Taking into account the 483 observation from the 2016 inspection and a discussion item from the 2017 inspection, OSIS recommends excluding the data from Vince & Associates Clinical Research for study CHS-1701-04.

ABSOLUTE NEUTROPHIL COUNT (ANC)

Note: Inspections of sites that reported ANC data were conducted for only study CHS-1701-05.

ORA investigators Martinez, Reno, and Worley audited the clinical portions that focused on the ANC data at the sites listed in the table above during January through March 2017.

At **Medpace Reference Laboratories** and **ICON Early Phase Services,** no issues were observed for the reported ANC data and no discussion items or Form FDA-483s were issued at the close of the inspections.

However, a four item Form FDA-483 was issued to **Wisconsin Diagnostic Laboratories** at the close of inspection.

Form FDA 483 observations, Firm's Response to Form 483 observations, and OSIS Assessment

Form FDA 483 observations

1) Procedure "Client Service Holds, (b) (4)" was not followed for entering a CSHold. No documented order note exists that includes a detailed description of the issue/problem that occurred for eight (8) samples received on 3/2/16 from Spaulding Clinical for testing. The manifest includes the following barcodes ((b) (6), (b) (6), (b) (4)). No results exist for these barcodes. Hand written next to each barcode are the following barcodes respectively ((b) (6), (b) (6)). It is unclear whether the demographic information (subject ID, collection date/time) was verified to be the same for these bar coded specimens. Results were obtained for these samples and were reported to FDA as "unscheduled" and include the same subject ID, time-point/collection date/times as the original barcode set listed on the manifest.
2) Procedure "Test Not Performed Charge/Credit Procedure" was not followed for deletion of ordered test. No comment is recorded for reason test was canceled and deleted for specimen barcodes ((b) (6), (b) (6)).
3) Result obtained manually for specimen (b) (6) (absolute neutrophil 35.42) was not reported to FDA.
4) Procedure "Refrigerator and Freezer Monitoring, (b) (4) (b) (4) was not followed. Temperature was not monitored for

eight (8) refrigeration units on the following dates (2/26/16, 3/1/16, 3/18/16, 3/27/16, 5/2/16, 5/8/16). The procedure's "Action Plan" was also not followed for out of range temperatures for the following dates and refrigeration units (3/3/16- R-Mon; 3/4/16- R-Wed; 4/2/16- R-Mon & R-Wed; 4/6/16- R-Wed; 4/14/16- R-Wed; 4/30/16- R80; 5/1/16- R-Wed). No documentation of procedure training exists for employees that performed this temperature monitoring.

Firm's response to Form FDA 483 observation

Observations 1, 2 & 4:
The firm intends to take corrective action including providing additional training.

Observation 3:
The firm acknowledges the importance of data transmission. The firm reports they will draft a policy/procedure to clarify the data transmission process for reconciling results.

OSIS assessment

- Observation 1:
  No information was provided in the firm's response whether original typed specimen (barcode) numbers match the handwritten specimen (barcode) numbers. These subjects' ANC samples were recorded as unscheduled in Wisconsin Diagnostic Lab (WDL) Spaulding ANC Report (Site 003). We recommend that the review division exclude these unscheduled ANC samples ((b) (6), (b) (6)) from the ANC analysis for study CHS-1701-05 due to the fact that there is uncertainty regarding the identification of the samples. The corresponding subject numbers for these unscheduled ANC samples are included in the Wisconsin Diagnostic Lab (WDL) Spaulding ANC Report (Site 003).

- Observation 2:
  Although these samples are listed, no value is reported. Therefore, this observation does not impact the acceptability of the ANC data for study CHS-1701-05.

- Observation 3:
  OSIS recommends that the review division include the result of this missing sample for subject (b) (6) into the ANC analysis for study CHS-1701-05.

- Observation 4:
  As indicated in Exhibit 3, according to the temperature monitoring logs for the refrigeration units, when the

refrigeration units were out of range, the temperature varied by a few degrees, dropping from 4 degrees Celsius to the lowest observed temperature of 0 degrees Celsius. This slight fluctuation in temperature would not affect the integrity of the samples and therefore the results obtain from the analysis of these sample would not impact the reliability of the data from study CHS-1701-05.

Other Issues Discussed in the EIR

Wisconsin Diagnostic Laboratories also had two discussion items at the close of inspection:

A) The need to improve documentation practices to ensure corrections are made appropriately (i.e. lining out mistake, initial, dating, and footnoting explanation when necessary instead of overwriting or scribbling out).

B) The maintenance of records according to the record retention requirement.

OSIS assessment

It appears that discussion item A is related to documentation for instruments. However, no significant issues were observed with calibration, quality control or maintenance. Therefore, these observations would not impact the reliability of the data for study CHS-1701-05.

For discussion item B, there were no specific issues related to study CHS-1701-05 that were discussed in the EIR.

Recommendation

Following the evaluation of the EIRs for Spaulding Clinical Research, LLC; Wisconsin Diagnostic Laboratories; WCCT Global, LLC; Medpace Clinical Pharmacology Unit; Medpace Reference Laboratories; Vince and Associates Clinical Research Inc.; and ICON Early Phase Services, this reviewer concludes that the clinical and absolute neutrophil count (ANC) data from the studies CHS-1701-05 and the clinical data from CHS-1701-04 (BLA 761039) are reliable and recommends accepting the data for further Agency (FDA) review, with the exceptions listed below.

Study CHS-1701-04

- Data from Vince & Associates Clinical Research should be excluded.
- The review division should evaluate the clinical significance of the laboratory abnormality (elevated ALT value) for subject (b) (6) at the Spaulding site.

Study CHS-1701-05

- OSIS recommends excluding the following results:
  A) Spaulding Clinical Research: subjects (b) (6), (b) (6).
  B) Wisconsin Diagnostic Laboratories: the unscheduled ANC samples ((b) (6), (b) (6), (b) (6) from the ANC analysis.
- OSIS recommends including the result of the missing sample for subject (b) (6) at the Wisconsin Diagnostic Laboratories site into the ANC analysis.

Final Site Classifications:

VAI – Spaulding Clinical Research, LLC, West Bend, WI
FEI: 3008921101

VAI – Wisconsin Diagnostic Laboratories, Milwaukee, WI
FEI: 2171821

NAI – WCCT Global, LLC, Cypress, CA
FEI: 3006237846

NAI – Medpace Clinical Pharmacology Unit, Cincinnati, OH
FEI: 3009858732

NAI – Medpace Reference Laboratories, Cincinnati, OH
FEI: 3009295831

NAI* – Vince and Associates Clinical Research Inc, Overland Park, KS
FEI: 3007544065
**Site inspection was preceded by a recent for-cause inspection that resulted in a Form FDA-483 issued to the clinical investigator and the final classification of VAI.*

NAI – ICON Early Phase Services, San Antonio, TX
FEI: 3007158681

cc:
OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Cho/Choi/Skelly/Au/Cobourne-Duval
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OND/DHOP/Farrell

Draft: MCD 04/14/2017; 04/17/2017; 04/18/2017; 04/19/2017
Edit: SA 4/18/2017; JC 4/18/2017

ECMS:
Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Spaulding Clinical, West Bend,, WI, USA/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Wisconsin Diagnostic Laboratories, Wisconsin, WI/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ WCCT Global LLC, CYPRESS, CA/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Medpace Clincal Pharmacology Unit, Cincinnati, Ohio/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Medpace Reference Laboratories, Cincinnati, Ohio/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Vince Associates Cliinical Research, Overland Park KS/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ ICON Development Solutions and ICON Early Phase Services LLC San Antonio,TX/BLA 761039_CHS-1701 Proposed biosimilar to Pegylated Filgrastim

OSI file #: 7288
FACTS: 11684349

Attachment 1: Additional clarification from ORA investigator regarding the auditing of the ANC data for the ICON, San Antonio site.

Attachment 1

From: Martinez, Joel
To: Cobourne-Duval, Makini
Subject: RE: EIR_ & EIR Endorsement_ ICON Development Solutions_BLA 761039
Date: Wednesday, April 12, 2017 11:20:11 AM

Hi Makini,

1. I found no issues with the firm's lab instrumentation and in addition, the lab is CLIA certified and I reviewed proficiency testing results and found no issues.
2. I found no evidence to show samples were re-analyzed. All ANC results were consistent with what was reported in the CSR.
3. All WBC and ANC counts were reported in the firm's lab reports. I considered those to be the raw data and did not find any issues.
4. I saw no evidence of any samples being stored overnight and having to be read manually the following day.

Joel Martinez
Investigator
Bioresearch Monitoring Specialist
U.S. Food & Drug Administration
San Antonio Resident Post/Dallas District
PHONE: (210 308-1409
FAX: (210) 308-1420

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

From: Cobourne-Duval, Makini
Sent: Tuesday, April 11, 2017 2:00 PM
To: Martinez, Joel
Cc: Au, Stanley
Subject: FW: EIR_ & EIR Endorsement_ ICON Development Solutions_BLA 761039

Hello Joel,

I am composing the EIR review for BLA 761039 which includes the inspection you covered at ICON Early Phase Services in San Antonio. There were 2 studies (CHS-1701-05 and CHS-1701-04) that were requested for inspection, but study CHS-1701-05 also had two requested inspection components: one for the clinical portion and a separate clinical lab portion with a focus on the ANC data. Does the EIR you submitted cover both components of study CHS-1701-05?

If both components were covered in the submitted EIR, can you provide more details regarding the information that was audited for the clinical lab portion ? For example, the potential items that are recommended for auditing include the following:

1) Please audit the maintenance records, verify that the instruments have been calibrated, confirm that the raw laboratory data matches that in the study report submitted to the Agency, and determine if there were any issues/problems encountered that may have impacted the reported results.

2) Please determine if there were any samples that were reanalyzed but the lab didn't document and if so, why they were reanalyzed or where the final concentration wasn't consistent with the study report info.

3) Please check for the existence of a standardized method for measuring white blood cells in order to derive the ANC.

4) Please determine if any samples stored overnight that could not be read automatically and required a manual count or were samples freshly processed/analyzed?

Can you provide detailed information to add to the EIR along these lines?

Thanks,

Makini

Makini K. Cobourne-Duval, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
FDA/OMPT/CDER/OTS/OSIS
WO Bldg 51, Rm 5323
(301) 348-3006

From: Nkah, Shila
Sent: Friday, March 31, 2017 9:27 AM
To: Au, Stanley; Cobourne-Duval, Makini; Miller, Dinah
Subject: EIR_ & EIR Endorsement_ ICON Development Solutions_BLA 761039

Hi Stanley,

We received the EIR for ICON Development Solutions under BLA 761039.

Since Makini prepared the inspection memo and background package for this site, she is automatically assigned to finalize the review unless you determine otherwise.

Note that the OSIS review due date for this BLA is April 19, 2017.

Let me know if you have questions.

@ Dinah, Please update complis with the following

- EIR receipt date - **March 20, 2017**
- Field class - NAI
- Kindly upload the EIRs in ECMS under the site folder.

Clinical	Medpace Reference Laboratories (ANC), Cincinnati, OH
Clinical	Wisconsin Diagnostic Laboratories (ANC) Formerly Dynacare, , Milwukee, WI
Clinical	ICON Early Phase Services, LLC (ANC), San Antonio, TX ,
Clinical	Consolidated Medical Bio-Analysis, Inc. (ANC),Cypress, CA
Clinical	Medpace Clinical Pharmacology Unit,, Cincinnati, OH-
Clinical	ICON Early Phase Services, LLC (ANC), San Antonio, TX,
Clinical	West Coast Clinical Trials,, Cypress, CA -
Clinical	Spaulding Clinical Research, West Bend, WI –
Clinical	Vince & Associates Clinical Research, Overland Park, KS

Thanks,
Shila

From: Scullard, Donald
Sent: Monday, March 27, 2017 10:59 AM
To: Nkah, Shila
Cc: Cummings, Patrick
Subject: Wisconsin Diagnostic Laboratories Assignment - Complete

Shila,

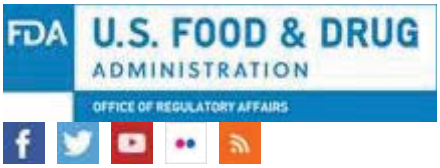
This email is to notify you the assignment for Wisconsin Diagnostic Laborites has been completed. All inspection documents are available for review on OSAR. Let me know if there is anything else you need.

http://osar.fda.gov/oraosar/#/search/2171821

Wisconsin Diagnostic Laboratories
FEI: 2171821
Assignment: 11684349
Date: 3/7/2017

Don Scullard
Consumer Safety Technician
Minneapolis District Office

Office of Regulatory Affairs
U.S. Food and Drug Administration
Tel: 612-758-7228
Donald.Scullard@fda.hhs.gov



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/s/

MAKINI COBOURNE-DUVAL
04/19/2017

STANLEY AU
04/19/2017
Acting Team Lead

SEONGEUN CHO
04/19/2017

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 18, 2017

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

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

Xiaohan Cai, Ph.D.
Staff Fellow
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

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

THROUGH: Sam H Haidar, Ph.D., R.Ph.
Deputy Director,
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Analytical inspection at (b) (4) , covering BLA 761039

Inspection Summary:

At the request of the Office of New Drugs (Division of Hematology Products), the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portions of studies CHS-1701-04 and CHS-1701-05 conducted at (b) (4) in (b) (4). Based upon the results of this inspection, we

recommend that: **1)** study data from pharmacokinetic (PK) studies (b) (4)20076307 and (b) (4)20090980 be accepted for agency review, with the exception of specific study samples listed in **Table 1**, but that the review division evaluate the updated study data in (b) (4)20076307 Report Amendment 1 and (b) (4)20090980 Report Amendment 1; **2)** study data from anti-drug antibody (ADA) studies (b) (4)20076308/ (b) (4)20079609 and (b) (4)20090979 be accepted for agency review, but that the review division note several concerns (see below); and 3) study data from neutralizing antibody (NAb) studies (b) (4)20076308/ (b) (4)20079609 and (b) (4) 20090979 **not** be accepted for agency review.

Studies audited during this inspection:

Study Number: CHS-1701-04 (BLA 761039)
Study Title: "A Randomized, Double-blind, Two-period, Parallel-arm Study to Assess the Immunogenicity of Two Subcutaneous Doses of CHS-1701 (Pegfilgrastim-(b) (4) with Two Subcutaneous Doses of Neulasta® in Healthy Subjects"
Clinical Dates: April 20, 2015 through December 18, 2015

Study Number: CHA-1701-05 (BLA 761039)
Study Title: "A Randomized, Single-Blind, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Bioequivalence of CHS-1701 (Coherus Pegfilgrastim) with Neulasta® in Healthy Subjects"
Study Dates: January 12, 2016 through June 21, 2016

OSIS scientists Kara A. Scheibner, Xiaohan Cai, and Amanda E. Lewin, along with ORA Investigator Thea Grome, conducted the inspection of analytical portions of these studies from (b) (4).

The bioanalytical audit included a thorough review of facilities and equipment, training records, current bioanalytical SOPs, study records and correspondence, method validation records, and interviews and discussions with CRL's management and staff.

At the conclusion of the inspection, a seven-item Form FDA-483 was issued at (b) (4) (**Attachment 1**). Additional minor observations were discussed throughout the week, and at the closing meeting. We received a formal response to the FDA-483 observations from (b) (4) on (b) (4) (**Attachment 2**), and additional information on (b) (4). The FDA-483 observations, (b) (4)

response, and our evaluation of the observations and responses follow.

(b) (4)

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(b) (4)

Recommendation:

Following review of the EIR and bioanalytical data for studies CHS-1701-04 and CHS-1701-05, we recommend the following:

Pharmacokinetic Assays: We recommend that study data from pharmacokinetic (PK) studies (b) (4)20076307 and (b) (4)20090980 be accepted for agency review. However, we note that specific study samples listed in Table 1 be excluded from analysis given that interference from hemolyzed samples impacted results at the QC1 level (400 pg/mL), and hemolyzed samples with a concentration lower than the QC3 concentration may not be accurate. In addition, we recommend evaluating the updated study data in (b) (4) 20076307 Report Amendment 1 and (b) (4)20090980 Report Amendment 1.

Anti-Drug Antibody Assays: We recommend that study data from ADA studies (b) (4)20076308/(b) (4)20079609 and (b) (4)20090979 be accepted for agency review, but recommend evaluating updated study data in the amended reports. However, we note that revised titer values and re-evaluation of study data using the new cut points were not included in the amended study reports for Studies (b) (4)20076308 and (b) (4)20090979. We also note that potentially ADA-positive samples were not captured in the screening assay, due to the potential variability of low ADA-positive study samples in the absence of a relevant LPC.

Neutralizing Antibody Assays: We recommend that study data from NAb studies (b) (4)20076308/(b) (4)20079609 and (b) (4)20090979 **not** be accepted for agency review.

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

Xiaohan Cai, Ph.D.
DGDBE, OSIS

Amanda E. Lewin, Ph.D.
DNDBE, OSIS

Final Classification:

VAI: (b) (4)
(FEI#: (b) (4))

CC:
OTS/OSIS/Kassim/Choe/Taylor/Turner-Rinehardt/Fenty-Stewart/Nkah/Miller/Kadavil/Mitchell
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Lewin
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au/Scheibner/Cai
Draft: XHC 03/22/2017, KAS 04/18/2017
Edit: MFS 04/18/2017; SHH 04/18/2017
OSIS file #: BE7288
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4)
FACTS: (b) (4)

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/s/

AMANDA E LEWIN
04/18/2017

XIAOHAN CAI
04/18/2017

KARA A SCHEIBNER
04/18/2017

SAM H HAIDAR
04/18/2017

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, 2017

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

FROM: Stanley Au, Pharm.D., BCPS
Pharmacologist (Acting Team Lead)
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

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

SUBJECT: **Decline to conduct biopharmaceutical inspection: Consolidated Medical Bio-Analysis, Inc. site (BLA 761039-pegfilgrastim)**

The Office of Study Integrity and Surveillance (OSIS) received a biopharmaceutical inspection request for BLA 761039 from the Division of Hematology Products dated September 19, 2016. One of the requested inspection sites was Consolidated Medical Bio-Analysis located at 10700 Walker Street, Cypress CA 90630. Specifically, an inspection of the absolute neutrophil count (ANC) data was requested.

OSIS declines to conduct a bioequivalence inspection of the Consolidated Medical Bio-Analysis site. According to the Office of Regulatory Affairs, due to resource limitations, the inspection at Consolidated Medical Bio-Analysis has not been initiated as of April 11, 2017.

In order to meet the April 19, 2017 OSIS review due date that was requested by the review division for an establishment inspection report (EIR) review and to maintain good review management practice (GRMP) timelines for the application, OSIS determined that an inspection of the Consolidated Medical Bio-Analysis site could not be accomplished within the specified timelines.

Inspections of the other requested sites that reported absolute neutrophil count (ANC) data for BLA 761039 are complete. The EIR review for these inspections will be provided when it is finalized.

CC:
OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah/
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au/Cobourne-Duval

Draft: SA 04/11/2017, 04/12/2017
Edits: JC 4/11/2017, 4/12/2017
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/
Clinical Sites/Consolidated Medical Bio-Analysis, Cypress, California

BE File #: 7288 (BLA 761039)

FACTS: 1168434

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/s/

STANLEY AU
04/12/2017

SEONGEUN CHO
04/12/2017

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: March 13, 2017

To: Joslyn Brunelle, Biologist
Office of Biotechnology Products (OBP)
Division of Biotechnology Review & Research IV
Center for Drug Evaluation and Research (CDER)

From: LCDR Keith Marin, Senior Regulatory Review Officer

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for BLA 761039

Applicant	Coherus
Indication for Use	For decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Drug / Biologic Constituent	Udenyca, pegfilgrastim-xxxx (biosimilar)
Device Constituent	Pre-filled syringe

Recommendation: Based on information reviewed BLA 761039, the sponsor has provided sufficient information for the pre-filled syringe. All interactive review questions have been satisfactorily addressed; As a result, CDRH/ODE recommends approval for the BLA for this combination product.

Digital Signature Concurrence Table	
Reviewer	Keith G. Marin -A Digitally signed by Keith G. Marin -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -A, 0.9.2342.19200300.100.1.1=0011250397 Date: 2017.03.13 13:51:54 -04'00'
Branch Chief	Alan M. Stevens -S Alan M. Stevens -S 2017.03.22 07:29:49 -04'00'

Review Contents

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I. Purpose / Background

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding a review request for BLA 761039. The device constituent of this combination product consists of a pre-filled syringe designed to deliver Udenyca, pegfilgrastim-xxxx for injection. Udenyca, pegfilgrastim-xxxx, a biosimilar is indicated for decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

The original consult request from CDER indicates that, "Please review to ensure that there are no issues from the engineering, design and compatibility perspective that may impact the overall product."

The device presentation that is being evaluated within this review is a pre-filled syringe. Device performance will be the focus of this review. Device/drug compatibility will be deferred to CDER.

There is no record of past CDRH interaction related to this combination product.

Reviewer's Note: CDER initial contacted us late in the review cycle (midcycle meeting) after being notified by CDRH/OC that the review division needed to consult ODE. For the midcycle review, the file was briefly reviewed to see if all of the information was present to begin our review. Based on the initial review, the sponsor was asked interactively for additional information (which is detailed at the end of this review memo).

Product	Indications for Use
Udenyca, pegfilgrastim-xxxx	Indicated for decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

II. Administrative

Documents Reviewed:

Document Title	Document Number	Date -Version	Location

3.2.P.2.4 Container closure system	BLA 761039 SN 0001	01/19/2017	GSR Sequence 0032(33)
3.2.P.5.2 Analytical Procedure	BLA 761039 SN 0026	01/06/2017	GSR Sequence 0026(27)
3.2.P.7 Container Closure	BLA 761039 SN 0001	08/09/2016	GSR Sequence 0001(1)
3.2.P.3.5 Process Validation and/or Evaluation	BLA 761039 SN 0022	12/15/2016	GSR Sequence 0022(23)

CDRH Review Team:

Team Member	Role	Deficiencies
LCDR Keith Marin,CDRH/ODE/GHDB)	Lead Reviewer – Nurse Consultant	Found at end of memo

III. Device Description and Performance Requirements

(b) (4)

The primary container closure system for UDENYCATM solution for injection, is the (b) (4) ™ pre-fillable syringe comprised of the following primary packaging components:

- (b) (4) 1-mL long syringe barrel with (b) (4) needle shield (b) (4))
- 29 gauge thin walled ½" needle (supplied as a unit with the syringe)
- (b) (4) plunger stopper

The following components are secondary packaging components, not directly in contact with the UDENYCA drug product:

- Rigid needle shield (b) (4)) (supplied as a unit with the syringe)
- UltraSafe (b) (4) ™ Passive Needle Guard
- Plunger rod

The medical devices constituent part of the combination product is an UltraSafe (b) (4) ™ Passive Needle Guard cleared by CDRH under the 510(k) pathway (b) (4) Each syringe is inserted into a passive

needle guard to protect health care staff from inadvertent needle sticks. The UltraSafe (b) (4) ™ passive needle guard system functions with a plunger rod designed specifically for the UltraSafe (b) (4) ™ system. The rigid needle shield supplied as a unit with the syringe.

Materials:

(b) (4)

Reviewer's Note: The container closure (b) (4) DMF (b) (4) and UltraSafe (b) (4) passive needle guard system has been reviewed several times by this reviewer along with other reviews within the branch. It is unexpected that there will be new safety and functional issues associated with these components.

Device Characteristic	Description / Specification
Visual Inspection	Components match the specification description and description on the certificate of conformance.

Dimensional testing	Overall length: (b) (4) mm Barrel ID: (b) (4) mm Barrel OD: (b) (4) mm Barrel Length: (b) (4) mm Plunger stopper height: (b) (4) mm Crown Diameter: (b) (4) mm max
Injection force (maximum load, break force, glide force, maximum glide force)	(b) (4)
Needle Safety Device Override Force	(b) (4) N
Needle Shield Removal Force	(b) (4)
Container closure integrity	No dye ingress
Dose accuracy	(b) (4) ml
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	29G thin walled ½'' needle, pre-staked
Type of Use (e.g. single use, disposable, reusable, other)	Single use
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	(b) (4)
Injection mechanism (e.g., manual piston, spring, gas, etc.)	(b) (4)
Method of actuation	(b) (4)
Residual Medication	(b) (4) ml
Delivered Volume (for single dose or selectable volume range for multidose pens)	0.6ml (6mg administered, concentration 10mg/ml)
Drug Container Type	Pre-filled syringe
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Mg/ml
Environments of use	(b) (4)
Storage conditions and expiry	Store refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light, syringes stored at room temperature for more than 48 hours. Shelf life 36 months
Graduation marks / fill lines	The UDENYCA 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 UDENYCA 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.
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	Remove the carton from the refrigerator and allow the UDENYCA prefilled syringe to reach room temperature for a minimum of 30 minutes. Visually inspect parenteral drug products (prefilled syringe) for particulate matter and discoloration prior to administration, whenever solution and container permit.
Safety Features • Needle safety	Needle safety feature: (b) (4) UltraSafeTM (b) (4) Passive Needle Guard (b) (4)
Material composition of syringe	Glass barrel: (b) (4) Needle: (b) (4) Rigid Needle Shield: (b) (4) Plunger Stopper: (b) (4)

Reviewer's Note: The sponsor states that as the syringe does not have gradiations, dosing less than 0.6ml is not recommended due to dosing errors. However, they include in the labeling, "table 1" which describe dosage for pediatric patients weighing less than 45 kg (all of which are below 0.6ml). It is not clear why the sponsor has included this as this could lead to a dose error. Based on discussion with the RPM Joslyn Brunelle, DMEPA is aware of this issue and is following up with the sponsor. They sent the following IR basically stating that the proposed presentation(s) may need Human Factors studies to demonstrate that users can accurately measure the doses. DMEPA requested that they update their plan to address PREA, and revise sections 1.9.4.5 and 1.9.4.7 accordingly.

IV. Design Control Review

A. Design Review Summary

During development of the drug product, the sponsor has given consideration to relevant guidance pertaining to medical devices. These guidances include, but are not limited to:

- FDA Quality System Regulations (21 CFR Part 820)
- FDA Guidance on Applying Human Factors and Usability Engineering to Optimize Medical Device Design (2011)
- ISO 13485:2003 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes

B. Design Control Documentation Check

<table>
<tr><th rowspan="2">Design Control Requirement*</th><th colspan="2">Signed/Dated Document Present</th><th rowspan="2">Submission Location</th></tr>
<tr><th>Yes</th><th>No</th></tr>
<tr><td>Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer</td><td>X</td><td></td><td>3.2.P.5.1
<table>
<tr><th>Test Category</th><th>Method, Pharmacopoeia Reference</th><th>Acceptance Criteria</th></tr>
<tr><td rowspan="4">Device Functionality*</td><td>Injection Force (Maximum Load [b], Break Force, Glide Force, Maximum Glide Force [c])</td><td rowspan="4">(b) (4)</td></tr>
<tr><td>Needle Safety Device Override Force</td></tr>
<tr><td>Needle Shield Removal Force</td></tr>
<tr><td>Dose Accuracy</td></tr>
</table>
* Tested on assembled prefilled syringe (PFS) with Needle Safety Guard
[b] Highest load force from the start of stopper movement until the syringe safety is triggered
[c] Highest point within the glide force test region
<table>
<tr><td>Safety *</td><td>Container Closure Integrity (CCIT)</td><td>No Dye Ingress</td></tr>
</table></td></tr>
<tr><td>Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.</td><td>X</td><td></td><td>3.2.P.2.4
Table 23: Device Functionality Verification Summary
<table>
<tr><th>Design Validation Parameter</th><th>Acceptance Criteria</th><th>Result</th></tr>
<tr><td>The product shall contain a 1 mL long syringe</td><td>Documentation specifies 1 mL long syringe</td><td>Pass</td></tr>
<tr><td>The product shall contain a passive needle safety device</td><td>Documentation specifies passive safety device</td><td>Pass</td></tr>
<tr><td>The product shall deliver not less than 0.60 mL of drug</td><td>Delivered volume (b) (4) mL</td><td>Minimum volume = 0.62 mL (n=5)
Pass</td></tr>
<tr><td>All components that come in direct contact with the user shall be biocompatible</td><td>Conformance to ISO 10993</td><td>Pass</td></tr>
<tr><td>The rigid needle shied shall be latex-free</td><td>Latex-free</td><td>Pass</td></tr>
<tr><td>The syringe shall be made of Type 1 glass</td><td>Documentation specifies (b) (4) glass</td><td>Pass</td></tr>
<tr><td>The needle gauge shall be 29G or smaller</td><td>Documentation specifies 29G needle</td><td>Pass</td></tr>
<tr><td>The needle length shall be ½”</td><td>Documentation specifies needle length is ½”</td><td>Pass</td></tr>
<tr><td>The container closure of the PFS shall maintain its integrity through the end of shelf life</td><td>N/A</td><td>See Table 13 in Section 3.2.P.8.3, Stability Data
Pass</td></tr>
</table></td></tr>
</table>

			<table><tr><th>Design Validation Parameter</th><th>Acceptance Criteria</th><th>Result</th></tr><tr><td>Labeled syringe shall be able to rotate in at least one direction</td><td>All tested syringes must be able to rotate in one direction</td><td>Pass</td></tr><tr><td>Maximum injection force (including glide and NSD activation force) shall be less than (b) (4)</td><td>Injection Force (b) (4) N</td><td>Maximum injection force = 8.9 N (n = 119) Pass</td></tr><tr><td>Rigid needle shield removal force shall be less than (b) (4)</td><td>Removal force (b) (4) N</td><td>Maximum removal force = 15.5 N (n = 119) Pass</td></tr><tr><td>Needle safety device override force shall be greater than (b) (4)</td><td>Override Force (b) (4) N</td><td>Override force > 80.5 N Pass</td></tr><tr><td>Passive NSD shall activate at the end of injection cycle</td><td>NSD must activate on all tested syringes</td><td>Pass</td></tr><tr><td>Leachables throughout the combination product shelf life shall be acceptable based on a health-based assessment conducted by a toxicologist</td><td>Leachables throughout the combination product shelf life shall be acceptable based on a health-based assessment conducted by a toxicologist</td><td>See Section 3.2.P.2.4.2.3</td></tr></table>
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.P.2.4 Sponsor submitted a FMEA that characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable misuse, and potential system failure states. The FMEA describes the system hazards and the initial risk category based on initial scoring based on potential causes of failure and current controls in place to reduce the risk of those hazards. There were no unacceptable risks identified from the 15 evaluated.
Validation Data • Human factors • Clinical data	X X		3.2.P.2.4.3.1 Human factors study conducted validate the verification activities as noted by the FMEA.

***Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.**

C. Design Verification and Validation Review

Summary of Design V&V Attributes:

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		X		
To-be-marketed device was used in the pivotal clinical trial?				X
Verification methods relevant to specific use conditions as described in design documents and labeling		X		
Device reliability is acceptable to support the indications for use		X		
Traceability demonstrated for specifications to performance data		X		
Conformance to applicable standards demonstrated	USP 660: Glass syringe barrel			
	AISI 304 -- Needles	X		
	European Pharmacopoeia 3.2.9 and USP 381: Needle shield	X		
	ISO 10993 --Biocompatibility	X		

Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		X		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	X		
	Sterility	X		
	Human Factors		X	

Coherus conducted a comprehensive use related risk analysis. This task based application failure modes and effect analysis (aFMEA) included a comprehensive and systematic evaluation of all the steps involved in using UDENCYA, the errors that a user might commit or the tasks they may fail to perform taking into account known problems for similar products, and the potential negative clinical consequences of use these errors or task failures. Results of the risk analysis demonstrate that the probability and severity of these errors pose little risk to the intended use of the product and the end user. Based on this assessment, Coherus concluded that a summative human factors study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and correct use of the product is not necessary to assess the adequacy of the combination product user interface design to eliminate or mitigate potential use-related hazards.

Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase III Study utilized the to-be-marketed device		X	
Bioequivalence Study utilized to-be-marketed device	X		
Simulated Actual Use Study utilized to-be-marketed device		X	

Phase III study was not conducted as this is a biosimilar and a phase III study is not required. The sponsor did conduct a bioequivalence (PK study). Sponsor did not conduct an actual use study with device.

Reviewer's Note: There does not appear to be a actual use study that could be located within the submission. The sponsor did conduct a phase 1 study using a pre-filled syringe (but it isn't clear whether this was the to-be-marketed device). However, as they have done a risk analysis with the device and the risks of this device are much lower than a more complicated device, the absence of this simulated actual use study is less concerning.

Design Verification Review

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Force (Maximum Load, Break Force, Glide Force, Maximum Glide Force)	(b) (4) N	3.2.P.2.4.3	3.2.P.2.4.3.1	Yes 3.2.P.8.3	Yes 3.2.P.3.5.3.3	Yes
Dose Accuracy	(b) (4) ml	3.2.P.2.4.3	3.2.P.2.4.3.1	Yes 3.2.P.8.3	Yes 3.2.P.3.5.3.3	Yes
Needle Safety Device Override Force	(b) (4) N	3.2.P.2.4.3	3.2.P.2.4.3.1	Yes 3.2.P.8.3	Yes 3.2.P.3.5.3.3	Yes
Needle Shield Removal Force	(b) (4) N	3.2.P.2.4.3	3.2.P.2.4.3.1	Yes 3.2.P.8.3	Yes 3.2.P.3.5.3.3	Yes

Container Closure Integrity	No dye ingress	3.2.P.2.4.3	3.2.P.2.4.3.1	Yes 3.2.P.8.3	Yes 3.2.P.3.5.3.3	Yes

Description of Injection Forces:

Figure 1: Syringe Injection Force Curve

Coherus has defined injection force to be inclusive of breakloose/glide force. As presented in Figure 1 the injection force curve includes the force required to actuate the injector (breakloose force) as well as the glide force.

Table 13: Supportive Long-term Stability Results for Lot 23721101 (with NSD) at 5 ± 3 °C- Post Shipping Validation Study

Test Attribute	Acceptance Criteria	Time Point (Months) 0	1	3	6	9	12	15	18	24	36
Device Functionality											
Injection Force (Maximum Load [a], Break Force, Glide Force, Maximum Glide Force [b])	(b) (4)	8.1	8.0	8.3	8.1	8.3	T	T	T	T	T
Needle Safety Override Force		> 80	> 80	> 80	> 80	> 80	T	T	T	T	T
Needle Shield Removal Force		11.2	9.8	10.9	11.3	11.6	T	T	T	T	T
Quality											
Dose Accuracy (Extractable Volume)		0.63 0.64 0.63 0.63 0.63	0.63 0.64 0.64 0.64 0.64	0.62 0.63 0.64 0.63 0.63	0.63 0.63 0.63 0.64 0.63	0.64 0.64 0.63 0.64 0.63	T	T	T	T	T
Safety											
Container Closure Integrity (CCIT) [c]	No Visible Ingress	Pass[d]	NS	NS	NS	NS	T	NS	NS	T	T

T = test scheduled; NS = test not scheduled
[a] Highest load force from the start of stopper movement until the syringe safety is triggered
[b] Highest point within the glide force test region
[c] CCIT performed *in lieu* of sterility testing (every 12 months and at expiry)
[d] CCIT performed at t=0 demonstrates that syringe plunger movement during air transportation does not impact product sterility
[e] Specification at the time of testing was (b) (4) mL

Biocompatibility Testing: The syringe barrel and needle shield underwent biocompatibility testing by (b) (4) (cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, pyrogenicity, and hemolysis testing).

Component	Test Article	Test Article Number
(b) (4) Syringe	Cell Cytotoxicity / Elution Test	12-0518-001
	Indirect Contact Hemolysis Test	12-0518-001
	Intracutaneous Reactivity	12-0518-001
	Acute Systemic Toxicity	12-0518-001
	Maximization Sensitization Method	12-0518-001
	Rabbit Pyrogen	12-0518-001

***IN VITRO* STUDIES, Test Article TA 12-0518-001**

Test	Results
ISO 10993-5 Cell Cytotoxicity	Cytotoxicity : mild Score = 2
ISO 10993-4 Indirect Contact Hemolysis	Non hemolytic 0% Hemolysis

***IN VIVO* STUDIES, Test Article TA 12-0518-001**

Test	Result
ISO 10993-10 Intracutaneous Reactivity	Negligible Irritant PII = 0 ((b) (4) PII = 0.1
ISO 10993-11 Acute systemic Toxicity	Non toxic ((b) (4)
ISO 10993-10 Guinea Pig Maximization Test	Nonsensitizer Grade = 0 (b) (4) Grade = 0 (b) (4)
ISO 10993-11 Rabbit Pyrogen	Non pyrogenic No rabbit shows an individual rise in temperature of 0.5°C or greater

***IN VITRO* STUDIES, Test Article TA 12-0502-008**

Test	Results
ISO 10993-5 Cell Cytotoxicity	Cytotoxicity : none Score = 0
ISO 10993-4 Indirect Contact Hemolysis	Non hemolytic 0% Hemolysis

Studies results summary for TA 12-0502-025 (b) (4) shield from (b) (4) syringe):
Qualification of the (b) (4) shield

***IN VIVO* STUDIES, Test Article TA 12-0502-025**

Test	Result
ISO 10993-10 Intracutaneous Reactivity	Negligible Irritant PII = 0 ((b) (4)
ISO 10993-11 Acute systemic Toxicity	Non toxic ((b) (4)
ISO 10993-10 Murine Local Lymph Node Assay	Nonsensitizer SI = 0.66 (b) (4) / SI = 0.66 ((b) (4)

Studies results summary for TA 07-0502-006 (b) (4) shield from (b) (4) syringe):
Qualification of the (b) (4) shield

***IN VIVO* STUDIES, Test Article TA 07-0502-006**

Test	Result
ISO 10993-11 Rabbit Pyrogen	Non pyrogenic Rabbits had 0° C increase temperature

Shipping validation was conducted as part of design verification to ensure device functionality is maintained post shipping. The shipping validation study utilized an ASTM D4169D Distribution Cycle (DC) 13 at Assurance Level (AL) 1 simulated transport standard to subject UDENYCA DP in its intended commercial primary container and representative secondary and tertiary packaging to conditions that simulate the worst case physical hazard elements encountered by the package during shipping transportation. The study evaluated the ability of the shipment packaging system to protect the product from exposure to potential distribution environments, including temperature changes, manual handling, vehicle stacking, loose load vibration, altitude test (varying air pressure), vehicle vibration, and concentrated impact. Shippers were subjected to a package performance test according to the ASTM D4169. The integrity of assembled CHS-1701 Drug Product with safety device in commercial packaging was evaluated following exposure to transportation stresses. The validation protocol followed ASTM D4169D guidelines and represents a worst-case transport environment. As described below, results from all tests demonstrated that the packaging provides adequate protection for the device throughout the shipping lifecycle

Table 20: AST4169 Distribution Challenge 13 Assurance Level (AL) I

Input	Assurance Level I
Drops (20 to 40 lbs)	21"x 11 / 42" x 1
Compression	100% Calculated Value
Vibration (loose load) Rotary motion	~4Hz x 60 Minutes
Vibration (random) Truck (60 Min) / Air (120 Min)	0.73 Grms / 1.49 Grms
Altitude	14,000 Feet
Concentrated Impacts 1 x each side (6)	32"

Reviewer's Note: The sponsor has provided the verification and validation testing for the subject device. Furthermore, the device has been tested after aging and shipping. The proposed specifications are adequate fort he intended clinical use.

D. Risk Analysis

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

Summary of Risk Analysis

The sponsor has provided a FMEA that addresses tasks that must be performed by a user in order to properly administer a dose of CHS-170 1 using the pre-filled syringe. The scope of the aFMEA includes the interactions of the user with the product in home and clinical settings. The following inputs were used for this assessment.

- User instruction
- Storage of combination product
- Pre-injection handling ofthe product
- Preparation for the injection
- Injection
- Post-injection and disposal

This aFMEA does not consider the drug itself except with respect to the impact that the drug has on the patient in the event of a use error. Each potential risk was scored and is considered acceptable according to TP.DV.0012 (CHS-1701 Risk Management Plan).

Coherus BIOSCIENCES	Document Code: TP.DV.0013.01	
	Supersedes: TP.DV.0013.00	Page 4 of 11
	CHS 1701 Application Failure Modes and Effects Analysis	

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
Storage and Handling	Product not stored in carton at 2-8 C	1. Drug subjected to elevated temperatures for more than 48 hours 2. Drug is frozen 3. Drug is exposed to light	1. Degradation of drug 2. Loss of container closure integrity 3. Degradation of drug	1. Infection due to low white cell count 2. Infection due to non-sterility 3. Infection due to low white cell count	4	• user is not aware of maximum storage temperature requirements • Storage environment is not within required temperature range • Product is not stored in opaque container	2	• IFU instructs user to store product between 2 to 8 C • IFU instructs user to not freeze • Shelf carton protects product from light • IFU instructs user to keep PFS in original container until ready for use • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			
	Product is not allowed to warm to room temperature	1. Injection force too high 2. Drug is cold	1. Missed or partial dose 2. Drug is cold	1. Infection due to low white cell count 2. Pain	4	• user is not aware that drug should be injected at room temperature	2	• IFU recommends that product sit at room temperature for 30 minutes • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			

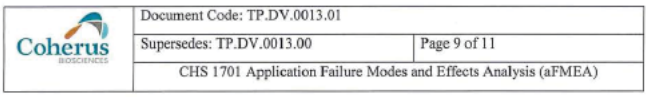
Coherus BIOSCIENCES	Document Code: TP.DV.0013.01	
	Supersedes: TP.DV.0013.00	Page 5 of 11
	CHS 1701 Application Failure Modes and Effects Analysis (aFMEA)	

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
	Product stays at room temperature for more than 48 hours or is actively heated	Drug thermal history either exceeds ambient or duration	1. Degradation of drug	1. Infection due to low white cell count	4	• user is not aware of maximum storage temperature requirements	2	• IFU states that product left at room temperature for more than 48 hours be disposed • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			
	Product damaged during removal from package	Stopper is damaged	1. Loss of container closure integrity 2. Missed or partial dose	1. Infection due to non-sterility 2. Infection due to low white cell count	4	• user does not know how to remove the PFS from the tray	2	• IFU instructs user to grasp the PFS at the middle of the syringe body • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
	Expiration date is not checked	Drug is expired	1. Degradation of drug	1. Infection due to low white cell count	4	• user does not know how to verify that product is not expired	2	• Standard clinical practice • Expiration date is clearly marked • IFU instructs user to verify expiration date • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			
	Syringe and contents are not inspected	1. Syringe is damaged 2. Liquid is not clear	1. Loss of container closure integrity 2. Degradation of drug	1. Infection due to non-sterility of drug substance 2. Infection due to low white cell count	4	• user does not know that the syringe must be inspected • user does not know that the drug substance appearance must be clear	2	• IFU instructs user to inspect the syringe • PFS allows easy visualization of drug substance • IFU instructs the user how to determine if the drug substance appearance is acceptable and not to use if it is not • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			

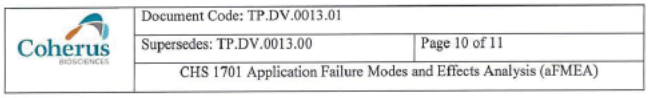
Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
	Syringe is shaken	Liquid is foamy	1. Degradation of drug	1. Infection due to low white cell count	4	• user does not know that shaking is not permitted	2	• IFU provides a warning to not shake • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			
Injection Site Selection	Suitable injection site is not used	Drug is not administered subcutaneously	1. Missed dose or partial dose	1. Infection due to low white cell count	4	• user does not know how to select an acceptable injection site	2	• Standard clinical practice • IFU provides a graphic that identifies acceptable injection sites • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
Cleaning of Injection Site	Injection site is not properly cleaned	Injection site is contaminated	1. Foreign bodies are introduced	1. Infection due to foreign bodies	4	• user does not know how to properly clean site	2	• Standard clinical practice • IFU explains how to clean site • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			
Removal of Rigid Needle Shield	Cap not removed or not removed properly	1. Can't perform injection 2. user contacts needle	1. Missed dose 2. Needle stick injury	1. Infection due to low white cell count 2. Pain	4	• user does not know how to remove the RNS	2	• Standard clinical practice • RNS has features that facilitate removal • IFU explains the required maneuver for removing the RNS • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			



Coherus BIOSCIENCES	Document Code: TP.DV.0013.01	
	Supersedes: TP.DV.0013.00	Page 9 of 11
	CHS 1701 Application Failure Modes and Effects Analysis (aFMEA)	

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
Pinch Skin	Maneuver not performed properly	Needle tip extends into muscle layer	1. Partial dose	1. Infection due to low white cell count	4	• user does not know how to administer a subcutaneous injection	2	• Standard clinical practice • IFU illustrates how to perform • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections			
Insert Needle	1. Syringe not gripped properly 2. Needle does not access subQ layer	1. Premature pressing of plunger 2. Drug PK/PD not achieved	1. Missed or partial dose 2. Partial dose	1. Infection due to low white cell count 2. Infection due to low white cell count	4	• user does not know how to hold the syringe during needle insertion • user does not what needle angle is required	2	• Standard clinical practice • IFU explains where to hold the syringe • IFU specifies angle range • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			



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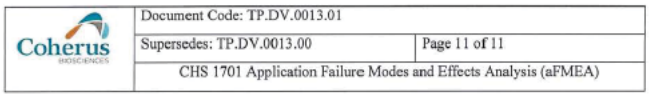
	Supersedes: TP.DV.0013.00	Page 10 of 11
	CHS 1701 Application Failure Modes and Effects Analysis (aFMEA)	

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
	Plunger is not fully depressed	1. Full dose is not delivered 2. NSD is not engaged and needle is exposed	1. Missed or partial dose 2. Needle stick injury	1. Infection due to low white cell count 2. Pain and blood-born pathogen exposure	4	• user does not know that the plunger must be fully depressed	2	• Standard clinical practice • IFU states that the plunger must be pushed down until it will go any further • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			
Deliver Drug and Engage Needle Safety Device	Drug is delivered to pediatric patient weighing less than 45 kg	1. Full dose is delivered	1. overdose	1. Possibility of leukocytosis or leukamoid reaction, 2. Possible thrombosis, hypercalcemia and fever due to underlying disease factors 3. Possible splenic events, or any other AESI as noted in the reference product PI	4	• Syringe does not have graduation that enable accurate dosing less than a full dose	2	• IFU states that direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			



Coherus BIOSCIENCES	Document Code: TP.DV.0013.01	
	Supersedes: TP.DV.0013.00	Page 11 of 11
	CHS 1701 Application Failure Modes and Effects Analysis (aFMEA)	

Task	Failure Mode	Failure Effects	Hazard	Harm	Initial Scoring					Recommended Mitigations and/or Actions	Responsibility / Target Completion Date
					SEV	Potential Causes of Failure	PROB	Current Controls	RC		
Activate Needle Safety Device	Pressure on the plunger is not relieved, thus preventing the plunger from rising	2. NSD is not activated	2. Needle stick injury	4. Pain and blood-born pathogen exposure	4	• user does not know how to allow activation of NSD	2	• IFU states that the plunger should be allowed to fully return before removing the syringe from the injection site • Only patients deemed capable by their HCP, and instructed on proper use are allowed to perform home injections •			
Administer dose within the recommended time interval	Drug is delivered too soon after chemotherapy	1. Drug is not administered at the optimal time	1. Loss of drug efficacy	1. Infection	4	• user does not know when to administer the drug	2	• PI states the when the dose should be given relative to chemotherapy timing			

This risk assessment identified and prioritized risks associated with use of the product by healthcare professionals in a clinical setting and patients or their caregivers in a home setting. The current risks identified totaled 15. There were no unacceptable risks identified. The residual risk level is remains acceptable based on risk reduction achieved by current controls in place which includes the restriction of

home injections to patients and caregivers determined to be capable, after instruction by their caregivers. The sponsor has concluded that no further mitigation is required.

Reviewer's Note: The sponsor has provided FMEA risk analysis. The stated failure modes, hazards, and mitigations are appropriate. I have no further concerns.

E. Labeling

UDENYCA is administered subcutaneously via a single prefilled syringe for manual use.

Prior to use, remove the carton from the refrigerator and allow the UDENYCA prefilled syringe to reach room temperature for a minimum of 30 minutes. Discard any prefilled syringe left at room temperature for greater than 48 hours.

Visually inspect parenteral drug products (prefilled syringe) for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer UDENYCA if discoloration or particulates are observed.

CONTRAINDICATIONS: Do not administer UDENYCA to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.
WARNINGS AND PRECAUTIONS: Splenic Rupture- Splenic rupture, including fatal cases, can occur following the administration of UDENYCA. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving UDENYCA.

F. Design Transfer Activities – Release Specifications

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5.1:

Attribute	**Specification**	**Test Method**
Injection Force	(b) (4) N	Test method described in 3.2.P.5.2.15
Needle Safety Device Override Force	N	Test method described in 3.2.P.5.2.16
Needle Shield Removal Force	N	Test method described in 3.2.P.5.2.17

Dose Accuracy	(b) (4) ml	Test method described in (b) (4) Specification (weighing)
Container closure integrity	No dye ingress	Test method described in 3.2.P.5.2.14

V. Information Requests – Sent January 6, 2017

- In your 3.2.P.5.1 specifications, you do not list dose accuracy, breakloose/glide force, and barrel compression force as part of your essential performance specifications. Please update this section to provide this information.
- Please provide the location of the verification and validation performance testing that supports the stated specifications you have listed for your device.
- Please provide the release specifications for the essential performance characteristics for the syringe.
- Provide location of the biocompatibility testing for the final finished device
- Please provide the location of the device aging/stability testing that validates the device/combination product functions at the end of the shelf life
- Provide the location of the shipping studies conducted on the final finished device.
- Please provide risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.
- You have referenced (b) (4) UltraSafe (b) (4) for the needlestick prevention feature. Please provide a LOA that allows us to review the information in this 510(k).

VI. Outstanding Deficiencies

None

VII. Post-Market Commitments / Post-Market Requirements

None

VIII. Recommendation: APPROVAL

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

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Date:	January 26, 2017
To:	Joslyn Brunelle, CDER/OND/ OPQ/OBP/DBRRIV, WO71 RM2214, Tel: 240-402-9235, E-mail: Joslyn.Brunelle@fda.hhs.gov
CC:	Office of combination products at combination@fda.gov
Through:	Francisco Vicenty, Branch Chief, CDRH/OC/DMQ/REGO, WO-66, Rm 3426
From:	Rakhi Dalal, Ph.D, CDRH/OC/DMQ/REGO, WO-66, Rm 3454
Applicant:	Coherus BioSciences, Inc 333 Twin Dolphin Drive Redwood City CA 94065 FEI: 3012839919
Application #	BLA761039
Product Name:	Udenyca, pegfilgrastim-xxxx (biosimilar) Pre-filled Syringe, Solution for Injection, 6 mg / 0.6 mL
ICCR (CTS)#	ICC1600756
Device Constituent:	(b) (4) glass syringe barrel with a (b) (4) rubber stopper (b) (4) (plunger); ULTRASAFE (b) (4) PASSIVE NEEDLE GUARD ((b) (4)
Intended Use:	Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Consult Instructions:	510(k) (Special). (b) (4) 1mL long glass syringe barrel - Letter of authorization for DMF (b) (4) found in eCTD section 1.4.1 (with 29 gauge 1/2" thin wall needle with (b) (4) rigid needle shield (b) (4) rubber stopper) (b) (4) UltraSafe (b) (4) syringe needle safety guard - Letter of authorization for DMF (b) (4) found in eCTD section 1.4.1 - See eCTD secion 3.2.P.2.4 and 3.2.P.7 for more detailed information on container closure system. Please identify relevant device constituent facilities and determine their acceptability to support the application.
Pre-Approval Inspection:	**Yes, Inspection Guidance, Page 27.**
Documentation Review:	**BLA 761039 IR information –Adequate**
CDRH/OC Recommendation:	**Approval, Page 26.**

Background:
The CDER consult request is for a complete review of the Initial submission BLA761039 and the Firm's IR Response dated January 19, 2017, for the combination product UDENYCA™, a.k.a. pegfilgrastim-xxxx (biosimilar) Pre-filled Syringe, Solution for Injection, 6 mg / 0.6 mL, sc, which is claimed to be biosimilar to Neulasta. UDENYCA™ drug product (DP) is supplied in a single use, sterile solution for injection in a 1 mL long (b) (4) glass prefilled syringe (PFS) with a 0.6 mL fill volume for subcutaneous (SC) injection. Each syringe contains 6 mg pegfilgrastim- (b) (4) in a sterile, clear, colorless, preservative-free (b) (4) solution. The protein is formulated in (b) (4) (b) (4), (b) (4) sorbitol and (b) (4) polysorbate 20, pH 4.0. UDENYCAis provided at a single strength using the same formulation as that of the US licensed reference product, Neulasta® (US). The intended use of the Udenyca is 'Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia'. Photostability studies confirmed that upon direct light exposure in the primary container closure, UDENCYA drug product (DP) is light/photosensitive [per ICH Q1B (illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter) results in an increase in oxidized species as measured by RPC and dimer/diPEG and oligomer species as measured by SEC], and should be protected from light during the long term storage. The memo contains Facilities/Regulatory History and documentation review for the BLA 761039. The CDRH/OC recommendation (Approvable) is provided on Page 26 in the memo.

I. Facility/Regulatory History Review: Application of 21 CFR 820s under 21 CFR Part 4

Firm/Address/FEI	Responsibility	Regulatory History
Coherus BioSciences, Inc, 333 Twin Dolphin Drive Redwood City CA 94065 FEI: 3012839919	Applicant of the combination product Maintenance of design history file (DHF, CHS-1701).	No inspection conducted of this facility per FACTS. Also a new BLA product. Recommend facility inspection prior to BLA approval.
KBI Biopharma, Inc. 2500 Central Avenue Central Avenue, Boulder, CO 80301 FEI: 3011326133	(b) (4); DS (manufacture, in-process testing, release testing, stability testing), primary storage of the master cell bank, primary storage of the working cell bank, manufacture of the working cell bank, DP (release & stability testing)	Review deferred to CDER
(b) (4)	DS (release & stability testing), DP(release & stability testing)	Review deferred to CDER
	Manufacture of the master cell bank, testing of MCB, functional performance testing of the safety device	Last inspected (b) (4)

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

	(b) (4)

CDRH/OC Recommendation: The UDENYCA™, a.k.a. pegfilgrastim-xxxx, is a new product, BLA761039. Therefor recommend pre-approval inspection of the facility(ies) as above. See Inspection Guidance for additional information.

II. Documentation Review:

Design Controls, 21 CFR 820.30:

Primary Container Closure System (CCS)

3.2.P.1.3 Primary packaging components

The primary container-closure system (CCS) for UDENYCA DP is comprised of a 1 mL (b) (4) glass syringe barrel with a fixed needle and **latex free** needle shield, and a (b) (4) plunger stopper (Table 2). A complete description of the container closure system, the specification and a rationale for selecting this primary container is provided in Section 3.2.P.7, *Container Closure System* and Section 3.2.P.2.4, *Container Closure System*.

Table 2: Primary Packaging Components

Component	Description
Prefilled long syringe	(b) (4) 1 mL long glass syringe barrel
Plunger stopper	(b) (4) rubber stopper
Needle and needle shield	29 gauge thin walled 1/2" needle with a rigid needle shield

3.2.P.1.4 Secondary Packaging Components

Each syringe is inserted into a passive needle guard to minimize the likelihood of inadvertent needle sticks. UltraSafe (b) (4)™ passive needle guard system including a plunger rod designed specifically for the UltraSafe (b) (4)™ system is listed in Table 3. A complete description of secondary packaging is provided in Section 3.2.P.7, *Container Closure System*. The UDENYCA primary packaging system, including primary and secondary packaging components, is shown in Figure 1.

Table 3: Secondary Packaging Components

Container Closure Component	Manufacturer/Supplier	Manufacturer's Information
Syringe needle safety guard, UltraSafe (b) (4)	(b) (4)	(b) (4)
(b) (4) Plunger rod, (b) (4)	(b) (4)	

Figure 1: UDENYCA Primary Packaging System

Section 3.2.P.2.4 Container Closure System (UDENYCA, Solution for Injection)
The UDENYCA™ DP container closure system (CCS) is composed of a single-use (b) (4) (b) (4) pre-fillable syringe (PFS) assembled within a safety needle device for sc. administration. The DP CCS is designed to deliver 6 mg of UDENYCA in 0.6 mL of aqueous solution. Per Section 3.2.P.2.4.1 Primary Container Closure System, the primary components of the system include a (b) (4) glass syringe barrel with a (b) (4) rubber stopper. (b) (4) The components of the device constituent are provided in the Table 1, below. Per the firm, these components comply with relevant USP, Ph. Eur and JP monographs, where applicable, and described in Section 3.2.P.7, *Container Closure System*. Development of the CCS and DP manufacturing process are in Section 3.2.P.2.3, *Manufacturing Process Development*.

The PFS is a manually-operated, single-use, disposable system. The primary CCS includes a syringe needle safety device, which may reduce the potential occurrence of accidental needle-sticks to healthcare professionals and patients after administration and during disposal of a used prefilled syringe.

Table 1: Container Closure System Details

Component	Component Details	Manufacturer
Prefillable syringe barrel system	(b) (4)	
Syringe plunger stopper		
Syringe needle safety device		

Per the firm, during the DP development, consideration was given to relevant guidance pertaining to medical devices. The guidance included, but not limited to:

- FDA Quality System Regulations (21 CFR Part 820)
- FDA Guidance on Applying Human Factors and Usability Engineering to Optimize Medical Device Design (2011)
- ISO 13485:2003 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes

Guidance relevant to the needle safety device was addressed in the design and selection process (Section 3.2.P.2.4.3). The selection of the container closure system for the intended use of the DP and suitability of the container closure system for storage and transportation is in the Section 3.2.P.2.4.2 and Section 3.2.P.2.4.4.

3.2.P.2.4.2 Suitability of the Container Closure System

Suitability of the primary CCS to provide a safe and accurate dose of UDENYCA was assessed through studies summarized in Table 2. Syringe barrels and stoppers are obtained [redacted] (b) (4) as described in Section 3.2.P.7, *Container Closure System*. 100% [redacted] (b) (4) is performed as part of the manufacturing in-process testing described in Section 3.2.P.3.3. *Description of Manufacturing Process and Process Controls*.

To support the integrity of the container, UDENYCA DP batches are tested for sterility and extractable volume upon batch release (Section 3.2.P.5.1, *Specifications*), and available data (Section 3.2.P.5.4, *Batch Analysis*) shows that all batches to date conform to acceptance criteria. Container closure integrity and extractable volume are tested as part of the device functionality stability program (Section 3.2.P.8.1, *Stability Summary and Conclusions*).

To support the compatibility of the container with UDENYCA DP, batches are also routinely tested for product quality per batch release criteria. Potency and particulates are tested upon UDENYCA drug product batch release (Section 3.2.P.5.1, *Specifications*) and as part of the stability program (Section 3.2.P.8.1, *Stability Summary and Conclusion*). Critical quality attributes of strength by UV spectrophotometry as well as purity by RPC and SEC are also measured at batch release and as part of the stability program. The stability data obtained with the prefilled syringe container closure system have shown no increase in any of the aforementioned parameters that could be attributed to incompatibility of the dosage form with the container closure (see Section 3.2.P.8.3, *Stability Data*).

Table 2: Container Closure Suitability Studies

Study	Section Summary
Container Closure Integrity Testing	Section 3.2.P.2.4.2.1
[redacted] (b) (4) Compatibility	Section 3.2.P.2.4.2.2
Extractables and Leachables ([redacted] (b) (4)	Section 3.2.P.2.4.2.3
Exposure to Moisture	Section 3.2.P.2.4.2.4
Exposure to Light (ICH Photostability Testing and User Handling)	Section 3.2.P.2.4.2.5
User Handling Injection Speed Related Shear Stress	Section 3.2.P.2.4.2.6
Shipping Temperature Excursion (Frozen)	Section 3.2.P.2.4.2.7

3.2.P.2.4.3 Suitability of the PFS with Needle Safety Device

This section documents the results of design verification studies performed to show that the UDENYCA PFS with Needle Safety Device (PFS w/NSD) will meet the design input requirements. Design functionality testing procedures (Section 3.2.P.5.2, *Analytical Procedures*) and the validation of the procedures (Section 3.2.P.5.3, *Validation of Analytical Procedures*) are used in the design input assessments. A risk based-approach, using the severity of harms and a confidence/reliability level to achieve, was used to determine the sample sizes for design functionality testing.

For the design verification studies, commercially representative batch of DP assembled into NSD, Lot 23721101 was used. Design verification, including functionality testing, was performed

on a lot that were exposed to simulated distribution stress. Design verification results, including the user requirements being verified are summarized in Table 23. The study verified the functionality of the CCS after system assembly and simulated distribution stress.

Table 23: Device Functionality Verification Summary

Design Validation Parameter	Acceptance Criteria	Result
The product shall contain a 1 mL long syringe	Documentation specifies 1 mL long syringe	**Pass**
The product shall contain a passive needle safety device	Documentation specifies passive safety device	**Pass**
The product shall deliver not less than 0.60 mL of drug	Delivered volume (b) (4) mL	Minimum volume = 0.62 mL (n=5) **Pass**
All components that come in direct contact with the user shall be biocompatible	Conformance to ISO 10993	**Pass**
The rigid needle shied shall be latex-free	Latex-free	**Pass**
The syringe shall be made of Type 1 glass	Documentation specifies (b) (4) glass	**Pass**
The needle gauge shall be 29G or smaller	Documentation specifies 29G needle	**Pass**
The needle length shall be ½"	Documentation specifies needle length is ½"	**Pass**
The container closure of the PFS shall maintain its integrity through the end of shelf life	N/A	See Table 13 in Section 3.2.P.8.3, *Stability Data* **Pass**

Design Validation Parameter	Acceptance Criteria	Result
Labeled syringe shall be able to rotate in at least one direction	All tested syringes must be able to rotate in one direction	**Pass**
Maximum injection force (including glide and NSD activation force) shall be less than (b) (4) N	Injection Force < (b) (4) N	Maximum injection force = 8.9 N (n = 119) **Pass**
Rigid needle shield removal force shall be less than (b) (4) N	Removal force < (b) (4) N	Maximum removal force = 15.5 N (n = 119) **Pass**
Needle safety device override force shall be greater than (b) (4) N	Override Force (b) (4) N	Override force > 80.5 N **Pass**
Passive NSD shall activate at the end of injection cycle	NSD must activate on all tested syringes	**Pass**
Leachables throughout the combination product shelf life shall be acceptable based on a health-based assessment conducted by a toxicologist	Leachables throughout the combination product shelf life shall be acceptable based on a health-based assessment conducted by a toxicologist	See Section 3.2.P.2.4.2.3

Device validation

Per the firm, Device validation has also been completed. In Section 3.2.P.2.4.3.1 Human Factors Studies, the medical devices constituent part of the combination product UDENYCA with an UltraSafe (b) (4) Passive Needle Guard was cleared under (b) (4) The reference product for this

BLA, i.e., Neulasta (US), also uses a 1-mL long Prefilled syringe and marketed as a combination integrated with a (b) (4) UltraSafe Needle Guard system to the same intended user population claimed to be cleared by as a 510(k), although the 510(k) number is not provided in this BLA.

However, per the firm the device used on the Neulasta (US) DP is an older version, similar in appearance but requires the user to "actively" advance (slide) the needle shield over the needle after the injection. In contrast, the UDENYCA proposed biosimilar product uses the (b) (4) UltraSafe (b) (4) Passive Needle Guard system which "passively" (without an additional action by the user) advances the shield over the used needle (b) (4) activated by the device at the end of the injection.

Per the firm, despite the differences, both the **Neulasta (US) DP and** UDENYCA devices are cleared with Indications for Use "that included use by healthcare professionals, use by patients who self-inject doctor prescribed medications and use by individuals that assist self-injecting patients for use in parenteral administration with an unrestricted patient population that can include children and adults. The indication for use for the (b) (4) UltraSafe Passive Needle Guard systems is:

> *Indication for use for (b) (4) UltraSafe Passive Needle Guards:*
> *Single use devices that are indicated for use as an accessory with pre-filled ISO Standard glass syringes to aid in the protection of healthcare professionals, patients who self-inject doctor prescribed medications and individuals that assist self-injecting patients, from accidental needlesticks. The intended patient population is unrestricted and may include children and adults, and parenteral methods of administration.*

Given that UDENYCA is a proposed biosimilar to Neulasta (US), the product does not present any additional risks than those already present in the approved the Neulasta (US) combination product. The updated "Passive" system potentially provides additional risk mitigation for the risk of accidental needle stick injuries."

Coherus has conducted risk analysis which is task based application failure modes and effect analysis (aFMEA) that included a systematic evaluation of steps involved in using UDENCYA, and comparing with known problems for similar products and the potential negative clinical consequences of use these errors or task failures to the end user.

Based on this assessment, Coherus concluded that a summative human factors study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and correct use of the product is not necessary to assess the adequacy of the combination product user interface design to eliminate or mitigate potential use-related hazards.

Per BLA 761039/Sequence 0013, Section 1.14.1.3. Draft Labeling, "The needle cap on the prefilled syringe is (b) (4)."

CDRH/OC Review Comments:

- The (b) (4) holder per records is (b) (4). The finished device is composed of a guard, body, (b) (4) and plunger, non-sterile and for single use. The activation of the

UltraSafe (b) (4) Passive Needle Guard device remains the same. Upon completion of the injection, the guard will slide forward, cover and lock over the needle of the syringe. It is a visual and/or tactile and/or audible recognition that the device safety feature has activated. The (b) (4) was originally submitted as a Special 510(k) but was converted to a Traditional 510(k) on December 10, 2012 due to changes in the Indications for Use from the predicate devices. For the BLA 761039/S00, the design validation studies are deferred to CDRH/ODE for review.

- Sequence 0013, Section 1.14.1.3. Draft Labeling, "(b) (4) " CDRH does not recognize (b) (4)" due to safety concerns. Alternate language can be proposed to state "This product is not made with natural rubber latex". The review is deferred to CDRH/ODE.
- If (b) (4) is used as the device constituent part in the BLA 761039, applicable Design Controls under 21 CFR 820.30 requirements will be applied through the Supplier Agreements under the 21 CFR 820.50 Purchasing Controls with the BLA 761039 holder.
- If the (b) (4)™ Syringe System (excluding the (b) (4)) and (b) (4) Needle Shield™ without a 510(k) is used for the delivery of DP in the BLA 761039, the 21 CFR 820.30 Design Controls needs to be appropriately addressed. See the deficiency for the firm.
- (b) (4)™ Syringe System (excluding the (b) (4)) and (b) (4) Needle Shield™ and/or (b) (4) should be managed/controlled by the BLA 761039 holder under Purchasing Control, 21 CFR 820.50

(b) (4)

Production and Process Controls, 21 CFR 820.70:
3.2.P.2.3.1 Manufacturing Development History

(b) (4)

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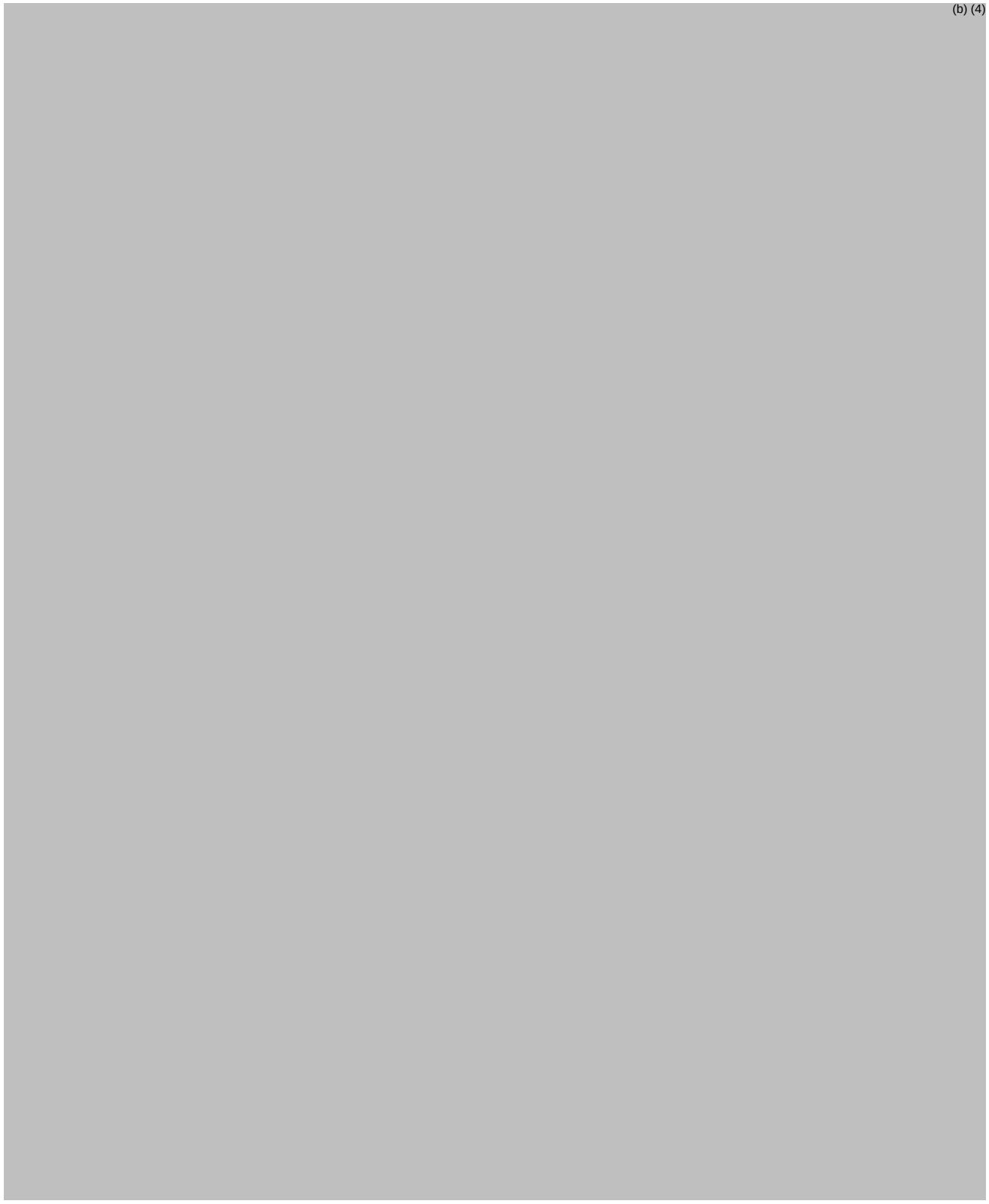
(b) (4)



Deficiencies to be communicated to the sponsor/BLA Holder:
None

CDRH Office of Compliance Recommendation

1. UDENYCA™, BLA 761039 IR information –Adequate. No Deficiencies remaining.
2. BLA 761039 - Approvable
3. Pre-approval inspection recommended. Inspection guidance, Page 27.

Rakhi M. Panguluri -S

Digitally signed by Rakhi M. Panguluri -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13002002 10, cn=Rakhi M. Panguluri -S
Date: 2017.01.26 16:17:32 -05'00'

Rakhi Dalal, Ph.D.

Inspectional Guidance
CDRH recommends the inspection under the applicable Medical Device Regulations of:

1. **Coherus BioSciences, Inc,**
   333 Twin Dolphin Drive
   Redwood City
   CA 94065
   FEI: 3012839919

Responsibility: BLA Holder
Guidance: A comprehensive inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

2. (b) (4)

Responsibility: Contract facility responsible for functional performance testing of the safety device for release.
Guidance: A comprehensive medical device inspection recommended focusing on Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

3. (b) (4)

Responsibility: Contract facility, responsible for pre-filled syringe assembly.
Guidance: A comprehensive inspection recommended focusing on Management Responsibility (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

4. (b) (4)

Responsibility: Contract facility, responsible for (b) (4) and assembly of the needle safety device, labeling and tray sealing and packaging (BLA 761039 SN 0022, Section 3.2.P.3.5.3.2 Assembly, Labeling and Packaging Validation).
Guidance: A comprehensive medical device inspection recommended focusing on Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

5. [redacted] (b) (4)

Responsibilities: [redacted] (b) (4) for ULTRASAFE [redacted] (b) (4) PASSIVE NEEDLE GUARD (finished device) used in BLA761039.
Guidance: A comprehensive medical device inspection recommended focusing on Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), Final Acceptance Activities (21 CFR 820.80) and CAPA (21 CFR 820.100).

REGULATORY STRATEGY
The establishment inspection report (EIR) for the firm should be shared with CDRH (through CDER to CDRH as a consult 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
Rakhi Dalal, Ph.D., CSO
REGO, DMQ, Office of Compliance, WO66 RM 3454
Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Francisco Vicenty, Branch Chief,
REGO, DMQ, Office of Compliance, WO66 RM 3426
Phone: 301-796- 5577

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