

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761039Orig1s000

PRODUCT QUALITY REVIEW(S)



Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	November 1, 2018
Reviewer:	Scott Dallas, RPh Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Ying-Xin Fan, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761039 Resub 57
Applicant:	Coherus BioSciences, Inc.
Submission Dates:	May 3, August 27, August 30, September 10, September 24, October 3, October 15, October 19, October 26 and November 1, 2018
Product:	Udenyca (pegfilgrastim-cbqv)
Dosage form(s):	injection
Strength and Container-Closure:	6 mg/0.6 mL Prefilled syringe
Indication, dose, route, and frequency of administration:	Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The dosage is 6 mg administered subcutaneously once per chemotherapy cycle.
Background and Summary Description:	The Applicant submitted an application seeking approval of BLA 761039. The applicant initially submitted the application on August 9, 2016. The Division of Hematology Products sent a Complete Response Letter (CRL) to the applicant on June 9, 2017. This resubmission is a complete response to the deficiencies outlined in the CRL. This drug product has been developed as a proposed biosimilar to BLA 125031, Neulasta (pegfilgrastim).
Recommendations:	The prescribing information, instructions for use, patient labeling, container labels, and carton labeling are acceptable from a quality labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION and CONCLUSION

This drug product is seeking approval as a biosimilar to BLA 125031 Neulasta (pegfilgrastim).

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, United States Pharmacopeia (USP) nomenclature and labeling standards, and FDA labeling practices and guidances to help ensure consistent labeling across products.

The prescribing information, patient labeling, instructions for use, container labels, and carton labeling were reviewed and found to be acceptable with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), USP standards, and FDA labeling practices and guidances.

The labels and labeling submitted on October 26 and November 1, 2018 are acceptable (see Appendix C) from a quality labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on May 3, 2018)
<\\cdsesub1\evsprod\bla761039\0056\m1\us\11413-drft-pi.docx>
- Patient Information (submitted on May 3, 2018)
<\\cdsesub1\evsprod\bla761039\0001\m1\us\114-labeling\1141-draft-label\11413-draft-label-text\11413-drft-pat-info.docx>
- Instructions for Use (submitted on May 3, 2018)
<\\cdsesub1\evsprod\bla761039\0013\m1\us\114-labeling\1141-draft-label\11413-draft-label-text\11413-ifu.docx>
- Container Labels (submitted on May 3, 2018)

(b) (4)

Appendix B: Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

<u>Regulations, Guidance and CDER Best Labeling Practices</u>	<u>Acceptable</u>
<u>Proper Name</u> (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: The nonproprietary name is at least half as large as the proprietary name and appears to have a commensurate prominence per 21 CFR 201.10(g)(2).	☒ Yes ☐ No ☐ N/A
<u>Manufacturer name, address, and license number</u> (21 CFR 610.60) <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: Partial label – Applicant’s response dated August 30, 2018: The container label only includes the manufacturer’s name which is acceptable, the address and license are on the carton and tray labeling. Applicant’s response dated September 24, 2018: The manufacturer’s name is still acceptable.	☒ Yes ☐ No ☐ N/A
<u>Lot number or other lot identification</u> (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100)	☒ Yes ☐ No ☐ N/A
<u>Expiration date</u> (21 CFR 610.60, 21 CFR 201.17) Applicant’s response dated October 19, 2018: The applicant revised the expiration date format to YYYYMMM.	☒ Yes ☐ No ☐ N/A
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.60	☐ Yes ☐ No ☒ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as “final container”) is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100 Comment/ Recommendation: Decrease the font size of the "Rx Only" statement as this information appears more prominent than the nonproprietary name on the PDP. (CDER Labeling Best Practice). Applicant's response dated August 30, 2018: Rx Only statement was removed which is acceptable, because it's a partial label.	☒ Yes ☐ No ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ Yes ☐ No ☒ N/A
No Package for container 21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Partial label 21 CFR 610.60 21 CFR 201.10 Comment/ Recommendation:	☒ Yes ☐ No ☐ N/A
No container label 21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Ferrule and cap overseal	☐ Yes ☐ No ☒ N/A
Visual inspection 21 CFR 610.60 Comment/ Recommendation: FOR VIALS: Confirm there is sufficient area on the prefilled syringe to allow for visual inspection when the label is affixed to the prefilled syringe and indicate where the visual area of inspection is located per 21 CFR 610.60(e). Applicant's response dated August 30, 2018: The applicant indicated that area(s) are allotted for visual inspection, providing a complete circumferential and longitudinal view per 21 CFR 610.60(e). Applicant's response dated September 24, 2018: The applicant revised the material for the label and more of the label is now transparent. This revision is acceptable.	☒ Yes ☐ No ☐ N/A

<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100 Comment/ Recommendation: Include the route of administration "For subcutaneous use" to appear above the package type term. Applicant's response dated August 30, 2018: The applicant revised the route of administration to read "For subcutaneous use".	☒ Yes ☐ No ☐ N/A
<u>Preparation instructions</u> 21 CFR 201.5	☐ Yes ☐ No ☒ N/A
<u>Package type term</u> 21 CFR 201.5 Comment/ Recommendation: Revise the package term from "(b) (4)" to "Single-Dose". "Single-Dose" is appropriate terminology for this prefilled-syringe, per United States Pharmacopeia (USP) General Chapters <659> Packaging and Storage Requirements. Refer to FDA Draft Guidance: 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. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf DMEPA/OBP combined comment reads: 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. <i>Also per Draft Guidance: 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 Guidance for Industry (e.g. single-dose vial)</i> Applicant's response dated August 30, 2018: The applicant did not include the package term on the container label, but this is acceptable because it is a partial label.	☒ Yes ☐ No ☐ N/A

Drugs <u>Misleading statements</u> 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Strength 21 CFR 201.10 21CFR 201.100 Comment/ Recommendation: Revise the expression of strength from "6 mg" to read "6 mg/0.6 mL" per USP General Chapters: <7> LABELING concerning injectable drug products. Applicant's response dated August 30, 2018: The applicant revised the expression of strength.	☒ Yes ☐ No ☐ N/A
Drugs <u>Prominence of required label statements</u> 21 CFR 201.15 Comment/ Recommendation:	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u> 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ Yes ☐ No ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ Yes ☐ No ☒ N/A
<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Ensure the linear bar code appears on the label. Ensure there is adequate white space around the linear bar code to facilitate scanning. Refer to the [Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011](#) and the [Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013](#)

Applicant's response dated August 30, 2018:

The applicant did not include a bar code. – still a deficiency.

Per 21 CFR 201.25(c)(2), the bar code must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act.

Applicant's response dated September 24, 2018:

The applicant was able to revise the label to incorporate a barcode. The revision is acceptable.

<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u> 21 CFR 610.68 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
<u>Net quantity</u> 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Dr. Fan was able to confirm the overfill volume is acceptable.	
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<u>Inactive ingredients</u> 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<u>Storage requirements</u>	☐ Yes ☐ No ☒ N/A
<u>Dispensing container</u> 21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Package Label⁵ Evaluation – Carton and Tray

Regulations, Guidance and CDER Best Labeling Practices	Acceptable
<u>Proper name</u> (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10) Comment/Recommendation: for carton and tray Revise the proper name to appear as: (pegfilgrastim-cbqv) Injection Please include the dosage formulation "injection" to appear directly below the proper name. The comment is addressed in a combined DMEPA/OBP general comment. Consider displaying the proper name and dosage formulation in a darker font to increase the prominence of this important information. Applicant's response dated August 30, 2018: The applicant placed the dosage form below the proper name and is using a darker font color.	☒ Yes ☐ No ☐ N/A
<u>Manufacturer name, address, and license number</u> 21 CFR 610.61 Comment/Recommendation: For carton and tray If space permits, consider placing the U.S. License information directly beneath the manufacturer information as is the customary labeling format. Applicant's response dated August 30, 2018: The applicant's revision is acceptable.	☒ Yes ☐ No ☐ N/A
<u>Lot number or other lot identification</u> 21 CFR 610.61	☒ Yes ☐ No ☐ N/A
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17 Applicant's response dated October 19, 2018: The applicant revised the expiration date format to YYYY MMM on the carton and tray labeling.	☒ Yes ☐ No ☐ N/A
<u>Preservative</u> 21 CFR 610.61	☒ Yes ☐ No ☐ N/A

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Comment/Recommendation:	
A statement is included that reads "No Preservative".	
Number of containers 21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: For carton and tray Revise the expression of strength to read "6 mg/0.6 mL" and ensure one expression of strength statement appears directly beneath the dosage formulation, "injection". Refer to USP General Chapters <7> Labeling. Applicant's response dated August 30, 2018: The applicant's revised expression of strength is acceptable.	
Storage temperature/requirements 21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: For carton and tray Revise the Storage and Handling statement to read: " [REDACTED] " (b) (4) [REDACTED] ." Dr. Fan was able to confirm the storage conditions described above are acceptable. Applicant's response dated August 30, 2018: The applicant's revised storage statement is acceptable, which reads: "Store Refrigerated at 2° to 8°C (36° to 46°F) in the Carton to Protect from Light. Do Not Freeze. Do Not Shake."	
Handling: "Do Not Shake", "Do not Freeze" or equivalent (21 CFR 610.61)	☒ Yes ☐ No ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Carton: Consider increasing the size and prominence of the route of administration, "For Subcutaneous Use (b) (4)".

Applicant's response dated August 30, 2018:

The applicant indicated the size and prominence of the route of administration statement was increased, but the size and prominence could be further enhanced. A follow-up comment will be sent.

Carton: Consider further enhancing the size and prominence of the route of administration, "For Subcutaneous Use".

Applicant's response dated September 24, 2018:

The applicant enhanced the size of the route of administration statement. It is acceptable.

Known sensitizing substances

21CFR 610.61

- Yes
- No
- N/A

Comment/Recommendation:

Dr. Fan was able to confirm the product is "Not made with Natural Rubber latex". The statement "Not made with Natural Rubber latex" appears on the tray and carton labeling, which is acceptable.

Inactive ingredients

21 CFR 610.61

21 CFR 201.100

- Yes
- No
- N/A

Comment/Recommendation:

The order of the inactive ingredients follows the same order as found with the reference product, Neulasta BLA 125031 and another biosimilar, BLA 761075. Therefore, the alphabetical order of the inactive ingredients will not be revised.

Dr. Fan was able to confirm the Q & Q for the inactive ingredients "containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in Water for Injection, USP" is accurate.

Source of the product

21 CFR 610.61

- Yes
- No
- N/A

Comment/Recommendation:

Dr. Fan confirmed the source was derived from E. coli

Minimum potency of product

21 CFR 610.61

- Yes
- No
- N/A

Comment/Recommendation:

Please include the statement "No U.S. standard of potency" per 21 CFR 610.61(r).

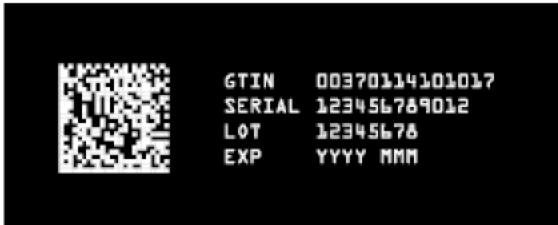
Dr. Fan confirmed there is no U.S. standard of potency.

Applicant's response dated August 30, 2018:

The applicant added the statement "No U.S. standard of potency" to the back panel of the outer carton and it is acceptable.

Rx only 21CFR 610.61 21 CFR 201.100 Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
Divided manufacturing 21 CFR 610.63	☐ Yes ☒ No ☐ N/A
Distributor 21 CFR 610.64	☐ Yes ☐ No ☒ N/A
Bar code 21 CFR 610.67 21 CFR 201.25 Comment/Recommendation: For carton and tray Please indicate the location of a linear bar code per 21 CFR 610.67. Ensure barcode has sufficient white space so that it can be scanned. https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm267392.pdf A combined DMEPA/OBP general comment was added to address this issue. Applicant's response dated August 30, 2018: The applicant added the linear bar code to the carton and tray labeling, which is acceptable.	☒ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Preparation instructions 21 CFR 201.5	☐ Yes ☐ No

	☒ N/A
<u>Package type term</u> 21 CFR 201.5 Comment/Recommendation: For carton and tray Revise the package term from "(b) (4)" to "Single-Dose". "Single-Dose" is appropriate terminology for this vial, prefilled-syringe, per United States Pharmacopeia (USP) General Chapters <659> Packaging and Storage Requirements. Applicant's response dated August 30, 2018: The applicant revised the package term on the carton and tray labeling to read "Single-dose", which is acceptable.	☒ Yes ☐ No ☐ N/A
<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15 Comment/Recommendation: DMEPA has a comment concerning the graphic. Applicant's response dated August 30, 2018: The applicant decreased the prominence of the graphic on the carton, which appears to be acceptable pending DMEPA's review.	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u> 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21	☐ Yes ☐ No ☒ N/A
<u>Sulfites; required warning statements</u> 21 CFR 201.22	☐ Yes ☐ No ☒ N/A
<u>Net quantity</u> 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	☒ Yes ☐ No

☐ N/A	
Comment/ Recommendation: Not required per the biologic regs. No statement is on the reference product Neulasta BLA 125031. The tray contains a dosage statement and the carton does not contain a statement. DMEPA is asking to place the usual dosage statement on the carton and not on the tray.	
Dispensing container 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ Yes ☐ No ☒ N/A
Other	☒ Yes ☐ No ☐ N/A
Comment/ Recommendation: The applicant's October 19, 2018 response: The applicant submitted carton labeling with a 2D bar code Drug Supply Chain Security Act.	
	
In addition, the applicant removed (b) (4) from the tray labeling. The removal (b) (4) is acceptable.	
The applicant's October 26, 2018 response. The applicant included a NDC above the GTIN and this is acceptable.	

Prescribing Information and Patient Labeling Evaluation

Regulations	Acceptable
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION	☒ Yes

21 CFR 201.57(a)(7)	☐ No ☐ N/A
<u>DOSAGE FORMS AND STRENGTHS</u> 21 CFR 201.57(a)(8)	☒ Yes ☐ No ☐ N/A
Full Prescribing Information	
<u>2 DOSAGE AND ADMINISTRATION</u> 21 CFR 201.57(c)(3)	☒ Yes ☐ No ☐ N/A
<u>3 DOSAGE FORMS AND STRENGTHS</u> 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
Comment/ Recommendation: Revised to include the identifying characteristics per 21 CFR 201.57(c)(4). Need to add "clear, colorless". The revised statement should read: Injection: 6 mg/0.6 mL clear, colorless solution in a single-dose prefilled syringe for manual use only. Dr. Fan confirmed the identifying characteristics "clear, colorless" are acceptable. The applicant revised the label to include the identifying characteristics.	
<u>6.2 IMMUNOGENICITY</u> Draft Guidance for Industry: Labeling for Biosimilar Products	☒ Yes ☐ No ☐ N/A
Comment/ Recommendation: Revised the first paragraph to be in alignment with the Guidance for Industry: Labeling for Biosimilar Products: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf "As with all therapeutic proteins*, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other pegfilgrastim products may be misleading." The revised guidance has a change in the last sentence of the paragraph above. The applicant revised the label to include the paragraph in the final guidance.	
<u>11 DESCRIPTION</u> (21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

The proprietary name was deleted from the first paragraph and replaced with the proper name because this paragraph discusses the drug substance. (revise to Pegfilgrastim-xxxx is a)

The proper name and dosage formulation was added to the second paragraph per 21 CFR 201.57(c)(12). (revise to UDENYCA (pegfilgrastim-xxxx) injection

Each syringe contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

Dr. Fan preferred to include the inactive ingredients based upon the delivered amount because there is an overfill. The release spec is "(b) (4) ml). Dr. Fan confirmed the names of the ingredients and quantities are correct.

Revise to reflect submitted DP specifications for appearance 3.2.P.5.1. "clear, colorless"

Dr. Fan proposed to include the sentence "During the pegfilgrastim manufacturing process, fermentation is carried out in nutrient medium containing the antibiotic kanamycin. However, kanamycin is cleared in the manufacturing process and is not detectable in the final product".

All of the applicant's revisions to the Description section are acceptable.

16 HOW SUPPLIED/ STORAGE AND HANDLING

21 CFR 201.57(c)(17)

- Yes
- No
- N/A

Comment/Recommendation:

Revise the first sentence to include the dosage formulation and identifying characteristics per 21 CFR 201.57(c)(17). (revise to "UDENYCA (pegfilgrastim-xxxx) injection is a clear, colorless preservative free solution supplied in a prefilled single-dose syringe with an UltraSafe Passive Needle Guard containing 6 mg pegfilgrastim-xxxx.)

The applicant has included the sentence: (b) (4)

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM342872.pdf>

Dr. Fan confirmed "The shield formulation is a non-latex containing, (b) (4) and is assembled with a (b) (4) " and it was acceptable to revise the sentence to "The needle cap of the prefilled syringe is not made with natural rubber latex".

Use the statement "Not made with natural rubber latex" if the product does not contain latex and the manufacturing of the product and container did not include the use of natural rubber latex or synthetic derivatives of natural rubber latex. Avoid statements such as "latex-free" or "does not contain latex" because they do not address the potential for accidental contamination of a product or container with latex during or after manufacturing.

May include a statement that certain components of the product are not made with latex, such as "the vial cap is not made with natural rubber latex."

Revise the third sentence to read UDENYCA is provided in a dispensing pack containing one 6 mg/0.6 mL prefilled syringe (NDC 70114-xxx-xx).

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.

Dr. Fan was able to confirm the storage condition statements were accurate.

The applicant's revisions to the How Supplied section are acceptable.

MANUFACTURER INFORMATION

For BLAs: 21 CFR 610.61, 21 CFR 610.64
For NDAs: 21 CFR 201.1

- Yes
- No
- N/A

Comment/Recommendation:

Insert the U.S. License number directly beneath the manufacturer's address.

The applicant's October 26 response:
The applicant was able to incorporate a U.S. License number.

INSTRUCTIONS FOR USE AND PATIENT INFORMATION

TITLE (NAMES AND DOSAGE FORM)

- Yes
- No
- N/A

Comment/Recommendation:

Instructions for Use:
Revise the title block to include the proprietary name, proper name, dosage formulation, and consider adding the route of administration. Consider the format below:

UDENYCA
(pegfilgrastim-xxxx)
Injection
for subcutaneous use

The applicant's August 27, 2018 response:
Is acceptable.

STORAGE AND HANDLING

- Yes
- No
- N/A

INGREDIENTS

- Yes

	☐ No ☐ N/A
MANUFACTURER INFORMATION For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1 Comment/ Recommendation: Instructions for Use: Please include the U.S. license number per 21 CFR 610.61(b) after the manufacturer's name and address at the end of the document. The applicant's October 26 response: The applicant was able to incorporate a U.S. License number.	☒ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on October 31, 2018)
<\\cdsesub1\evsprod\bla761039\0078\m1\us\11423-final-pi.docx>
- Instructions for Use (submitted on October 31, 2018)
<\\cdsesub1\evsprod\bla761039\0078\m1\us\11423-final-ifu.docx>
- Patient Information (submitted on October 31, 2018)
<\\cdsesub1\evsprod\bla761039\0078\m1\us\11423-final-ppi.docx>
- Container Labels (submitted on October 26, 2018)





Scott
Dallas

Digitally signed by Scott Dallas
Date: 11/01/2018 08:58:26AM
GUID: 508da712000294048aa136a18a6af06a



Ying Xin
Fan

Digitally signed by Ying Xin Fan
Date: 11/01/2018 10:02:56AM
GUID: 508da6dc000266e7f77d37bc2e4a5a87

Recommendation: Approval

**BLA 761039
Review 2
October 15, 2018**

Drug Name/Dosage Form	UDENYCA (pegfilgrastim-cbqv) /injection
Strength/Potency	6mg/0.6mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
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
Applicant/Sponsor	Coherus BioSciences, Inc.

Product Overview

UDENYCA (pegfilgrastim-cbqv) is a pegylated recombinant granulocyte colony stimulating factor (PEG-G-CSF). G-CSF is a growth factor that stimulates production of neutrophils and neutrophil precursors by binding the G-CSF receptor on blood cells of the neutrophilic granulocyte. The binding initiates signal transduction that leads to the survival, proliferation, and differentiation of neutrophil progenitor cells into mature neutrophils. UDENYCA (pegfilgrastim-cbqv) is a single-dose pre-filled syringe for subcutaneous injection.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/ DIVISION
Drug Substance (DS)	Ying-Xin Fan	OBP/DBRR-IV
Drug Product (DP)	Ying-Xin Fan	OBP/DBRR-IV
Analytical Similarity	Ying-Xin Fan	OBP/DBRR-IV
Immunogenicity Assays	Haoheng Yan	OBP/DBRR-IV
Immunogenicity Data	Fred Mills	OBP/DBRR-IV
Business Regulatory Process Manager	Anh-Thy Ly	OPQ/OPRO
Facilities	Marion Michaelis, Peter Qiu	OPF/DIA
Microbiology	Monica Commerford (DS), Jessica Hankins (DP), Reyes Candau-Chacon (QAL), Patricia Hughes (Branch Chief)	OPF/DMA
Labeling	Scott Dallas	OBP
Application Technical Lead	Joslyn Brunelle	OBP/DBRR-IV
Review Chief	Joel Welch	OBP/DBRR-IV

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/ DIVISION
RPM	Natasha Kormanik	OHOP/DHP
Cross-disciplinary Team Lead	Nicole Gormley	OHOP/DHP
Medical Officer	Bindu Kanapuru	OHOP/DHP
Pharm/Tox	Michael Manning, Chris Sheth	OHOP/DHP
Clinical Pharmacology	Olanrewaju Okusanya, Sarah Schrieber	OTS/OCF
Statistics	Jingjing Ye, Lei Nie	OTS/OB
CMC Statistics	Meiyu Shen, Tsong Yi	OTS/OB/DBVI
Biosimilar Policy	Carla Lankford, Sue Lim, Leah Christl	OND/TBBS

- a. Names
 - i. Company Code: CHS-1701
 - ii. Non-Proprietary: pegfilgrastim- cbqv
 - iii. CAS registry number 208265-92-3
 - iv. Compendial Name: PEGylated Granulocyte-Colony Stimulating Factor (G-CSF), pegfilgrastim
 - v. OBP systematic name:
CONJ: RPROT P09919 (CSF3_HUMAN); PEG [CHS-1701]

- b. Pharmacologic category: Leukocyte Growth Factor

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	5/3/18
IR response (sequence 0059, inspection)	Received 5/30/18
IR response (sequence 0061, inspection)	Received 6/6/18
IR response (sequence 0062, CDRH)	Received 6/14/18
IR response (CDRH)	Email response 7/10/18
IR response (sequence 0063, DMA)	07/27/18
IR response (sequence 0064, DMA, OBP)	08/14/18
IR response (sequence 0070, OBP)	09/20/2018
Correction (Sequence 0073)	10/9/18

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	Type III	(b) (4)	(b) (4)	2/3	Adequate (review dated 6/2/2016)	
	Type III			3	N/A	
	Type III			3	N/A	
	510(k)			3	N/A	
	Type II			3	N/A	
	Type V			3	N/A	
	Type V			3	N/A	
	Type III			3	N/A	

		(b) (4)			
(b) (4)	Type III		3	N/A	

¹Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available;6 – Other (explain under "Comments")

²Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

3. CONSULTS:

DISCIPLINE/ TOPIC	DATE of REVIEW	STATUS	RECOMMENDATION	REVIEWER
CDRH ODE	July 10, 2018	completed	Adequate	Keith Marin
CDRH OC	July 26, 2018	completed	Adequate	Louis Corbin

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761039 for UDENYCA, (pegfilgrastim-cbqv), a proposed biosimilar to US-licensed Neulasta manufactured by Coherus Biosciences, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of UDENYCA is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

The analytical similarity data submitted by the applicant support a demonstration that UDENYCA is highly similar to US-licensed Neulasta notwithstanding minor differences in clinically inactive components. The data also support that UDENYCA has the same strength as US-licensed Neulasta.

Finally, the CR deficiencies and additional comments described in the June 9 2017, complete response letter were adequately addressed by Coherus Biosciences, Inc. in the May 3, 2018 resubmission in each case.

b. Draft approval action letter language

- Manufacturing locations
 - Drug Substance: KBI Biopharma, Inc., Boulder, CO
 - Drug Product: (b) (4)
- Presentation, fill size, strength, dosage form: single-dose, prefilled syringe, 6mg/0.6ml, injection
- Dating period
 - Drug substance: (b) (4) months at (b) (4) °C
 - Drug Product: 36 months at 2-8°C
- Exempt from lot release

c. Benefit/Risk Considerations

The proposed biosimilar UDENYCA has been evaluated and compared to US-licensed Neulasta using a variety of structural, physicochemical, and functional assays. A total of 13 lots of CHS-1701 Drug Product and 22 lots of US-licensed Neulasta were evaluated in the analytical similarity assessment. A tiered approach was used when comparing both product and the tier assignment was based on the criticality risk ranking and method capabilities. Table A below lists the analytical methods and their corresponding tier assignments.

Biological Function	Attribute	Method	Tier
Efficacy and immunogenicity	Primary structure (including amino acid sequence and disulfide structure)	Peptide map by Glu-C digest with LC-MS/MS	NA ^a
Efficacy	Biological activity (percent potency)	Proliferative bioassay	1
Efficacy	Protein content (mg/mL)	Protein Content by UV	1
Efficacy	Receptor binding (KD)	SPR	2
Efficacy	Molar mass (kDa)	SEC-MALS	2
Efficacy	Mass (Mw) of PEG conjugate (kDa)	SEC-MALS	2
Efficacy	PEG polydispersity (Pd)	SEC-MALS	2
Efficacy	PEG polydispersity (Pd)	LC-MS	3
Efficacy and immunogenicity	HMW species (including dimer/diPEG, oligomers) (percent area)	SEC-MALS	2
Efficacy and immunogenicity	HMW species (including dimers/diPEG and oligomers)	SDS-PAGE	3
Efficacy and immunogenicity	unPEGylated filgrastim	SEC	3
Efficacy and immunogenicity	Clips	SEC	3
Efficacy and immunogenicity	Clips	SDS-PAGE	3
Efficacy	diPEGylated species (percent area)	CEC	2
Efficacy and immunogenicity	Total oxidized species (percent area)	RPC	2
Efficacy and immunogenicity	Total deamidated species (percent area)	RPC	2
Efficacy and Immunogenicity	Partially reduced species	RPC	3
Efficacy and immunogenicity	Norleucine misincorporation	RPC	3
Immunogenicity	SVPs $\geq 2 \mu\text{m}$ (total counts/mL)	MFI	2
Efficacy	Intact mass and PEG linker analysis	LC-MS	3 ^b
Efficacy and immunogenicity	unPEGylated N-terminus	Edman degradation	3
Efficacy and immunogenicity	free PEG	SDS-PAGE with iodine stain	3
Efficacy and immunogenicity	Secondary/tertiary structure	CD, 2D NMR, DSC, fluorescence, HDX	3
Efficacy	Extinction coefficient	SEC-UV-RI	3
Immunogenicity	HCPs	ELISA by Cygnus kit	3
Immunogenicity	Total protein pattern, including all impurities and HCPs	2D gels with silver stain	3
Efficacy and immunogenicity	Size profile: Sedimentation Behavior	AUC	3
Efficacy and immunogenicity	Charge profile	IEF gel	3
Immunogenicity	Clarity	Turbidimetry	3
Immunogenicity	Color	Visual inspection	3

Tier 1 includes assays that evaluate the clinically relevant mechanism(s) of action with a high level of precision and accuracy. Tier 1 attributes are potency and protein concentration; statistical equivalence testing was performed to demonstrate similarity, except for primary structure, where an identity match was confirmed.

Tier 2 contains assays with lower risk ranking, specifically those measuring attributes that impact clinical function only indirectly, those with lower levels of precision, or those measuring species present in low abundance. Similarity for these attributes was assessed based on quality ranges. One sided ranges were used for the following attributes: High Molecular Weight species, unPEGylated species and PEG polydispersity by SEC-MALS, total oxidized and deamidated species by reverse phase chromatography (RPC), diPEGylated species by cation exchange chromatography (CEC), and subvisible particles. Two sided ranges were defined for the following attributes: molar mass, mass of PEG conjugate, and receptor binding.

Tier 3 contains attributes that are evaluated based on qualitative results or attributes of low criticality. Similarity was assessed by comparisons of images or graphical representations of the raw data. No statistical analysis was performed for tier 3 attributes due to the qualitative nature of the data.

The categorization of attributes and corresponding analytical methods proposed by the applicant are appropriate and a sufficient number of lots is included to perform meaningful review of data. Overall, the purity is comparable between Udenyca and US-licensed Neulasta, with US-licensed Neulasta containing slightly higher product related variants due to the age of the material at the time of testing. The data provided support the conclusion that Udenyca is highly similar to US-licensed Neulasta.

Furthermore, the deficiencies related to immunogenicity described in the complete response dated June 7, 2017 have been addressed in the resubmission dated May 8, 2018. Coherus Biosciences, Inc., developed and validated a new neutralizing antibody (Nab) assay using the contract testing facility (b) (4). The assay was found to be acceptable. Based on this neutralizing assay, no treatment-emergent NAb were detected in any of the 4 clinical studies (Studies CHS-1701-01, CHS-1701-03, CHS-1701-04, and CHS-1701-05).

Coherus also provided additional information to address the differences in ADA incidence rates between the Udenyca and US-licensed Neulasta treatment arms in Study CHS-1701-04. Coherus Biosciences Inc. provided a new anti-G-CSF titer assay which was found to be acceptable. ADA were classified as anti-PEG and/or anti-G-CSF. Using the new anti-G-CSF titer assay, the majority of G-CSF titers were transient. When focusing only on the measurable G-CSF titers, there was a low absolute incidence with 2 in the CHS-1701 arm compared to 1 in the US-licensed Neulasta arm. Thus, there is no significant difference related to G-CSF titers.

Overall, the difference in ADA incidence between the Udenyca and US-licensed Neulasta groups is driven by non-neutralizing, low titer, PEG-reactive ADA. The anti-PEG ADA are commonly present in healthy subjects. The anti-PEG antibodies found in CHS-1701 studies were at low titers, which are not clinically relevant. Furthermore, the clinical data from CHS-1701 studies does not indicate any impact to efficacy, PK, or safety.

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II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below lists the critical quality attributes (CQAs) for pegfilgrastim-cbqv. CQA's are monitored and controlled during release and stability testing.

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy
Potency	Efficacy	Intrinsic to the molecule	(b) (4)
HMW species including Dimers, Oligomers, diPEG <i>(Product related variants)</i>	Efficacy and Immunogenicity	Formed during manufacturing process and storage	
Oxidation <i>(Product related variants)</i>	Efficacy and Immunogenicity. Oxidized species demonstrate reduced potency.	Formed during manufacturing process and storage	
Deamidation <i>(Product related variants)</i>	Efficacy and immunogenicity	Formed during the manufacturing process and storage	
diPEGylated species <i>(Product related variants)</i>	Bioavailability	Formed during the pegylation step	
Double size PEG species <i>(Product related variants)</i>	Bioavailability	Formed during pegylation step	
Non-pegylated species	Bioavailability	Unreacted during pegylation step	

<i>(Product related variants)</i>			(b) (4)
Clips and truncations <i>(Product related variants)</i>	Efficacy and Immunogenicity	Formed during the manufacturing process and storage	
Reduced species <i>(Product related variants)</i>	Efficacy and Immunogenicity	Formed during (b) (4)	

B. CHS-1701 Drug Substance Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 provides a summary of critical quality attributes (CQAs) that are derived from the drug substance manufacturing process.

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy
Host Cell Proteins (HCP)	Safety and Immunogenicity	(b) (4)	(b) (4)
DNA	Safety and Immunogenicity	(b) (4)	
Bacterial endotoxins	Safety, purity, and immunogenicity	Raw materials and manufacturing process	
Bioburden	Safety, purity, and efficacy (degradation or modification of	Raw materials and manufacturing process	

(b) (4)

	the product by contaminating microorganisms)		
Protein concentration	Efficacy (dosing)	Final formulation occurs on drug substance	
(b) (4)	Stability	Final formulation occurs on drug substance	
(b) (4)			
Leachables from (b) (4)	Safety	Entire process	
(b) (4)	Safety	(b) (4)	
(b) (4)	Safety	(b) (4)	
m-PEG aldehyde	Safety	PEGylation	

			(b) (4)
(b) (4)	Safety	(b) (4)	
(b) (4) [redacted] [redacted]	Safety	(b) (4)	
Kanamycin	Safety	Fermentation	
(b) (4)	Safety	(b) (4)	

			(b) (4)
(b) (4)	Safety	(b) (4)	

a. Description

PEGylated G-CSF consists of a PEG molecule linked to recombinant methionyl human granulocyte colony stimulating factor (referred to as Coherus r-met-Hu-G-CSF). The total molecular weight is approximately 39 kDa.

The "Coherus r-met-Hu-G-CSF" protein is the human G-CSF sequence with an additional methionine on the amino terminus. It is produced in *E. coli*, is non-glycosylated, and is a single polypeptide chain with a total of 175 amino acids and has an approximate molecular weight of 19 kDa.

The PEG molecule (approximately 20kD) is attached by a stable covalent amide bond to the N-terminal methionine of r-met-Hu-G-CSF.

b. Mechanism of action

G-CSF is a haematopoietic growth factor that regulates the production of neutrophils within the bone marrow. Activity is initiated by binding to the G-CSF receptors on cells of myeloid lineage, such as granulocytic precursors and mature neutrophils. G-CSF stimulates growth and differentiation of granulocytic precursor cells, shortens the transit time of developing granulocytes, and facilitates the migration of the mature cells into the peripheral blood. This results in a rapid induction and sustained elevation in absolute neutrophil counts (ANC) in blood, which is a direct measure of in vivo activity. The pegylation increases the size of the protein, which in turn reduces renal clearance and increases the half-life of the protein.

c. Potency Assay

The potency is assessed using a cell based proliferation assay with the NFS-60 cell line. NFS-60 is a murine myeloblastic cell line that expresses the G-CSF receptor and is dependent on G-CSF for growth and maintenance of viability. Cells are grown in a 96 well plate. Proliferation is measured by a colorimetric assay using Thiazolyl Blue Tetrazolium Bromide (MTT); MTT is a yellow tetrazole that is reduced to purple formazan in living cells. The amount of formazan can be measured using a spectrophotometer and is directly proportional to the number of living cells. Biological activity is reported relative to reference material.

d. Reference material(s)

The sponsor has primary reference standards to both unpegylated (169A14-02 pre-PEG RS) and pegylated G-CSF (169A14-02 PEG RS). The sponsor also provided protocol for future reference standard qualification.

e. Critical starting materials or intermediates

(b) (4)

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a. Container closure

(b) (4)

**h. Dating period and storage conditions**

The data supports a (b) (4) month shelf-life for drug substance when stored at (b) (4) °C. Note the (b) (4) month shelf life is granted based on Coherus' request; however, up to 24 months of stability data was collected for four primary registration batches and three supportive batches.

C. Drug Product [UDENYCA] Quality Summary

Table 3 provides a summary of the drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy
Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process	(b) (4)
Container Closure Integrity Testing (CCIT)	Safety	Container closure breaches during storage	
Endotoxin (Contaminant)	Safety and Purity	Raw materials, contamination may be introduced throughout the DP manufacturing	

		process	(b) (4)
Protein concentration	Efficacy (dosing)	(b) (4)	
Polysorbate 20	Stability		
Deliverable Volume	Efficacy (dosing)	Manufacturing process	
Clarity, Color, Visible particles	Efficacy and Safety	Formulation	
pH	Stability	Formulation	
Osmolality	Safety	Formulation	
Particulate matter	Safety and Immunogenicity	Container Closure System (CCS)	
Identity (peptide mapping)	Efficacy	N/A	
(b) (4)	Safety	Container Closure System (CCS)	

(b) (4)	Safety	Container Closure System (CCS)	(b) (4)
Leachables/extractables	Safety	Manufacturing equipment and CCS	
Device functionality tests	Safety and Efficacy	Container Closure System (CCS)	

- a. Strength: 6mg/0.6 mL
Single use, pre-filled syringe (PFS) for subcutaneous injection
- UDENYCA has the same strength as US-licensed Neulasta.
- b. Summary of Product Design
UDENYCA was developed to be a biosimilar to US-licensed Neulasta. It has the same route of administration, dosage form, and strength as the reference product.
- c. List of Excipients
(b) (4) (b) (4) sorbitol, (b) (4) polysorbate 20, pH 4.0
- d. Reference material(s)
The same reference material are used for DS and DP
- e. Manufacturing Process
(b) (4)
- f. Container Closure
The drug product container closure is a (b) (4) glass syringe barrel (b) (4) with (b) (4) rubber plunger stopper and 29 1/2 gauge needle. In addition, there is a needle safety device (b) (4)
- g. Expiration Date & Storage Conditions

The sponsor proposed 36 month shelf-life for drug product stored at 2-8°C. The data supports 36 months shelf-life based on real-time stability data (2-8°C) for four primary registration batches. Additional batches are included as supportive with 30 months of stability data.

h. List of co-packaged components – not applicable

D. Biopharmaceutics Considerations- Not applicable

E. Novel Approaches/Precedents-None

F. Any Special Product Quality Labeling Recommendations-None

G. Environmental Assessment

In Module 1, Coherus Biosciences Inc. is requesting a categorical exclusion under 21 CFR 25.31 from the need to prepare an environmental assessment.

The claim of categorical exclusion is accepted.

H. Establishment Information

OVERALL RECOMMENDATION: Approve Facilities					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/ FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug Substance Manufacturing, Release and Stability Testing	KBI Biopharma, Inc., Boulder, CO	079582679/ 3011326133	N/A	VAI Summary of five observations: (b) (4)	Approve



QUALITY REVIEW



				(b) (4)	
Drug Substance Release and Stability Testing	(b) (4)		Approve based on profile		Approve
				NAI	Approve
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER		INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug Product Manufacturing Drug Product	(b) (4)			VAI Summary of three	Approve

Release Testing	(b) (4)			observations: (b) (4)	
Drug product release and stability testing	(b) (4)		Approve based on profile		Approve
Drug Product Release and Stability Testing	KBI Biopharma, Inc., Boulder, CO	079582679/ 3011326133		VAI Summary of nine observations: - Instruction for	Approve

				defining where a batch begins was not clearly defined. - Annual GMP training lacked comprehensive GMP subject matter. -Storage of CHS-170 bulk drug substance, materials control, Standard Operating Procedure instruction and quality oversight were found to lack instruction or were inadequate in several areas.	
Assembly of the Safety Device Labeling and Packaging		(b) (4)	Approve based on profile		Approve
Combination Product – Medical Device Manufacturer	Coherus BioSciences, Inc., Redwood City, CA	078502849/ 3009682611		NAI	Approve
Functional performance testing of the safety device for batch		(b) (4)	Approve based on profile		Approve



QUALITY REVIEW



release and stability					

I. Facilities

The inspection of the drug substance manufacture and testing facility, KBI Biopharma, Inc. (KBI), was conducted from September 5-12, 2018 by ORA and CDER/OPQ/DMA and CDER/OPQ/OBP. The inspection was classified as VAI. The facility was approved based on the inspectional assessment.

The inspection of drug substance testing facility, (b) (4) was conducted (b) (4) by FDA /ORA and was classified NAI.

The inspection of the drug product manufacturing and testing facility, (b) (4) was conducted (b) (4) by CDER-DIA and was classified VAI. The facility was approved based on the inspectional assessment.

The inspection of the medical device manufacturer Coherus BioSciences, Inc. was conducted March 13-16, 2017 by San Francisco FDA District Office and was classified NAI.

For additional information see the Facilities Review: Division of Inspectional Assessment.

J. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved:



Post-approval Stability Protocol and Stability Commitment (pegfilgrastim-cbqv, KBI Biopharma)

- ii. Outstanding review issues/residual risk: none
- iii. Future inspection points to consider: none

b. Drug Product

i. Protocols approved:

Post-approval Stability Protocol and Stability Commitment (UDENYCA, Prefilled Syringe)

- ii. Outstanding review issues/residual risk: none
- iii. Future inspection points to consider: None

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Joslyn
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Welch

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Thuy Thanh
Nguyen

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Patricia
Hughes Troost

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To: Administrative File, STN 761039-Orig-1-Resub-57
From: Marion Michaelis, CSO, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Facility Review Updates for Resubmission-57 after CR Letter Dated June 9, 2017. This memo supplement DIA facility memo for Orig-1 dated 5/5/2017
US License: Pending
Applicant: Coherus Bioscience, Inc.
Mfg Facility: **Drug Substance:** KBI Biopharma, Inc., Boulder, CO
FEI: 3011326133
Drug Product: (b) (4)
FEI: (b) (4)
Product: Established/Proper Name: CHS-1701, proposed biosimilar to US-licensed pegfilgrastim
Dosage: Pre-filled Syringe, Solution for Injection (subcutaneous), 6 mg / 0.6 mL
Indication: 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
Due Date: 11/3/2018

RECOMMENDATION:

Approval is recommended from a facility perspective.

SUMMARY

Coherus Bioscience, Inc (Coherus) submitted a new Biologics License Application (BLA) dated August 9, 2016 for CHS-1701. The commercial CHS-1701 drug product has been developed as a proposed biosimilar to the reference product, Neulasta® (pegfilgrastim). A Complete Response (CR) Letter dated June 9, 2017 was issued to Coherus. The firm resubmitted the application May 3, 2018. This review memo for Resub-57 is an update of facilities information. The facility review memo dated May 5, 2017 for Orig-1 and uploaded in panorama is a comprehensive facility review for the BLA and approval was recommended for facilities during the first review cycle. As part of this BLA Resub-57 there were three pre-license/pre-approval inspections conducted which were the following:

- KBI Biopharma, Inc. (KBI), FEI:3011326133 – Drug Substance (DS) Manufacturing Inspection Conducted 9/5-12/2017 by ORA and CDER/OPF/DIA- Outcome classified as VAI (CMS Case #242579)
- Coherus Bioscience, Inc (Coherus Analytical Laboratory), FEI:3011671070 – Conducted 7/24-26/2017 by CDER/OPF/DIA. – Outcome classified -as NAI (CMS Case #241188)

- (b) (4), FEI: (b) (4) – Conducted (b) (4) by ORA– Outcome classified as NAI.

Facility inspection history with Resub-57 was updated for the following manufacturing and testing sites:

- (b) (4), FEI: (b) (4)
- (b) (4) FEI: (b) (4)
- (b) (4), FEI: (b) (4)
- (b) (4) FEI: (b) (4)

The scope of this review is an update of facility compliance status at the time of review of Resub-57. The facility updates are discussed in the “Review” section of this memo below. Additionally a CDRH consult memo was performed with this review cycle and details are discussed below. All facilities are in a favorable compliance status. From a facility perspective approval is recommended.

REVIEW:

With the submission of Resub-57 there was no changes to facility information for this application. This review is an update for facility compliance status to include information regarding the three inspections conducted under this Resub-57 review cycle.

Drug Substance Manufacturing

3.2.S.2.1 DS Manufacturers

Coherus is proposing the following manufacturing and testing facilities for CHS-1701 drug substance:

SITE INFORMATION	FUNCTION	FEI NUMBER
KBI Biopharma, Inc., 2500 Central Avenue, Boulder, CO 80301	CBI- Drug Substance Manufacturing, Release and Stability Testing	3011326133
(b) (4)	CTL- Drug Substance Release and Stability Testing	(b) (4)
(b) (4)	LMN- Drug Substance Release and Stability Testing (b) (4) testing DS and also cell bank testing)	(b) (4)

Inspection History:

KBI Biopharma, Inc. (FEI: 3011326133) – DS Manufacturing and Release and Stability Testing

The most recent inspection was a pre-license (PLI) inspection for this application and was conducted 9/5-12/2018. The inspection was classified as VAI with the issuance of a 5 item 483. A summary of the 5 items is the following: (b) (4)

(b) (4)

A compliance review was conducted under CMS Work ID #242579. KBI provided

adequate responses to the observations. Both OBP and DMA were consulted to verify adequacy of the firm's corrections. The compliance review indicates concurrence with the VAI recommendation.

Prior to this on 12/5-9/2016 a PLI for this application during the first review cycle for CHS-1701 DS manufacturing and first-time inspection of this Boulder, CO facility. The inspection was conducted in accordance with CP 7346.832, Pre-Approval Inspections, ICH Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Coverage during the inspection included facilities, equipment and processes, procedures and conformance to the application. The inspection resulted in the issuance of a 9-item FDA Form 483. A summary of the nine observations was the following: instruction for defining where a batch begins was not clearly defined, annual GMP training lacked comprehensive GMP subject matter, storage of CHS-170 bulk drug substance, materials control, standard operating procedure instruction and quality oversight were found to lack instruction or were inadequate in several areas. The initial field recommendation was withhold. The withhold recommendation was downgraded to VAI after reviewing the firm response to the 483 observations which is documented under CMS Work ID#151032.

(b) (4)

Drug Product Manufacturing

3.2.P.3.1. DP Manufacturers

Coherus is proposing the following manufacturing and testing facilities for CHS-1701 DP:

SITE INFORMATION	FUNCTION	FEI NUMBER
(b) (4)	SVS and IDD- Drug Product Manufacturing Drug Product Release Testing	(b) (4)
	CTL - Drug product release and stability testing	(b) (4)
KBI Biopharma, Inc., 2500 Central Avenue, Boulder, CO 80301	CBI - Drug Product Release and Stability Testing	3011326133

BLA 761039-Resub 57: CHS-1701, Coherus Bioscience, Inc.

(b) (4)	SVS - Assembly of the Safety Device Labeling and Packaging	(b) (4)
	CTL-Functional performance testing of the safety device for batch release and stability	(b) (4)
Coherus BioSciences, Inc., Redwood City, CA	IDD - Combination Product – Medical Device Manufacturer	3009682611
Coherus Analytical Laboratory, 4014 Camino Ranchero Suite A, Camarillo, CA, 93012	CTL – Biosimilarity assessment testing only (not a commercial manufacturing or testing site)	3011671070

Inspection History:



KBI Biopharma, Inc. (FEI: 3011326133) – DP and Release and Stability Testing

See inspection history documented above under “Drug Substance Manufacturing Section”



Coherus BioSciences, Inc. (FEI: 3009682611) Combination Product – Medical Device Manufacturer

The last inspection on 3/16/2017 was an initial inspection of this Coherus, Redwood City, CA facility. The inspection was conducted in accordance with CPGM 7383.001, Medical Device PMA Preapproval and PMA Postmarket Inspections, CPGM 7382.845, Inspection of Medical Device Manufacturers, the FDA Guide to Inspections of Quality Systems, the San Francisco FDA District Office FY17 work plan, and eNSpect Operation ID # 54697. This establishment inspection was directed as a premarket approval inspection by the Center for Devices and Radiological Health. This inspection covered the firm's combination product identified in part of this CHS-1701, BLA # 761039. The inspection was classified as NAI and profile IDD was covered.

Coherus Analytical Laboratory, FEI: 3011671070 – Biosimilarity Assessment Testing

The most recent and first time inspection of this facility was a pre-approval inspection for this BLA and took place 7/24-26/2018. The inspection was conducted by CDER/OPF/DIA. The inspection was conducted to verify data and other aspects of data acquisition and analysis as it relates to the analytical similarity assessment as associated with this BLA. This is not a commercial manufacturing or testing facility for this application. The inspection was classified as NAI. The compliance review of the inspection report and associated information related to the inspection was conducted under CMS Work #241188. The compliance decision concurred with the NAI recommendation.

CDRH Consult for Resub-57

A CDRH review memo dated 6/19//2018 was submitted for review of Resub-57. The consult request included an evaluation of the facilities involved in any aspect of the device component. There was a recommendation for several inspections, however OPF/DIA decided that the risk was very low and inspections would not be necessary. There was only one device inspection conducted for this application during the first cycle review. This inspection took place at Coherus Bioscience Inc. in Redwood City, CA. This is the offices of the applicant and a non-manufacturing site, and they are responsible for the design controls and device history file for the pre-filled syringe. The CDRH memo for Resub-57 recommends approval.

CONCLUSION:

Adequate information for facilities and equipment were provided for CHS-1701 DS and DP manufacturing which is documented in DIA facility review dated 5/5/2017. Review of facility compliance status and information from inspections conducted during this review cycle for Resub-57 are acceptable, and therefore approval is recommended from a facility perspective.

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Michaelis -S
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Date: 2018.10.19 07:41:18 -04'00'

Marion Michaelis
Consumer Safety Officer
CDER/OPQ/OPF/DIA/B1

Zhihao Qiu
-S

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Zhihao (Peter) Qiu, Ph.D.
Branch Chief
CDER/OPQ/OPF/DIA/B1



Marion
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Zihao Peter
Qiu

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BLA STN 761039
Product: Pegfilgrastim-cbqv
Manufacturer Coherus BioSciences

OBP CMC Review Data Sheet

1. BLA#: 761039
2. Review Date: September 12, 2018
3. Primary Review Team:
 - a. Medical Officer: Bindu Kanapuru
 - b. Pharm/Tox: Sriram Subramaniam
 - c. Product Quality Team: Ying-Xin Fan (Drug Substance, Drug Product, Analytical Similarity)
Haohang Yan (Immunogenicity Assays)
Fred Mills (Immunogenicity Data)
Monica Commerford (Micro/DS)
Jessica Hankins (Micro/ DP)
 - d. Facilities: Marion Michaelis
 - e. Clinical Pharmacology: Michael Manning
 - f. Statistics: Qing Xu/Yuan-Li Shen
 - g. OBP Labeling: Scott Dallas
 - h. RBPM: Anh-Thy Ly

4. Major GRMP Deadlines:

- a. Filing Meeting: June 15, 2018
- b. Mid-cycle meeting: August 1, 2018
- c. Wrap-up meeting: October 15, 2018
- d. Primary review due: October 10, 2018
- e. Secondary review due: October 17, 2018
- f. PDUFA action date: November 03, 2018

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request	July 31, 2018
Information Request	September 17, 2018

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761039/00056	May 03, 2018	Yes
STN 761039/00064	August 14, 2018	Yes
STN 761039/0070	September, 2018	Yes

7. Drug Product Name/Code/Type:
 - a. Proprietary Name: Udenyca
 - b. Trade Name: Udenyca
 - c. Non-Proprietary Name/USAN: Pegfilgrastim-cbqv
 - d. CAS Name:

- Colony-stimulating factor (human), 3-hydroxypropyl-N-methionyl-, 1-ether with a-methyl-w- hydroxypoly (oxy-1,2-ethanediyl)
- CAS registry number: 208265-92-3

e. Common Name: Pegylated G-CSF

f. INN Name: Pegfilgrastim

g. Compendial Name:

h. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [CHS1701]

i. Other names: CHS-1701

8. Pharmacological Category: Leukocyte growth factor

9. Dosage Form: Injection

10. Strength/Potency:

(i): The concentration/strength of the Drug Product: 6 mg/0.6 mL

(ii): Type of potency assay(s): cell proliferation potency assay

11. Route of Administration: Subcutaneous injection

12. Referenced Drug Master Files (DMF):

DMF # Type	HOLDER	ITEM REFERENCED	Letter of Cross- Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	(b) (4)	Yes	None
			Yes	None
			Yes	None
			Yes	None

13. Inspectional Activities:

The pre-approval inspection of the KBI Biopharma, Inc. drug substance manufacturing site in Boulder, CO, was conducted from Sep 4 to Sep 12 2018 and was classified VAI. The inspection team consisted of Jamie L. C. Dion, Consumer Safety Officer (ORA), Scott R. Nichols, PhD Microbiologist, (OPQ/OPF/DMA), and Ralph M. Bernstein, PhD Biologist (OPQ/OBP).

The pre-approval inspections for assessment of analytical similarity data of Coherus Analytical Laboratory in Camino, CA was conducted from July 24 to July 26. No issue was observed.

The inspection of (b) (4) that performs (b) (4) in-process test and MCB release tests by ORA is scheduled in October.

14. Consults Requested by OBP:

None

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

I recommend approval of BLA 761039 for Pegfilgrastim-cbqv manufactured by Coherus BioSciences. The data submitted in this Biologics License Application adequately support the conclusion that the manufacture of Udenyca (Pegfilgrastim-cbqv) is well controlled and leads to a product that is pure and potent. The conditions used in manufacturing process have been adequately validated by manufacture of multiple Drug Substance and Drug Product batches. The proposed shelf life of formulated Drug Substance is (b) (4) months at (b) (4) °C; the proposed shelf life for Drug Product is 36 months at 5 ± 3 °C. The proposed shelf lives are supported by the stability data in the submission. The Sponsor has employed a large number and wide range of orthogonal, highly sensitive methods to characterize structural and functional similarities between the biosimilar UDENYCA and its reference product, US-Neulasta. The results from the analytical similarity assessment adequately support that UDENYCA is highly similar to US-Neulasta.

It is recommended that Udenyca (Pegfilgrastim-cbqv) be approved for human use and under conditions specified in the package insert.

II. List of Deficiencies to be communicated: None

III. List of Post-Marketing Commitments/Requirements:

None

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

The Sponsor claims a categorical exclusion for Pegfilgrastim-cbqv pursuant to 21 CFR 25.20 and FDA guidance for industry, Environmental Assessment of Human Drug and Biologics applications (1998).

Reviewer comment: *Categorical Exclusion is appropriate for this product and is granted.*

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BACKGROUND

This BLA was initially submitted on August 9, 2016. The Agency issued a Complete Response Letter (CRL) on June 9, 2017 to the Sponsor after review of the original submission. This resubmission (SN#0056) was received on May 03, 2018.

Reviewer comment: *Since the Module 3 in the original resubmission was poorly prepared; the Sponsor extensively revised many sections in this module not only to address deficiencies listed in the CRL, but also to improve overall clarity and consistency throughout the BLA. The sections that have extensive changes will be reviewed in its entirety in the resubmission; for Sections with slight reversions, the changes in the resubmission will be summarized and reviewed.*

S. DRUG SUBSTANCE (DS)

3.2. S.1.1 Nomenclature

Table 1: General Information on pegfilgrastim-cbqv

INN	pegfilgrastim
Compendial names	PEGylated G-CSF, pegfilgrastim
Chemical name	Recombinant N-(3-hydroxypropyl) methionylcolony-stimulating factor (human), 1-ether with α -methyl- ω -hydroxypoly(oxyethylene)
Company code	CHS-1701
CAS registry number	208265-92-3
Non-proprietary name and suffix	pegfilgrastim-cbqv
Proprietary Name	UDENYCA™

CAS = Chemical Abstracts Service; G-CSF = granulocyte-colony stimulating factor; INN = International Nonproprietary Name

Reviewer comment: *The PEGylated DS was given a Non-proprietary name and suffix (USAN) “pegfilgrastim-cbqv” in the resubmission.*

Only change made in Sections 3.2.S.1.2 Structure and 3.2.S.1.3 General properties is that the experimental molecular weight for pegfilgrastim-cbqv is revised from 39 kD to 39.2 kD.

3.2. S.2 MANUFACTURE

3.2. S.2.1 Manufacturer(s)

The manufacturers and testing facilities for CHS-1701 DS are provided in Table 1.

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

3.2. R.1 ANALYTICAL SIMILARITY ASSESSMENT

Reviewer comment: Refer to Dr. Jacek Cieslak review of the Analytical Similarity Assessment of the original BLA in Panorama. Two (2) CR comments are related to similarity assessment: CR comment 1 on lack of potency evaluation in the forced degradation study and CR comment 2 on omission of potency result of US Neulasta lot 1054829 in the Tier 1 analyses.

The Sponsor's responses to these CR comments are reviewed below.

In the original BLA, the Sponsor provided results from a forced degradation study (referred to as "Study 1") to compare degradation behavior of CHS-1701 and US Neulasta under stressed conditions. The samples were subjected to forced degradation conditions including oxidation, light exposure, heat treatment, acid and base

exposure and analyzed by chromatographic methods (SEC, CEX, and RPC) and SDS-PAGE. However, the Sponsor did not evaluate the potency of CHS-1701 and US Neulasta in the forced degradation study. The CR comment 1 requests the Sponsor to provide CHS-1701 and US Neulasta potency data of samples subjected to forced degradation conditions. In the resubmission, the Sponsor provided data from an additional forced degradation study referred to as “Study 2”, in which the potency values of CHS-1701 and US Neulasta lots are directly compared under various stressed conditions.

Reviewer comment: *The results from Study 1 have been reviewed by Dr. Jacek Cieslak in his review of the original review and will not be repeated in this memo. I agree that Study 2 is more comprehensive than Study 1; all three HPLC methods (SEC, CEX, and RPC) as well as SDS-PAGE and bioassay tests were performed for each condition.*

The CHS-1701 DP lots and the US Neulasta lots used in forced degradation Study 1 and Study 2 are listed in Table 54 below. The three CHS-1701 lots used in Study 1 and 2 are same. Due to material limitations, two Neulasta lots (1053071 and 1057096) used in Study 1 were substituted with lots 1059900 and 1060883 in Study 2.

Table 54: UDENYCA and Neulasta (US) Drug Product Materials Used for Forced Degradation Studies

Biosimilar	Lot Number	Date of Manufacture	Age at Initiation of Study 1, Months	Age at Initiation of Study 2, Months
UDENYCA	2372-103	20 Mar 2015	11	27
	2372-104	25 Mar 2015	11	27
	2372-105	31 Mar 2015	11	27
Reference Product	Lot Number	Date of Expiry	Age at Initiation of Study 1, Months	Age at Initiation of Study 2, Months
Neulasta (US)	1053071	August 2017	18	NA
	1057096	November 2017	15	NA
	1057133	October 2017	NA	32
	1059900	April 2018	10	26
	1060883 ^a	August 2018	NA	22

Note: Neulasta expiries were assumed to be on the last day of the month. Age at initiation of study was calculated from the start of sample preparation (pull dates), which were March 8, 2016 for Study 1 and June 30, 2017 for Study 2.

^a This lot was not included in similarity testing, but was included for forced degradation Study 2, due to material limitations for the original lots.

Reviewer comment: *Two US-Neulasta lots (1053071 and 1057096) used in Study 1 were substituted with lots 1059900 and 1060883 in Study 2 due to sample limitation. Among the three US-Neulasta lots used in the new forced degradation Study 2, lot 1057133 was included in the similarity tests, lot 1059900 was included in clinical trial and analytical similarity tests; lot 1060883 was not included in similarity test or clinical study. The forced degradation results from lot 1060883 were comparable to the results of the other two US-Neulasta lots; therefore, including lot 1060883 in Study 2 does not impact the conclusion of the forced degradation study (see below for details).*

The forced degradation conditions in Study 2 are the same as that in Study 1 as listed Table 55.

Table 55: Forced Degradation Conditions Used for Both Studies

Stress	Concentration	Conditions	Time Point(s)			
			0% ^c Exposure	25% Exposure	50% Exposure	100% Exposure
Photo	10 mg/mL	Light Exposure (ICH Q1B option 2) ^a	0% ICH	25% ICH	50% ICH	100% ICH
Oxidation	10 mg/mL	0.05% H ₂ O ₂ at 37 °C	0 min	10 min	20 min	40 min
Heat	1 mg/mL	60 °C	0 min	20 min	40 min	60 min
Acid	N/A ^b	Titrate formulation buffer to pH 2 and buffer exchange samples; incubate 37 °C	0 hours	8 hours	24 hours	48 hours
Base	N/A ^b	Titrate formulation buffer to pH 8 and buffer exchange samples; incubate 37 °C	0 hours	8 hours	24 hours	48 hours

N/A = Not applicable

^a 1200 klux-hr of visible light and 200 W/m² of UV-A light

^b Acid and base stress samples were buffer exchanged back into formulation buffer (10 mM sodium acetate, 5% (w/v) sorbitol, pH 4.0) after incubation. Concentration was measured after buffer exchange.

Photo-stress

In the original BLA, the degradation under photo stress was only evaluated using RPC for oxidation and SEC and SDS-PAGE for aggregation. In Study 2, all three chromatographic methods (SEC, CEC, and RPC) as well as potency assay were included. A comparison of the representative SEC chromatograms of CHS-1701 and US Neulasta with various photo-exposures was provided in Figure 124. The formation of oligomers and corresponding degradation of main peak were found to be slower in CHS-1701 compared to US Neulasta as shown in Figure 127 and Figure 129 below.

Figure 124: SEC Chromatograms Following Incremental Photoexposure for Representative UDENYCA and Neulasta Lots

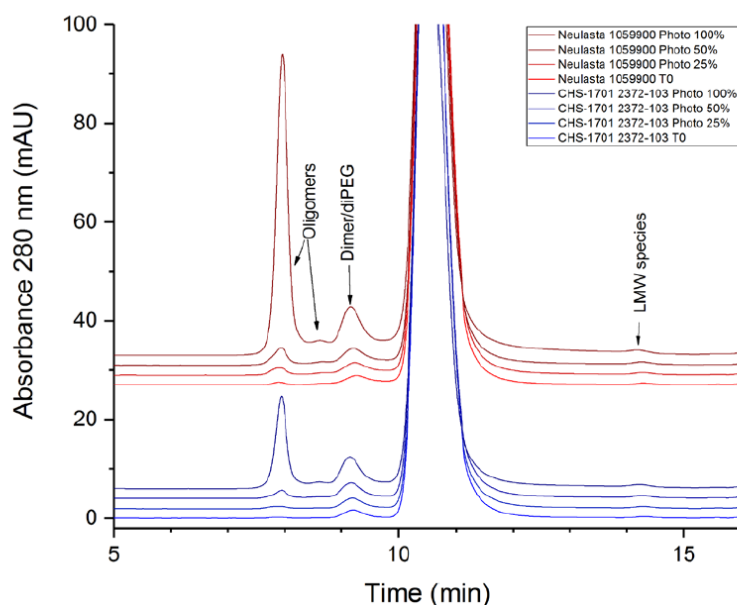


Figure 127:

SEC Oligomer Peak Area Percent vs. Photoexposure

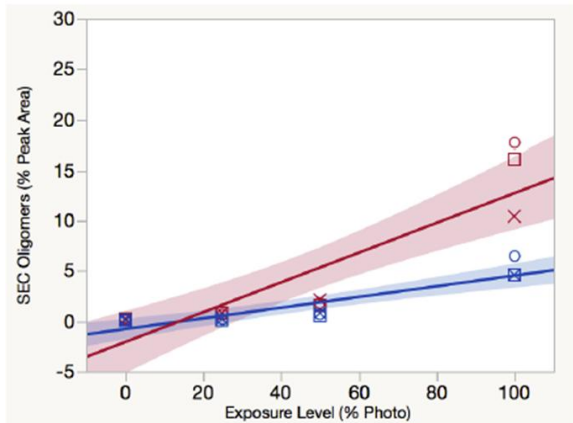
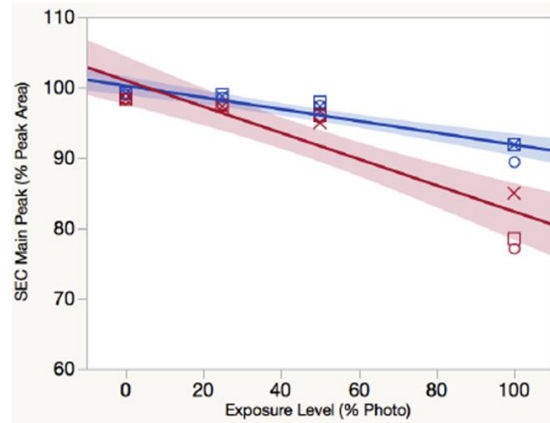


Figure 129:

SEC Main Peak Area Percent vs. Photoexposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comment: Comparison of the SEC chromatograms (see Figure 124) indicates that photo-exposure induces the formation of some oligomer species in CHS-1701 and US Neulasta, suggesting that the two products degrade in a similar mode qualitatively. However, the US -Neulasta lots showed more oligomerization at 100% exposure level (see Figure 127 and 129 above). This is not an issue since CHS-1701 is more stable compared to US Neulasta under photo-stress. The results from the original force degradation Study 1 also show that CHS-1701 has better photo-stability than US-Neulasta.

The representative CEC chromatograms of photo-exposed CHS-1701 and US Neulasta were compared in Figure 131. Overall, the changes observed by CEC are qualitatively similar between CHS-1701 and US Neulasta. However, the US Neulasta showed a greater extent of degradation in the post-peak region quantitatively in the main peak decrease and the post peak increase as indicated in Figure 135 and 136, respectively.

Figure 131: CEC Chromatogram of Incremental Photoexposure for Representative UDENYCA and Neulasta Lots

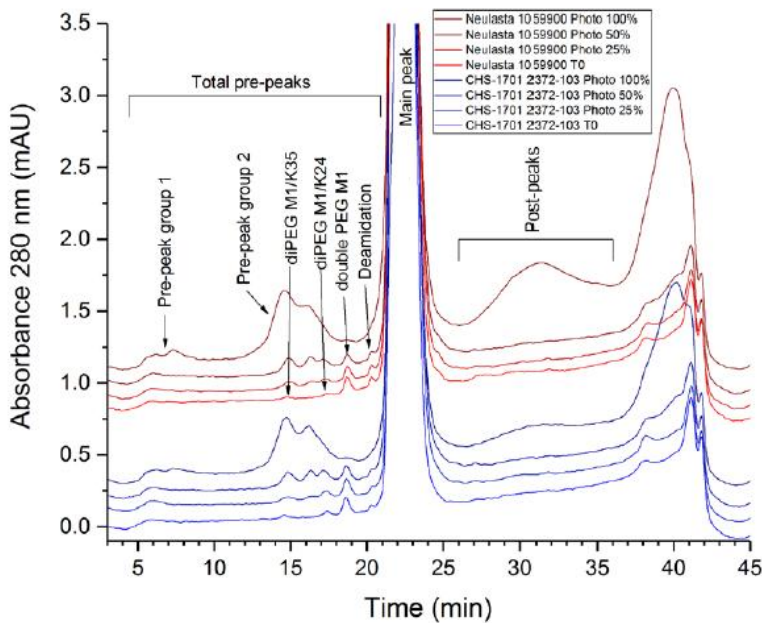


Figure 135:

CEC Main Peak Area Percent vs. Photoexposure

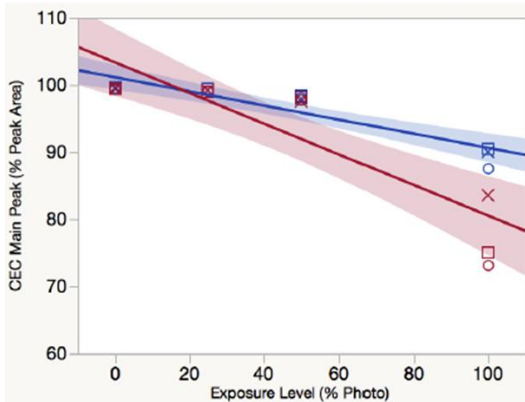
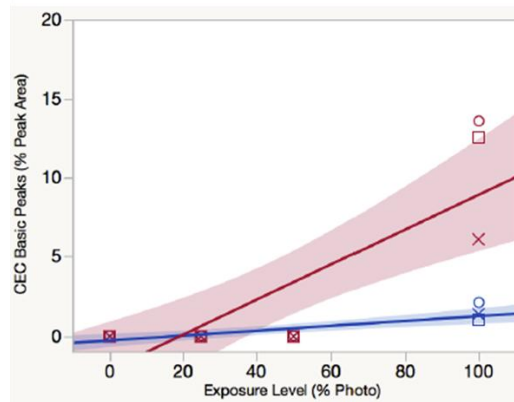


Figure 136:

CEC Post Peak Area Percent vs. Photoexposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comment: Comparison of CEC chromatograms (Figure 131) indicates that photo-exposure induces similar changes in the CEC peaks for CHS-1701 and US Neulasta; However, the US -Neulasta lots showed more significant changes at the 100% photo exposure level (see Figure 135 and 136 above). Consistent with the SEC results, CEC results also indicate that CHS-1701 are more stable compared to US-Neulasta.

Oxidation is the primary mode of degradation under photo stressed conditions. The oxidized species are detected as pre-peaks by RPC method as shown in Figure 137. CHS-1701 and US Neulasta exhibit similar degradation rates under photo stressed conditions when analyzed by the pre-peaks and the main peaks of RPC as shown in Figures 139 and 140, respectively.

Figure 137: RPC Chromatogram of Incremental Photoexposure for Representative UDENYCA and Neulasta Lots

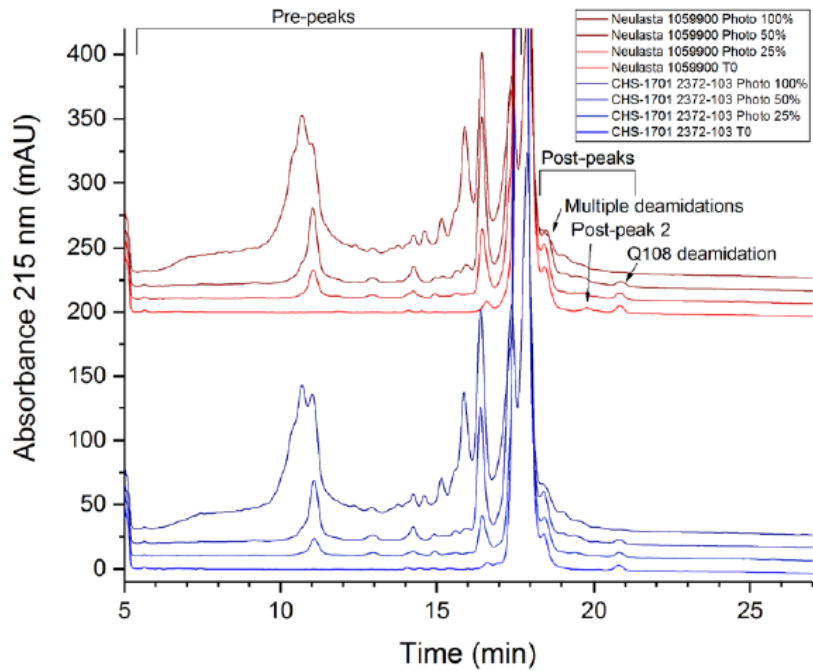


Figure 139:

RPC Pre Peak Area Percent vs. Photoexposure

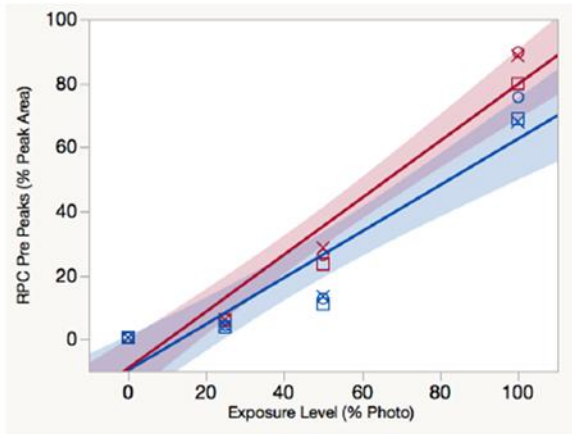
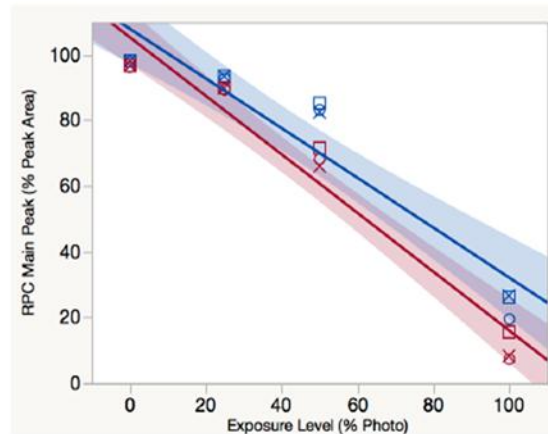


Figure 140

RPC Main Peak Area Percent vs. Photoexposure

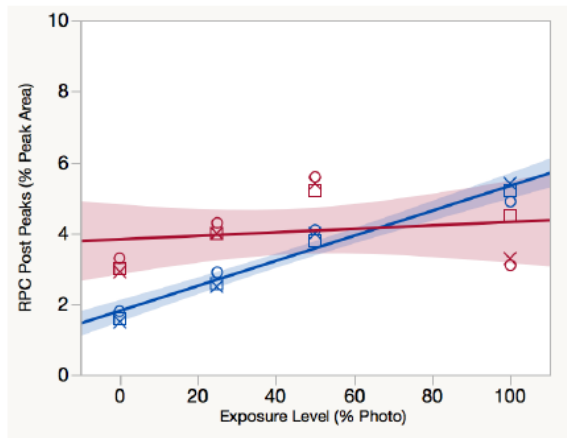


Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

The RPC post-peak (deamidated species) change under photo-stressed condition is shown in Figure 141.

Figure 141: RPC Post Peak Area Percent vs. Photoexposure

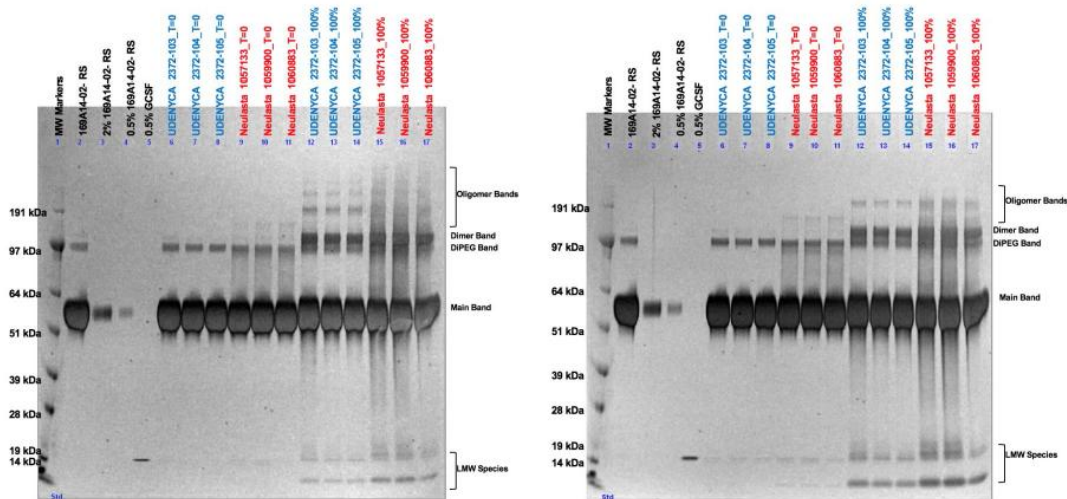


Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.
Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Review comment: For the RPC post-peaks, the change in the integrated peak of CHS-1701 appears to be greater compared to US-Neulasta. However, no major differences in the post-peaks were observed between CHS-1701 and US Neulasta in the stacked chromatograms in Figure 137. In my opinion, the quantitative differences in the integrated post-peak area shown in Figure 141 are mainly due to the dramatic overall RPC profile changes caused by massive oxidation and aggregation. The RPC results for photo-stressed degradation support a determination that CHS-1701 is highly similar to US Neulasta.

As shown in Figure 142, CHS-1701 exhibited degradation patterns similar to US-Neulasta under photo stress conditions when analyzed by SDS-PAGE. Photo-degradation caused formation of dimers and oligomers detected by SDS-PAGE are more pronounced in US-Neulasta than in CHS-1701.

Figure 142: SDS-PAGE Non-Reduced (Left) and Reduced (Right) Silver Gel Image in Photoexposed Samples

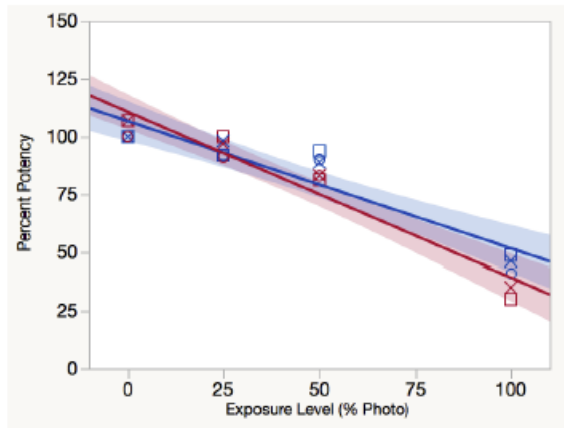


Legend: Lane 1: Molecular weight marker; Lane 2: pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 3: 2% pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 4: 0.5% pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 5: 0.5% filgrastim-chrs reference standard lot 169A14-02 (GCSF); Lane 6: UDENYCA lot 2372-103_T=0; Lane 7: UDENYCA lot 2372-104_T=0; Lane 8: UDENYCA lot 2372-105_T=0; Lane 9: Neulasta (US) lot 1057133_T=0; Lane 10: Neulasta (US) lot 1059900_T=0; Lane 11: Neulasta (US) lot 1060883_T=0; Lane 12: UDENYCA lot 2372-103_100%; Lane 13: UDENYCA lot 2372-104_100%; Lane 14: UDENYCA lot 2372-105_100%; Lane 15: Neulasta (US) lot 1057133_100%; Lane 16: Neulasta (US) lot 1059900_100%; Lane 17: Neulasta (US) lot 1060883_100%

Reviewer comment: The photo-exposure induced higher level of oligomers in US-Neulasta compared to CHS-1701; however, the overall patterns of the two products are similar. The results from SDS-PAGE are consistent to the results from SEC analysis.

The potency of CHS-1701 and US-Neulasta decreased with the increased photo exposure levels as shown in Figure 143. The potency decrease rate of CHS-1701 is slightly slower compared to US Neulasta.

Figure 143: Potency by Bioassay vs. Photoexposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comments: Overall, the results indicate that the qualitative degradation profiles of CHS-1701 and US-Neulasta are similar under photo-stress; however, CHS-1701 has a slightly slower degradation rate compared to the US-licensed Neulasta. The results from photo-forced degradation support a determination that CHS-1701 is highly similar to US Neulasta.

Peroxide Stress

In the original Study 1, only RPC analysis was used for evaluation of degradation under peroxide stress. In the resubmission, the changes under peroxide stress in both CHS-1701 and Neulasta were analyzed with SEC, CEC, SDS-PAGE and bioassay for potency.

Reviewer comment: The results from SEC and CEC assays were provided, but not copied since degradation following peroxide exposure was detected neither in CHS-1701 nor in US-Neulasta by SEC and CEC.

RPC is a sensitive method for evaluation of peroxide-forced degradation. The oxidized species are eluted as pre-peaks in the RPC as shown in Figure 158. The quantitative results of the Pre-peaks from RPC analyses in Figure 161 demonstrate that CHS-1701 and US-Neulasta exhibit similar degradation rates following peroxide exposure.

Figure 158: RPC Chromatograms Following Incremental Peroxide Exposure for Representative UDENYCA and Neulasta Lots

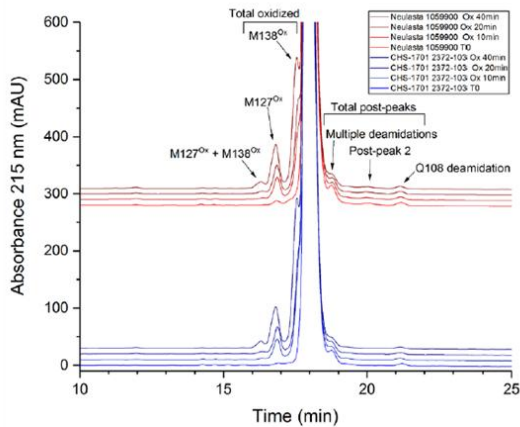
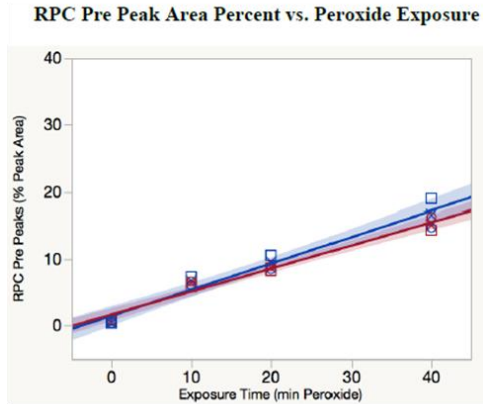
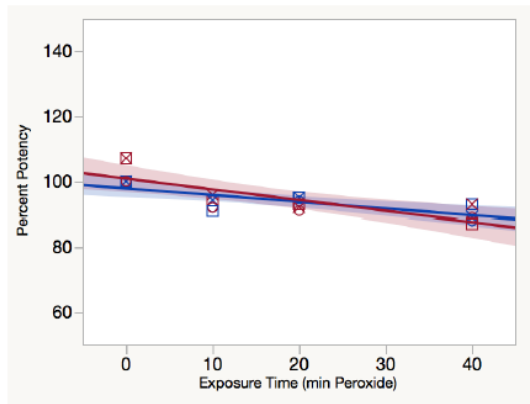


Figure 161:



Peroxide-induced potency decreases in CHS-1701 and US-Neulasta are also very similar as shown in Figure 165.

Figure 165: Potency by Bioassay vs. Peroxide Exposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comment: The results from RPC and potency assays demonstrate that CHS-1701 and US Neulasta have similar degradation mode under peroxide stress and support a determination that CHS-1701 is highly similar to US Neulasta.

Heat Stress at 60 °C

Degradation of CHS-1701 and US Neulasta by Heat Stress at 60 °C can be measured by an increase in oligomer level (Pre-peaks) by SEC, an increase in the basic species (post-peaks) by CEC, increases in both pre- and post-peaks in RPC as shown in Figures 169, 178, 182, and 184.

Figure 169:

SEC Oligomer Peak Area Percent vs. Heat Exposure

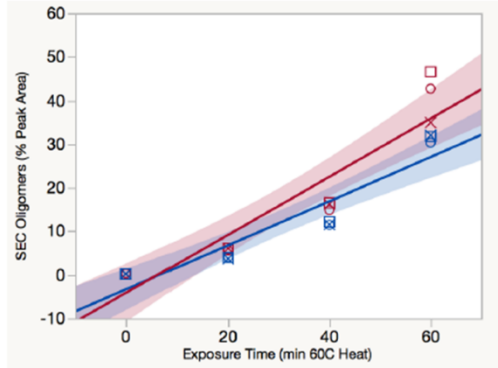


Figure 178:

CEC Post Peak Area Percent vs. Heat Exposure

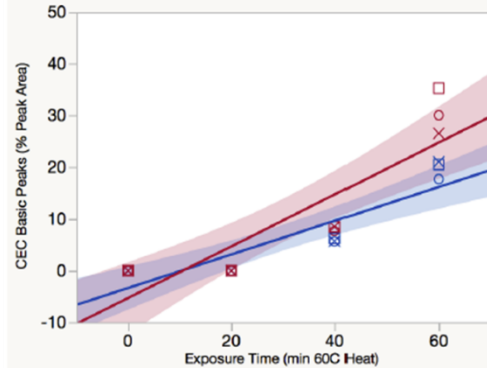


Figure 182:

RPC Pre Peak Area Percent vs. Heat Exposure

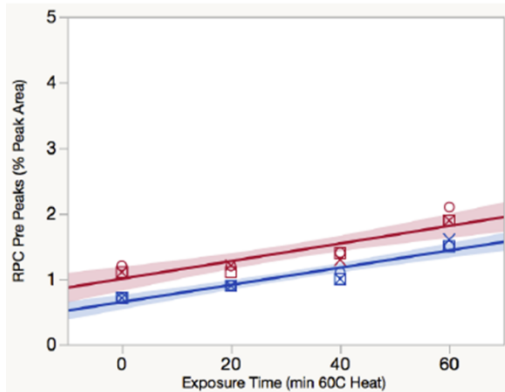
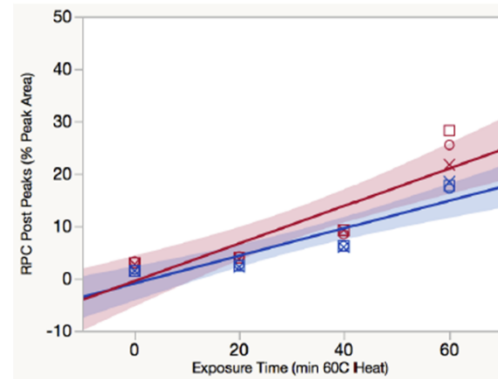


Figure 184:

RPC Post Peak Area Percent vs. Heat Exposure



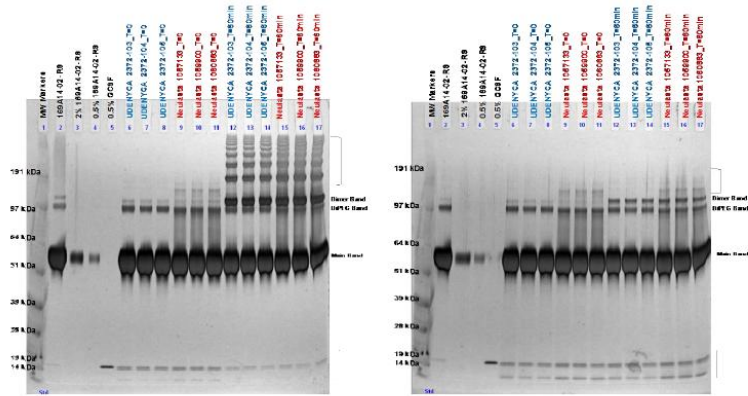
Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comment: The stacked representative chromatograms of samples following exposure to 60 °C heat stress from SEC, CEC, and RPC assays are provided but not copied. The profiles of CHS-1701 and US-Neulasta lots subjected to heat stress are similar.

The heat stressed CHS-1701 and US-Neulasta samples were also analyzed by SDS-PAGE and the results are shown in Figure 185.

Figure 185: SDS-PAGE Non-Reduced (Left) and Reduced (Right) Silver Gel Image in Heat Stressed Samples

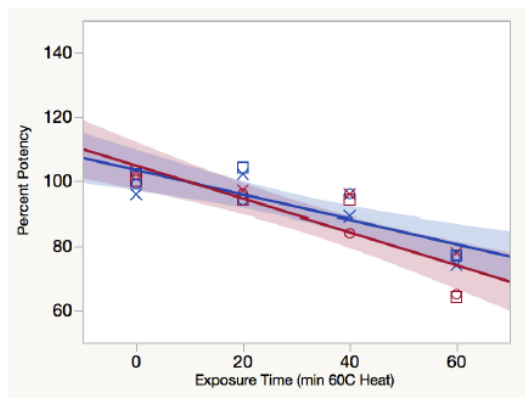


Legend: Lane 1: Molecular weight marker; Lane 2: pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 3: 2% pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 4: 0.5% pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 5: 0.5% filgrastim-chrs reference standard lot 169A14-02 (GCSF); Lane 6: UDENYCA lot 2372-103_T=0; Lane 7: UDENYCA lot 2372-104_T=0; Lane 8: UDENYCA lot 2372-105_T=0; Lane 9: Neulasta (US) lot 1057133_T=0; Lane 10: Neulasta (US) lot 1059900_T=0; Lane 11: Neulasta (US) lot 1060883_T=0; Lane 12: UDENYCA lot 2372-103_T=60min; Lane 13: UDENYCA lot 2372-104_T=60min; Lane 14: UDENYCA lot 2372-105_T=60min; Lane 15: Neulasta (US) lot 1057133_T=60min; Lane 16: Neulasta (US) lot 1059900_T=60min; Lane 17: Neulasta (US) lot 1060883_T=60min

Reviewer comment: The heat stressed CHS-1701 and US Neulasta samples have similar band patterns in the SDS-PAGE; however, the oligomer levels induced by heat in CHS-1710 are lower than in US Neulasta.

The heat-induced potency changes of CHS-1701 and US-Neulasta were compared in Figure 186.

Figure 186: Potency by Bioassay vs. Heat Exposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883. Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comments: Overall, the results from the heat-forced degradation study support the similarity of CHS-1701 and US-Neulasta.

Acid exposure

In the original Study 1, the degradation at pH 2 was monitored using RPC and CEC assays. In the resubmission, degradation under acidic condition was assessed with RPC, CEC, SEC, and potency assays. The SEC chromatograms (not copied) indicate slight increase of the oligomer (pre-peak). SEC detected increases in oligomerization in CHS-1701 and US-Neulasta are compared in Figure 191.

Deamidation is the primary degradation pathway under acidic conditions. The deamidated species can be detected by CEC pre-peaks and by RPC post-peaks and the results are shown in Figure 199 and Figure 206, respectively.

The acid-induced potency changes in CHS-1701 and US Neulasta are compared in Figure 208.

Figure 191:

SEC Oligomer Peak Area Percent vs. Acid Exposure

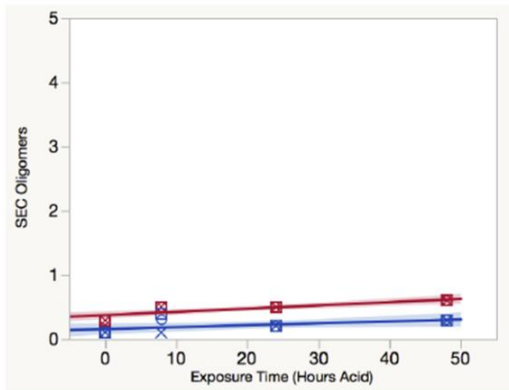
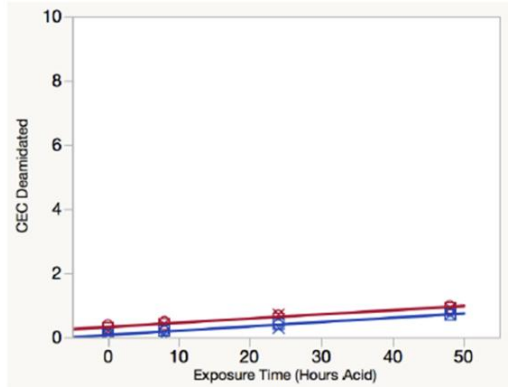


Figure 199:

CEC Deamidated Peak Area Percent vs. Acid Exposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Figure 206:

RPC Post Peak Area Percent vs. Acid Exposure

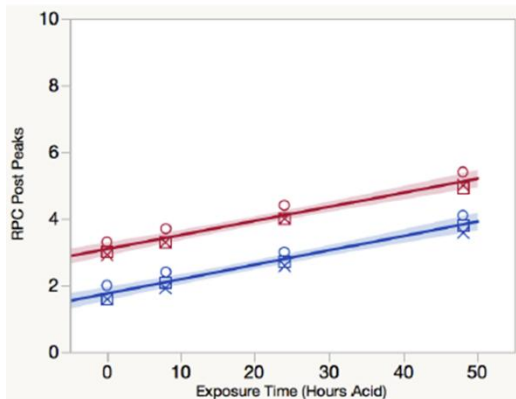
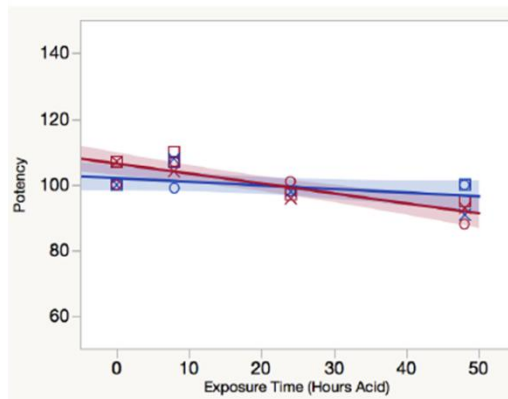


Figure 208:

Potency by Bioassay vs. Acid Exposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comment: The changes in CHS-1701 and US-Neulasta detected by the HPLC methods are parallel, indicating that the degradation of CHS-1701 and US-licensed Neulasta under acidic condition of pH 2 are qualitatively similar, although the biosimilar CHS-1701 lots have lower levels of oligomers and deamidated species compared to the US Neulasta lots. The deamidated species detected by RPC (Fig 206) appear to be higher compared to the levels detected by CEC (Figure 199). This is probably due to the sensitivity of the RPC assay, which can detect more deamidated species than the CEC method.

The difference in the potency change is statistically insignificant.

Overall the results from the forced degradation study under acidic conditions support a determination that CHS-1701 is highly similar to US Neulasta.

Base exposure

Aggregation is the major degradation mechanism under basic conditions, which promote disulfide scrambling and the formation of intramolecular disulfides. Pegfilgrastim is especially prone to disulfide scrambling under these conditions due to the free cysteine at C18. In the original submission, the only method used in degradation under

basic condition (pH 8) was SDS-PAGE. In the resubmission, the degradation under basic condition was also evaluated by SEC, CEC, RPC and potency assays.

The SEC chromatograms (Figure 210) and the quantitative results of the oligomer peak (Figure 214) clearly demonstrate the oligomer formation under the basic condition in both CHS-1701 and US-Neulasta.

Figure 210: SEC Chromatograms Following Incremental Base Exposure for Representative UDENYCA and Neulasta Lots

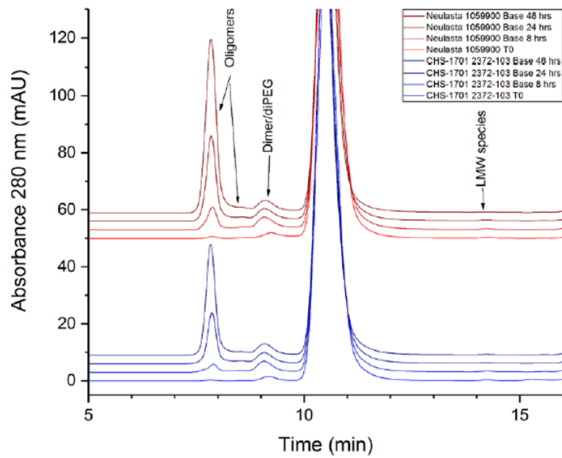
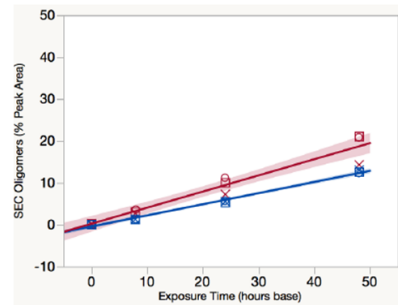


Figure 214: SEC Oligomer Peak Area Percent vs. Base Exposure



Blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

The oligomer formation is also reflected in the post-peaks in the CEC (Figure 217 and Figure 223) and RPC (Figure 224 and Figure 228).

Figure 217: CEC Chromatograms Following Incremental Base Exposure for Representative UDENYCA and Neulasta Lots

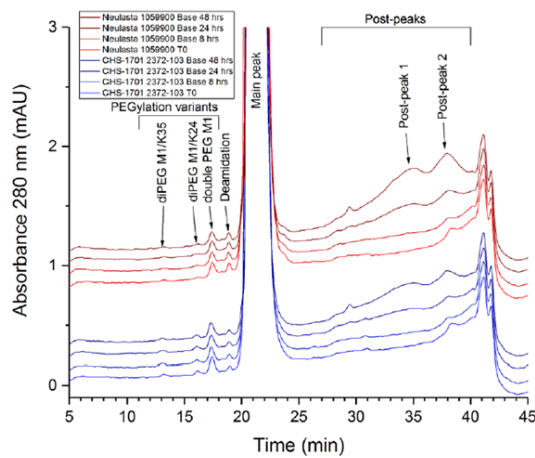
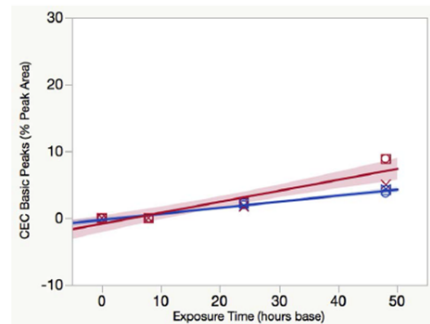


Figure 223: CEC Aggregate Peak Area Percent vs. Base Exposure



Blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Figure 224: RPC Chromatograms Following Incremental Base Exposure for Representative UDENYCA and Neulasta Lots

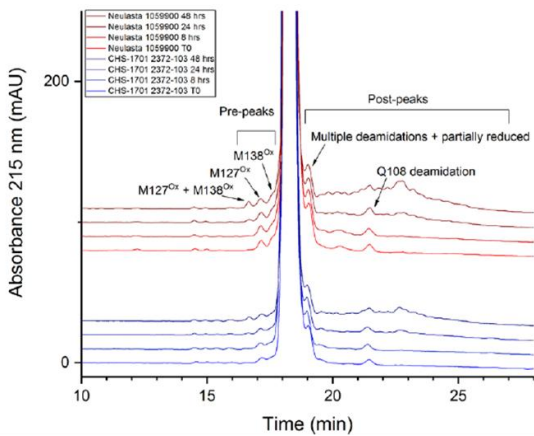
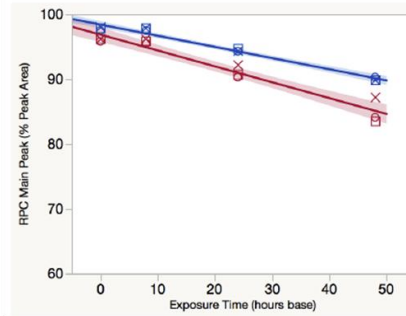


Figure 228: RPC Main Peak Area Percent vs. Base Exposure

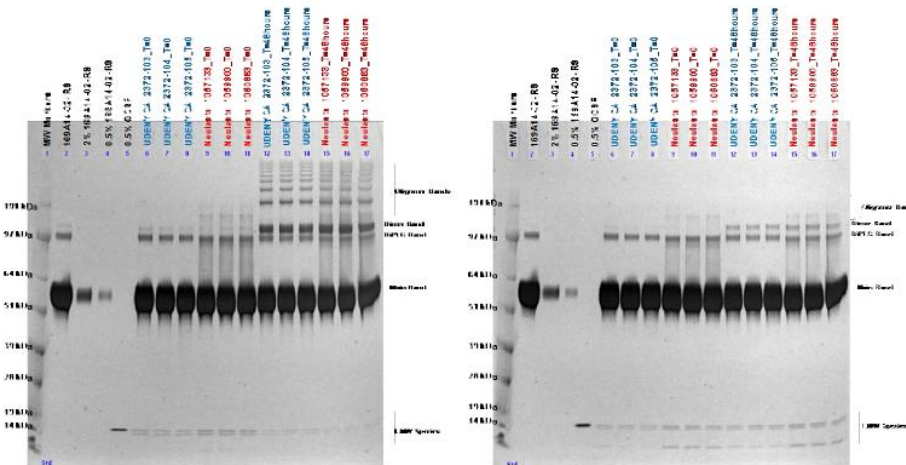


Blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1059133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883.

Reviewer comment: The SEC results clearly demonstrate CHS-1701 and US Neulasta have similar oligomerization profiles when exposed to basic conditions. The results from CEC and RPC also indicate oligomerization under basic conditions. The results from the three chromatographic analyses indicate that the CHS-1701 has a slightly slower oligomerization rate compared to US- Neulasta.

CHS-1701 and US Neulasta exposed to basic condition exhibit similar patterns in both non-reduced and reduced SDS-PAGE as shown in Figure 230. A series of oligomer bands were detected by non-reduced SDS-PAGE; however, most of the oligomer bands disappeared in the reduced gel. These results demonstrate that the majority of oligomers formed under basic conditions are linked by disulfide. No obvious change in LMW species was detected.

Figure 230: SDS-PAGE Non-Reduced (Left) and Reduced (Right) Silver Gel Image in Base Stressed Samples

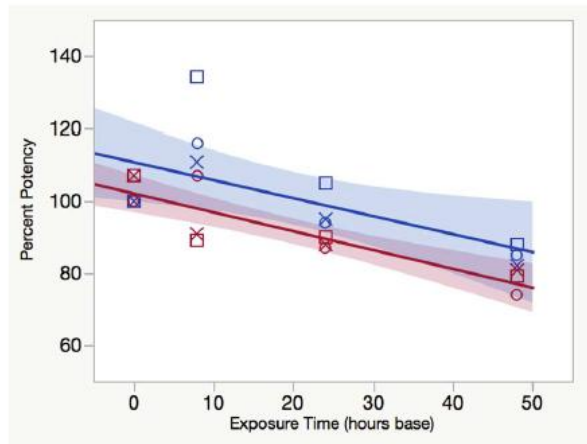


Legend: Lane 1: Molecular weight marker; Lane 2: pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 3: 2% pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 4: 0.5% pegfilgrastim-cbqv reference standard lot 169A14-02; Lane 5: 0.5% filgrastim-chrs reference standard lot 169A14-02 (GCSF); Lane 6: UDENYCA lot 2372-103_T=0; Lane 7: UDENYCA lot 2372-104_T=0; Lane 8: UDENYCA lot 2372-105_T=0; Lane 9: Neulasta (US) lot 1057133_T=0; Lane 10: Neulasta (US) lot 1059900_T=0; Lane 11: Neulasta (US) lot 1060883_T=0; Lane 12: UDENYCA lot 2372-103_T=48hours; Lane 13: UDENYCA lot 2372-104_T=48hours; Lane 14: UDENYCA lot 2372-105_T=48hours; Lane 15: Neulasta (US) lot 1057133_T=48hours; Lane 16: Neulasta (US) lot 1059900_T=48hours; Lane 17: Neulasta (US) lot 1060883_T=48hours

Reviewer comment: The SDS-PAGE results of forced degradation study under basic conditions support a determination that CHS-1701 is highly similar to US Neulasta.

The potency changes of CHS-1701 and US-Neulasta at basic conditions were compared in Figure 231.

Figure 231: Potency by Bioassay vs. Base Exposure



Legend: blue circles, CHS-1701 lot 2372-103; blue squares, CHS-1701 lot 2372-104; blue x markers, CHS-1701 lot 2372-105; red circles, Neulasta (US) lot 1057133; red squares, Neulasta (US) lot 1059900; red x markers, Neulasta (US) lot 1060883. Lines represent linear least squares fits from zero through 100% exposure. Shaded areas represent the 95% confidence intervals of the fits.

Reviewer comment: *There are no statistically significant differences between CHS-1701 and US Neulasta in the degradation under basic conditions when analyzed by bioassay.*

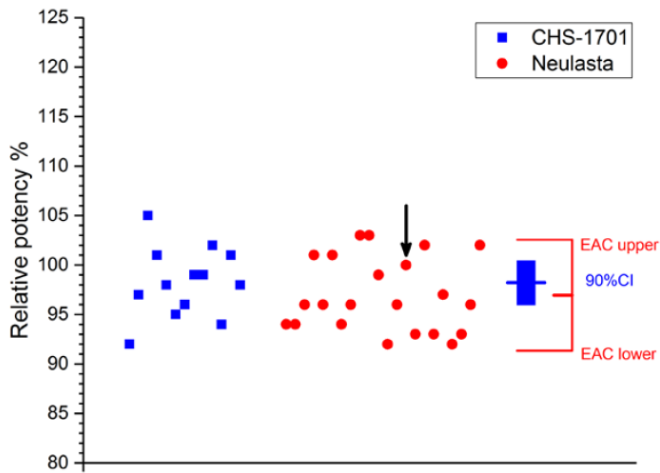
Overall the results from the forced degradation study support a determination that CHS-1701 is highly similar to US Neulasta.

Reviewer comment on analytical similarity between CHS-1701 and US-licensed Neulasta by forced degradation study: *As requested in CR comment 1, the Sponsor evaluated the potency of CHS-1701 and US Neulasta under each of forced degradation conditions (photo-exposure, peroxide, acid, base, and heat). In addition, forced degradation under each condition was also assessed by three HPLC methods (SEC, CEC, and RPC) and SDS-PAGE. Qualitatively, CHS-1701 and US-Neulasta exhibit similar modes of degradation under all stress conditions examined. However, quantitatively, CHS-1701 has slower degradation rates for oligomer formation under light stress and basic pH conditions. Overall, the results of forced degradation study 2 provided in the resubmission support a determination that CHS-1701 is highly similar to US Neulasta. CR comment 1 is adequately addressed.*

In addition, all three HPLC purity methods (RPC, SEC, or CEC) and potency assay were used to characterize degradation of CHS-1701 at each stress condition; therefore, the CR comment 27 regarding the degradation pathways is also adequately addressed.

The Sponsor used US Neulasta lot 1054829 in the clinical study but did not include this lot in the Tier 1 analyses of potency in the original BLA due to material limitation. CR comment 2 requests potency data for US Neulasta lot 1054829. Using a clinical retain sample, the potency of this lot is measured to be 100% relative potency. The Analytical Assessment was updated with this result. CHS-1701 still meets the Tier 1 acceptance criteria after inclusion of data from this US Neulasta lot as shown in the figure below (the arrow indicates US Neulasta lot 1054829).

Biological Potency of UDENYCA vs Neulasta (US)



Reviewer comment: CR comment 2 is adequately addressed.

Analytical similarity data inspection

Reviewer Note: DIA and OBP performed an inspection of the analytical similarity data at Coherus Analytical Laboratory, Camarillo, CA 93012 from July 24, 2018 to July 27, 2018. No issues were identified (see EIR for details).



Ying Xin
Fan

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Joslyn
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Date: 10/08/2018 09:56:14PM
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Joel
Welch

Digitally signed by Joel Welch
Date: 10/09/2018 08:18:23AM
GUID: 508da6dc0002673d83d264d81364d6cf

Memorandum of Review

STN:	BLA761039-0056 Resubmission
Subject:	Immunogenicity Review: Assay and Immunogenicity Clinical Data
Submission Date:	May 03, 2018
Review/Revision Date:	September 21, 2018
Primary Reviewer:	Haoheng Yan, MD, PhD (assays) Product Quality Reviewer, OPQ/OBP/DBRR IV Fred Mills, PhD (clinical immunogenicity data) Staff Scientist, OPQ/OBP/DBRR IV
Secondary Reviewer:	Joslyn Brunelle, PhD Team Leader, OPQ/OBP/DBRR IV
Consults:	Immunogenicity
Applicant:	Coherus
Product:	CHS-1701, PEGylated G-CSF, proposed biosimilar to US-licensed Neulasta
Indications:	Decreasing the incidence of infection in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Action Due Date:	November 3, 2018

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I. Summary Basis of Recommendation:

- a. Recommendation:** We recommend approval of this 351(k) BLA application for CHS-1701 (Udenyca) as a biosimilar to US-licensed Neulasta.

Justification:

The Sponsor obtained serum samples from subjects in clinical studies that included a parallel arm study designed to compare the immunogenicity of CHS-1701 and US-licensed Neulasta. Immunogenicity assays that are suitable for their intended purposes were used to analyze these samples for antibody incidence, titer, specificity for PEG and G-CSF, and neutralizing activity. The results of these analyses support no significant differences between CHS-1701 and US-licensed Neulasta.

II. Review

- Unless otherwise noted, figures and tables in the review were adapted or copied directly from the submission.
- The review sequence of the individual aspect of the assay validation may not follow the exact sequence in the submission.
- The "guidance" cited in the review refer to "FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016"
<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf>

Background:

In the complete response letter issued on June 09, 2017, the Agency found both the neutralizing antibody (NAb) assays submitted in the original BLA to be inadequate (Immunogenicity Question 3). Coherus has developed a third NAb assay (contractor: (b) (4)). On February 23, 2018, Coherus and the FDA held a BPD type 2 meeting to discuss the adequacy of the third NAb assay. Along with the meeting package, Coherus submitted an assay development report ((b) (4)-17-259-082-REP) and an assay validation report ((b) (4)-17-259-083-REP), which were reviewed as part of the meeting package. The new NAb assay was deemed adequate, with the exception that Coherus should submit additional assay precision data for the immunodepletion confirmatory assay in the re-submission. The review memo for the NAb assay (uploaded to DARRTS on 2/21/2018) is attached at the end of this review.

In the CRL, the Agency also requested Coherus provide anti-G-CSF antibody titer to understand whether the difference in ADA incidence rate (CHS-1701 vs. US-Neulasta) indicates a difference in factors impacting safety and efficacy (Immunogenicity Question 2).

In the re-submission, the sponsor submitted report ((b) (4) 17-259-083 which includes the assay precision data for the immunodepletion NAb confirmatory assay, and two validation reports for an anti-G-CSF titer assay.

Anti-drug Antibody Titer Assay:

The sponsor developed an anti-G-CSF antibody binding assay to assess anti-G-CSF specific titers in human plasma samples previously confirmed to have G-CSF specific anti-pegfilgrastim antibodies. Two validation reports/amendments were submitted:

(b) (4) 17-259-093.03-REP: Validation of an Electrochemiluminescent Assay for the Detection of Anti-G-CSF Antibodies in K2EDTA Human Plasma

(b) (4) 17-259-093.02-REP: amendment for revised LPC concentration due to the positive control issues identified in the confirmatory assay (*not relevant to titer assay*).

Reviewer's Comment:

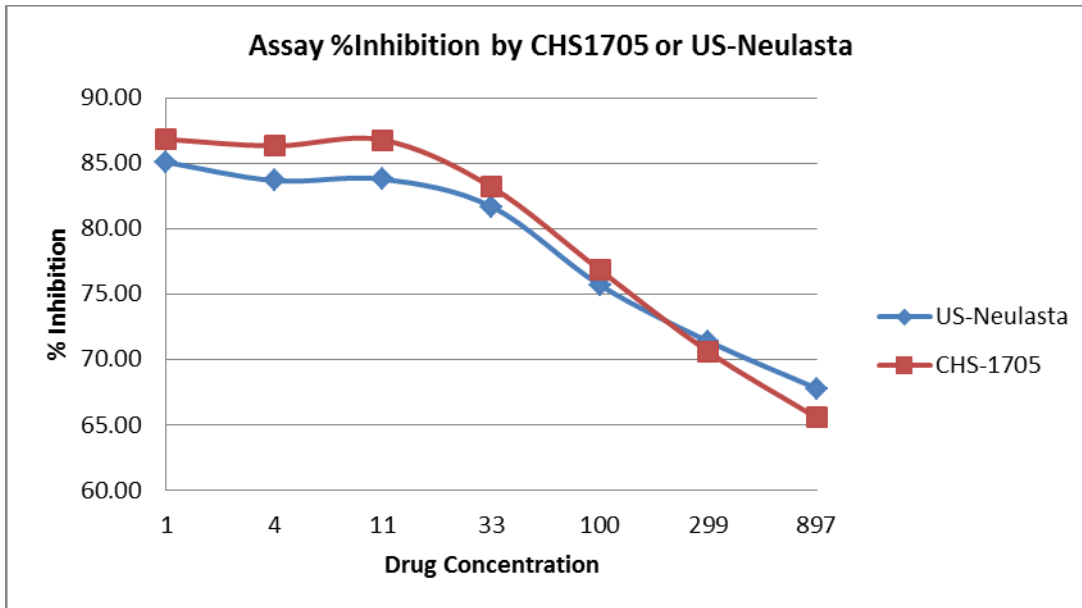
Although the assay is only used for titering the anti-GCSF antibody in the plasma samples, the validation report submitted is a full validation report for an ADA binding assay. Only the validation parameters relevant to titer testing are reviewed in the memo.

The screening assay is an electrochemiluminescence (ECL) based bridging assay. In brief, human plasma samples are incubated in a mixture of biotinylated G-CSF and ruthenylated G-CSF to form "Bio-G-CSF: anti-G-CSF antibody : Ru-G-CSF" complex. This complex is then added to a streptavidin coated plate and allowed to bind. After washing, the detection agent was added to the complex, and the luminescence signal is read by a plate reader.

In the titer assay, samples were 2-fold serial diluted in matrix diluent (PNHP) before subjected to the screening assay. The titer is determined to be the highest fold dilution that has an S/N ratio greater than or equal to the titer cut point. ADA confirmed positive samples that have a S/N ratio less than the titer cutpoint at MRD in this titer assay are reported as <2.

Reviewer's Comment:

It is not clear whether the capture agents, Biotinylated-G-CSF and Ruthenylated G-CSF, were based on the G-CSF material in CHS-1701 or other sources. Using the data reported in the assay interference section (Table 15 and 16 of the report), I generate a dose response curve comparing assay signal inhibition when different amount of drug were spiked into HPC (see figure below). Signal inhibition (of HPC) is similar between CHS-1701 and US-Neulasta, therefore the assay format is appropriate to measure anti-G-CSF titer for samples from CHS-1701 and US-Neulasta treated subjects.



Essential Reagents and Concentration

- Positive Control (PC): Anti-G-CSF rabbit polyclonal antibody, abcam ab9691
High, Medium and Low Positive Controls: 2000, 200 and 25ng/mL
- Normal human plasma: K₂EDTA, (b) (4)
Pooled normal human plasma (PNHP)
- Negative Control (NC): referred as Blank Test Sample (BTS) which is pooled human plasma purchased from (b) (4)
- G-CSF: (b) (4)
- Minimum Required Dilution: 2

Screening and Titer Cut Point Determination

Fifty different lots of normal human plasma were analyzed by 2 analysts over 18 total runs over 3 days, total 300 ECL values. The raw ECL values were normalized by dividing the mean ECL value of each sample by the mean of the NC values on each plate (after evaluation for NC outliers) and described as signal to noise ratios (S/N). Cut point analysis was based on the 300 log transformed S/N values, a parametric method with Tukey's biweight procedure was used to calculate the cut point using 232 S/N values. Screening and Titer cut point factors (SCP and TCP) were calculated as

$$\text{Parametric SCP factor} = 10^{[\text{Biweight Mean} + \text{Biweight SD} * t_{0.95, n-1}]}$$

$$\text{Parametric TCP factor} = 10^{[\text{Biweight Mean} + \text{Biweight SD} * t_{\alpha, n-1}]}$$

where $t_{\alpha, n-1}$ is the 95th or 99.9th percentile of the t-distribution.

SCP factor = 1.14

TCP factor = 1.28

Reviewer’s Comment

The SCP and TCP factors are acceptable.

Titer Assay Precision

HPC(2000ng/mL) and MPC(200ng/mL) were subjected to 2 fold serial dilution until the ECL signal fell below the titer cut point of 1.28. The dilution factor above which the signal fell below the cutpoint for the first time was used to calculate titer, i.e titer=dilution factor x MRD. Intra-assay precision was tested in with three independent preparations of the same sample per plate over 3 plates for a total of nine independent preparations of each samples. The inter-assay precision was tested over 3 days with 6 independent runs by 2 analysts.

Reviewer’s Comment

HPC and MPC titers are all within 1 step of dilution; therefore intra- and inter-assay precision is acceptable. The titer determination, i.e titer=dilution factor x MRD, is acceptable per guidance.

Assay Selectivity and Sensitivity

Selectivity was assessed in 10 individual normal human plasma samples unspiked and spiked with LPC (25 ng/mL). All LPC had S/N >titer cut point. Part of the selectivity data is shown below in Table 13.

Table 13. Selectivity Summary

Analyst	Run	Plasma Lot	Screening Assay (S/N)		
			HPC (2000 ng/mL)	LPC (25 ng/mL)	Unspiked
Analyst 1	34	Lot9	85.83	1.59	1.12
		Lot10	85.43	1.41	1.08
		Lot11	83.59	1.45	1.08
		Lot12	69.68	1.42	1.06
		Lot13	78.76	1.56	1.06

Reviewer’s Comment: *Titer and screening assays’ selectivity and sensitivity (at least 25ng/mL measured by LPC) are acceptable.*

Matrix Interference

HPC and LPC were spiked into 2 lipemic and 3 hemolytic samples. One LPC spiked in hemolytic sample had S/N=1.1 (lower than the SCP factor). All other spiked in sample were scored positive by the SCP.

Table 14 Matrix Interference Lipemic and Hemolyzed Samples

Run 37		Lipemic Samples			Hemolytic Samples		
		Sample 1	Sample 2	Sample 3*	Sample 1	Sample 2	Sample 3
HPC	Screen S/N	80.55	73.77	68.47*	59.37	51.44	52.12
LPC		1.30	1.31	2.46*	1.11	1.22	1.21
Unspiked		1.08	1.02	2.01	0.85	0.96	0.88

Reviewer’s Comment:

S/N values of HPC spiked hemolytic plasma are about ~80% that of HPC spiked pooled K2EDTA plasma (see Table 13). LPC and unspiked are also slightly lower. There might be matrix interference in the hemolytic samples. As the samples were serial diluted in pooled human plasma, i.e.non-hemolytic, the interference is probably attenuated with each dilution. The level of interference seen in the hemolytic samples is unlikely to affect the titer assessment.

Drug Tolerance

The sponsor evaluated the S/N values of HPC and LPC in the presence of different amount of CHS-1701, US-Neulasta and G-CSF. The results are presented in Table 15-17. Endogenous level of G-CSF in human plasma are reported at less than 100pg/mL (Cook KM et al. Journal American College Surgeons. 2013, 57-64)

Reviewer’s Comment:

According to the clinical pharmacology reviewer Sarah Schrieber, the level of CHS-1701 or US-Neulasta in the subjects from the CHS-1701-04 study (immunogenicity study) are lower than LOQ (of the PK assay, 0.15ng/mL) at the time points when the immunogenicity samples were taken. Based on the reported data, the screening assay can detect LPC in the presence of, at the least, 450ng/mL CHS-1701, 300ng/mL US-Neulasta, or 900ng/mL GCSF. The expected level of CHS-1701, US-Neulasta and GCSF are not expected to interfere with the detection of 25ng/ml of ADA in this assay.

Stability

Stability of control samples (HPC, LPC, LLPC and NC) were prepared in pooled human plasma and subjected to free-thaw (6 and 9 cycles), room temperature for 6 hours and 2-8°C for 24hours before tested in the screening assay.

Reviewer’s Comment

The anti-GCSF positive controls and NC are stable under the studied conditions.

Neutralizing Antibody Assay:

Immunodepletion NAb confirmatory assay – Assay Precision

Intra-assay precision for PCs included 3 sets of duplicates of the HPC (2000 ng/mL) and LPC (250 ng/mL) treated with Protein A/G/L beads or sepharose and untreated. Each plate included 3 sets of

duplicates of CHS-1701-induced control (DC) and the non-induced control (NC). The %CV are 5.0% and 19.6% for HPC and LPC.

Inter assay precision was calculated using 4 runs by 3 analysts over 3 day. HPC and LPC, untreated or treated with Protein A/G/L beads or sepharose, each in duplicate, were included in each run. Each run also included six determinations of DC and NC in duplicate. The %CVs are 14.8% and 20.4% for HPC and LPC.

Reviewer's Comment:

Assay precision is acceptable.

III. Review of Clinical Immunogenicity Data

Introduction, Study Descriptions, and Immunogenicity Study Endpoints

CHS-1701 has been developed as a proposed biosimilar to US-Neulasta, the reference product. The active component of CHS-1701 is a 39 kD pegylated recombinant granulocyte colony stimulating factor (G-CSF).

CHS-1701 is intended for use to decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. Coherus intends to extrapolate from healthy subjects to adult cancer patients and to pediatric patients for this indication. Coherus has performed the following studies on healthy volunteers in support of their BLA:

Table 1: List of CHS-1701 Clinical Studies

Protocol Number, Module	Study Design	Study Objectives	Dosage of Study Drug	Randomized / Completed	CHS-1701 Lot Numbers	Neulasta Lot Numbers	PD Endpoints	PK Endpoints	Immunogenicity Endpoints
CHS-1701-05 M5.3.1.2	Randomized, single-blind, partial reference-replicated 3-sequence, 3-period crossover	Primary: PK BE and PD BE Secondary: Safety, tolerability, immunogenicity	CHS-1701 6 mg SC Neulasta 6 mg SC	122/64	2372-103 (1701-DP-104)	1059900	ANC AUC _{0-last} , and ANC AUC ₀₋₄₈₀ , ANC _{max}	AUC _{0-∞} , AUC _{0-last} and C _{max}	ADA, NAb
CHS-1701-04 M5.3.1.2	Randomized, double-blind, 2-period, parallel-arm (no crossover)	Primary: immunogenicity (ADA and NAb), Secondary: PK, PD, safety, tolerability	CHS-1701 6 mg SC Neulasta 6 mg SC	303/271	2372-102 (1701-DP-103)	1048085, 1048834, 1054829, 1055572, 1057096, and 1057373	ANC AUC _{0-last} , ANC _{max}	AUC _{0-last} and C _{max}	ADA, NAb
CHS-1701-03 M5.3.1.2	Randomized, double-blind, single-dose, 2-period crossover	Primary: PK BE, PD BE Secondary: Safety, tolerability, immunogenicity	CHS-1701 6 mg SC Neulasta 6 mg SC	116/99	2372-102 (1701-DP-103)	1048834 and 1048085	ANC AUC _{0-last} , ANC AUC ₀₋₉₆₀ , ANC _{max}	AUC _{0-∞} , AUC _{0-last} and C _{max}	ADA, NAb
CHS-1701-01 (Supportive for safety only) ^a M5.3.1.2	Randomized, double-blind, single-dose, 2-period crossover	Primary: Dose-Adjusted PK BE Secondary: PD, safety, tolerability, immunogenicity	CHS-1701 6 mg SC Neulasta 6 mg SC	78/67	1-FIN-1501/4- FF-767	10031324	ANC Profile	AUC _{0-t} , AUC _{0-∞}	ADA, NAb

Study CHS-1701-04

Most important for immunogenicity was the parallel arm Study CHS-1701-04.

The primary objective of this study was to assess immunogenicity similarity between CHS-1701 and US-Neulasta. Success criteria included:

a) NAb: No treatment-emergent NAb with a 1-sided upper bound of the 95% confidence interval (CI) for the NAb rate <3.7% in each treatment group

b) ADA: 1-sided upper bound of the 95% CI ≤10% for the difference in ADA incidence between the groups

Incidence was defined as the percentage of subjects with a treatment-emergent, confirmed positive, titer ≥2 (minimum measurable titer), persistent ADA response (ADA Endpoint Subjects)

- Persistent was defined as at least 2 ADA-positive timepoints with at least 1 occurring after the second dose (Period 2)

The secondary objective of this study was to investigate any potential impact of ADA and NAb on the PK, PD (as measured by ANC response), safety profile, and tolerability of CHS-1701 or US-Neulasta.

The immunogenicity data for Study CHS1701-04 in the original BLA submission was evaluated by OBP reviewers Haoheng Yan and Fred Mills. This evaluation showed that the ADA incidence in the CHS-1701 arm was greater than the US-Neulasta arm, with an upper exact limit of 10.97%. Coherus also conducted statistical analysis of ADA incidence yielding a 1-sided exact upper limit of 10%. There was extensive discussion of these data within OBP, with a consensus that the difference created unacceptable uncertainty regarding the similarity of CHS-1701 and US-Neulasta. Therefore a complete response letter was issued for this BLA on June 9, 2017. A critical part of the CR were the following immunogenicity comments:

1. In Amendment 41 (received March 21, 2017), for treatment emergent persistent anti-drug antibodies (ADA) with a titer 2, you report an ADA incidence of 9.8% in the CHS-1701 arm and an incidence of 5.0% in the US-licensed Neulasta arm. FDA identified an additional subject (b) (6) as positive in the US-licensed Neulasta arm, which makes the ADA incidence 5.8%. Coherus conducted statistical analysis of ADA incidence yielding a 1-sided upper exact limit of 10%, while the FDA performed independent analysis of your data and obtained a 1-sided upper exact limit of 10.97%. Your observed difference in ADA between groups may not be sufficient to support a demonstration that there are no clinically meaningful differences between CHS-1701 and US-licensed Neulasta. An observed difference at or above the 10% threshold creates residual uncertainty regarding biosimilarity of CHS-1701 to US-licensed Neulasta because the actual baseline immunogenicity rate for pegylated G-CSF products is expected to be lower and the 10% difference was selected to support a feasible study design. In addition, the observed ADA difference needs to be considered in context of other factors that may affect safety and efficacy, such as titers, persistence, and whether the ADA response is against PEG or G-CSF. Provide additional information to address these concerns, such as data that clarifies whether anti-PEG or anti-G-CSF antibodies are driving the observed difference in ADA rates between CHS-1701 and US-licensed Neulasta. Depending on the information provided, further clinical studies may be needed to provide assurance that the difference in ADA rates between CHS-1701 and US licensed Neulasta treatment groups do not result in clinically meaningful differences between CHS-1701 and US-licensed Neulasta.

2. You did not provide data on anti-G-CSF antibody titers for subjects confirmed positive for anti-G-CSF antibodies. You also did not provide data for the incidence of neutralizing antibodies. Lack of these two pieces of information creates uncertainty about whether the difference in ADA incidence rates could be due to a difference in these two factors. To address this concern provide the following:

a) Anti-G-CSF titers for anti-G-CSF positive samples together with time courses for evolution of anti-G-CSF titers.

- b) Since our original discussions regarding neutralizing antibody testing, the Agency has found that anti-PEG ADA can be neutralizing. We recommend that you test all confirmed positive samples (both anti-PEG and anti-G-CSF) in your neutralizing antibody assay.
3. You provided validation reports for two neutralizing antibody (NAb) assays. The first Nab assay was submitted with the original BLA on August 9, 2016, and the second Nab assay was submitted in an amendment on January 18, 2017. Both NAb assays, in their respective current status, are inadequate for the reasons listed below (*not shown in this review*) and will not allow for meaningful evaluation of NAb in clinical samples. To resolve the lack of an adequate neutralizing assay, submit a fully validated NAb assay, including the assay validation report and the test method standard operational protocol.

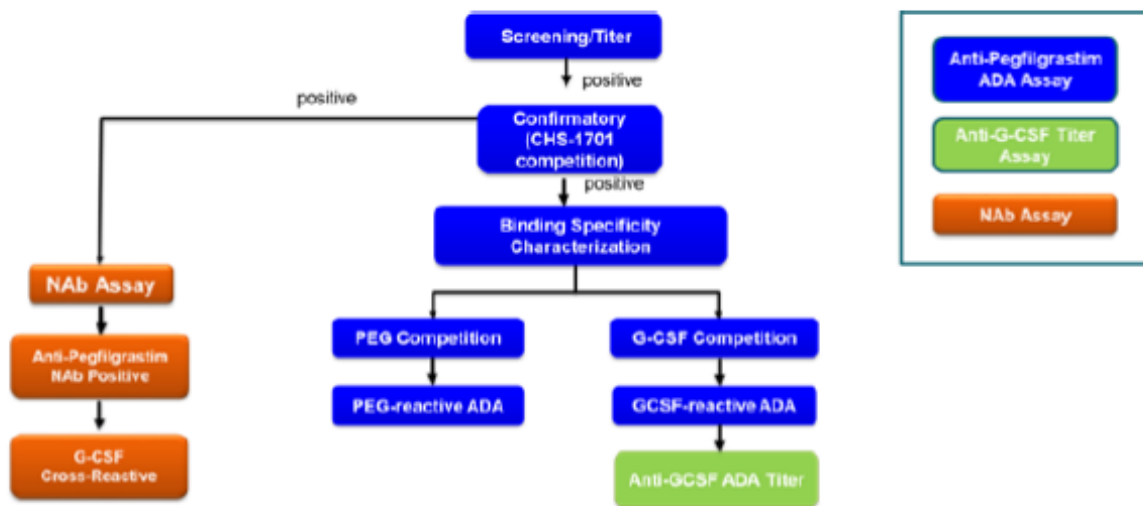
Immunogenicity data in the resubmission of BLA 761039

Coherus' resubmission of their BLA on May 3, 2018 contained new NAb and anti-G-CSF titer assays that were found to be appropriately validated and suitable for intended purpose by FDA reviewer Dr. Haoheng Yan.

NAb Data in Studies CHS-1701-01, CHS-1701-03, CHS-1701-04, CHS-1701-05

Using a newly developed and validated anti-pegfilgrastim assay developed by (b) (4) no treatment-emergent NAb were detected in any of the 4 clinical studies (Studies CHS-1701-01, CHS-1701-03, CHS-1701-04, and CHS-1701-05). In Studies CHS-1701-04 and CHS-1701-05, predose NAb were identified in 4 subjects with pre-existing PEG-reactive ADA (2 subjects in each study). These NABs were detected at the predose time point only and were not able to neutralize the activity of human G-CSF. Thus, the information is consistent with anti-PEG antibodies that have the potential to inhibit the activity of pegfilgrastim, possibly by steric hindrance. This observation is supported by data obtained during NAb assay development and validation that demonstrated that anti-PEG antibodies of IgG and IgM isotypes can specifically neutralize the activity of CHS-1701 in a dose-dependent manner, but do not neutralize the activity of G-CSF.

Figure 9-1: Tiered Immunogenicity Assessment



ADA = antidrug antibody(ies); G-CSF = granulocyte colony-stimulating factor; NAb = neutralizing antibody(ies); PEG = polyethylene glycol
Note: All screen positive samples were also tested in a competition assay with Neulasta (not shown in the figure), for information only.

NAb assay results

Brief NAb Assay description

(Reviewed by Dr. Haoheng Yan)

Dr. Yan found this assay to be appropriately validated and suitable for its intended purpose.

The NAb assay was developed and validated by (b) (4). A three tiered strategy is used to detect and characterize NAb. Samples are first tested in a CHS-1701 based NAb screening assay. Samples that screened positive are sequentially tested by a IL-3 based specificity assay and a Protein A/G/L immunodepletion confirmatory assay. All three assays are cell based assays using the M-NFS-60 cell line, which is dependent on G-CSF for cell growth. Addition of CHS-1701 or US-licensed Neulasta in the test system results in cell proliferation, while the presence of neutralizing antibodies inhibits pegfilgrastim-induced cell proliferation. IL-3 can also stimulate M-NFS-60 cell growth, which is the base for the specificity assay.

Based on the proposed three tier system, samples are considered positive for NAb against pegfilgrastim if they meet all three criteria:

1. inhibit CHS-1701 induced proliferation
2. do not inhibit mIL-3 induced proliferation
3. the inhibitory signal can be eliminated with Protein A/G/L treatment

In addition, all samples positive for NAb against pegfilgrastim will be tested in a cross reactivity assay, where samples are assessed for their ability to neutralize G-CSF.

The cutpoint for the confirmatory assay is 12.5% inhibition, which is a modest inhibition and therefore likely to detect even weak neutralizing activities

Suitability of the three-tier NAb assessment strategy

Prior to BLA re-submission, a Type 2 meeting was held on February 23, 2018 between the FDA and Coherus to discuss a number of immunogenicity issues. Important for the interpretation of NAb results, the FDA provided the following response

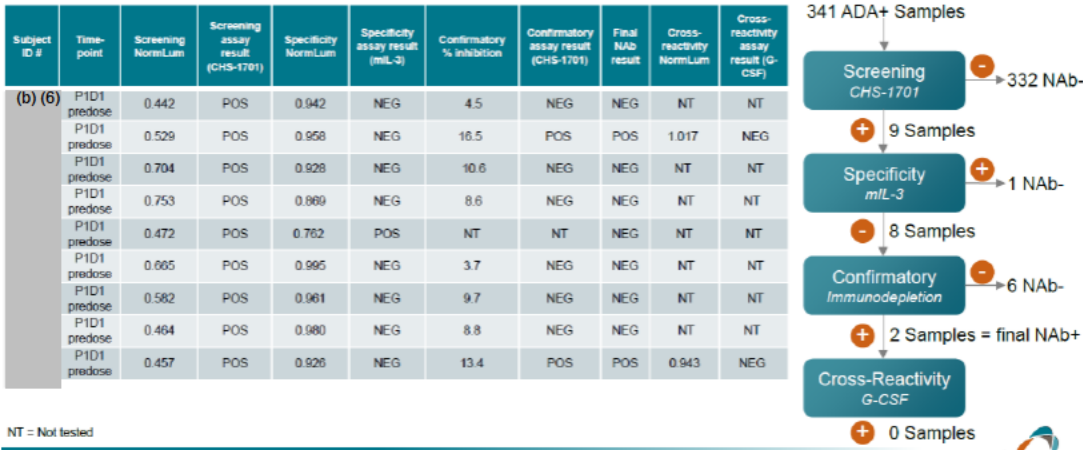
- **Question 12A:** The Agency is concerned that your three-tier approach may underestimate the neutralizing antibody positive rate (i.e., high false negative). For example, a sample with strong neutralizing response in the CHS-1701 based screening assay may show modest positive signal in the IL-3 based specificity assay, and thus be scored as negative. To help the FDA evaluate whether your three-tier approach is appropriate, submit a summary table to report the number of tested clinical samples and positive rate by the screening (CHS-1701), specificity (mIL-3), and immunodepletion assay in the complete response submission.

Tabulation of NAb assay results

A total of 341 ADA-positive samples from 109 ADA-positive subjects including those from Site 004, regardless of ADA titer, persistence and binding specificity were tested in the anti-pegfilgrastim NAb assay. For the February 23, 2018 Type 2 meeting, Coherus provided the following tabulated summary data below. These tabulated results on slide 12 include a subset of data (showing only samples that screened positive). Note that the complete tabulated data set can be found in

<\\cdsesub1\evsprod\BLA761039\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\chs-1701-04\16113-other-stdy-info.pdf>

Study CHS-1701-04: preliminary results for the screen positive samples



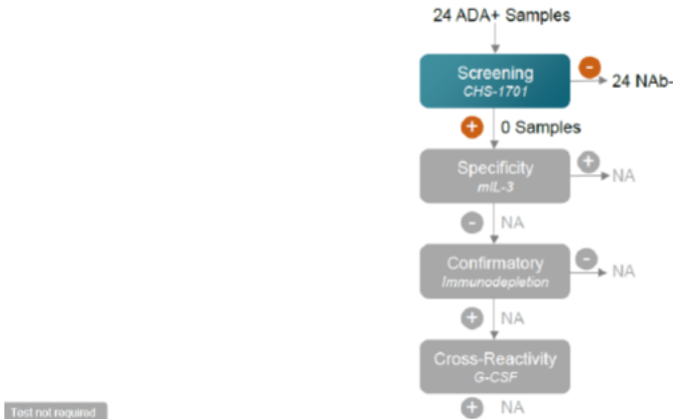
Study CHS-1701-05: preliminary results for the screen positive samples



Study CHS-1701-03: preliminary results for the screen positive samples



Study CHS-1701-01: No screen positive samples



Complete listings of NAb results all confirmed ADA positive samples from Studies CHS-1701-04 and CHS-1701-5 are found in BLA 761039, SN56 at the following locations:

CHS-1701-04

<\\cdsesub1\evsprod\BLA761039\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\chs-1701-04\16113-other-stdy-info.pdf>

CHS-1701-05

<\\cdsesub1\evsprod\BLA761039\0056\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\chs-1701-05\16113-other-rpts.pdf>

Review comments regarding adequacy of NAb evaluation

I have reviewed the complete listing of NAb data for Studies 1701-04 and 1701-05, and find these data to be in agreement with the tabulated NAb data shown above from the February 23, 2018 type 2 meeting.

The Sponsor has found that when they tested their screened positive NAb samples with the IL-3 specificity test, only one out of 17 subjects (subject (b) (6) in Study CHS1704-4) screened positive and was then reclassified as negative because the sample caused some neutralization of the IL-3 response. Thus the classification of almost all the screened positive samples was not affected by the IL-3 specificity test, and therefore the IL-3 specificity test does not appear to have an important impact on confirming subjects as NAb positive. More generally, the Sponsor's 3-tier NAb classification algorithm yielded only four subjects (two in CHS-1701-4 and two in CHS-1701-5) that could be confirmed positive on the basis of CHS-1701-5 inhibition greater than the confirmatory cutpoint, and all four were pre-dose positives whose samples could not be inhibited by G-CSF alone. The other 15 NAb screening positives showed CHS-1701 confirmatory inhibition that was less than the modest 12.5% inhibition confirmatory cutpoint. Thus I agree with the Sponsor that their studies provide no evidence for treatment-emergent NAb, and therefore meet this co-primary endpoint.

G-CSF Titer results

This assay was developed by (b) (4) and Dr. Haoheng Yan found it to be appropriately validated and suitable for its intended purpose.

Brief description of the anti-G-CSF titer assay

(reviewed by Dr. Haoheng Yan)

The screening assay is an electrochemiluminescence (ECL) based bridging assay. In brief, human plasma samples are incubated in a mixture of biotinylated G-CSF and ruthenylated G-CSF to form “Bio-G-CSF: anti-G-CSF antibody : Ru-G-CSF” complex. This complex is then added to a streptavidin coated plate and allowed to bind. After washing, the detection agent was added to the complex, and the luminescence signal is read by a plate reader.

In the titer assay, samples were 2-fold serial diluted in matrix diluent (PNHP) before being subjected to the screening assay. The titer is determined to be the highest fold dilution that has an S/N ratio greater than or equal to the titer cut point. ADA confirmed positive samples that have an S/N ratio less than the titer cutpoint at MRD in this titer assay are reported as < 2.

Study CHS-1701-4 Assay Results and Discussion

Table 11-7: Incidence of Subjects with Treatment-Emergent ADA – Safety Population

	CHS-1701 (N = 134)	Neulasta (N = 134)
Subjects with ADA Assessment Post Dose (excluding subjects with pre-existing ADA)	N = 121	N = 117
Treatment-emergent ADA, n (%)	39 (32.2%)	28 (23.9%)
Binding Specificity		
PEG		
PEG/G-CSF, n (%)	9 (7.4%)	7 (6.0%)
PEG Only, n (%)	23 (19.0%)	17 (14.5%)
G-CSF Only	0	0
None, n (%)	7 (5.8%)	4 (3.4%)

ADA = antidrug antibody(ies); G-CSF = granulocyte colony-stimulating factor; N = number of subjects with an ADA assessment post dose excluding subjects with pre-existing ADA; % = n/N; PEG = polyethylene glycol; None = not binding to PEG or G-CSF.

Note: Data from Site 004 was excluded because the wrong study drug was administered in Period 2.

Source: Table 14.2.1.4

Note that there were actually 109 ADA positive subjects, because there were 42 pre-treatment positives, as well as the 67 treatment emergent positives (39 subjects for CHS-1701 and 28 subjects for US-Neulasta =67 total)

Reviewer comments

ADA that are reactive to the G-CSF moiety of CHS-1701 or US-Neulasta are of critical concern because they may impact efficacy vis-à-vis blocking of binding to the G-CSF receptor, and may also pose a potential safety concern if they cross-react with endogenous G-CSF. On the other hand ADA to PEG are of less concern, as they are present at relatively high concentrations in normal individuals without apparent effect. Therefore, I have summarized below the confirmed G-CSF positives in Study CHS-1701-04:

CHS-1701 arm	5 pre-treatment	9 treatment emergent	14 total
US-Neulasta arm	1 pre-treatment	7 treatment emergent	8 total

Of these confirmed positives, there were a total of 18 Study 1701-04 subjects with un-measurable G-CSF titer (titer < 2), including pre-treatment and treatment-emergent G-CSF positives; i.e.

CHS-1701	9
US-Neulasta	7
Site 004	<u>2</u>
	18 total

Note that 2 subjects from site 004 were excluded from the analysis because of protocol deviation.

There were a total of 6 Study 1701-04 subjects with measurable G-CSF-titers; i.e.

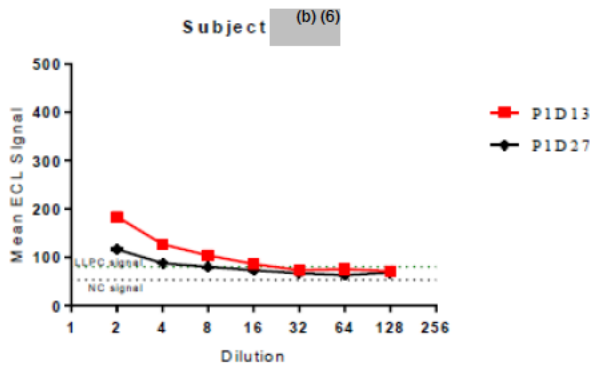
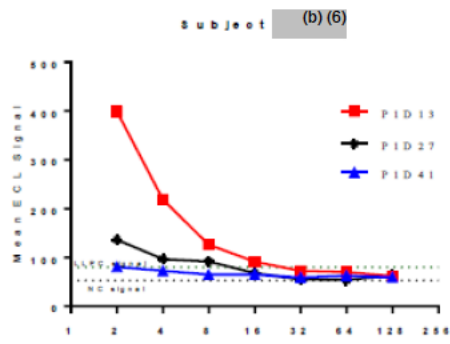
CHS-1701	5
US-Neulasta	<u>1</u>
	6 total

However, the Sponsor found that 3 of the measurable titer CHS-1701 arm subjects had unreliable assessments. The titer curves for all the measurable titer subjects are shown below:

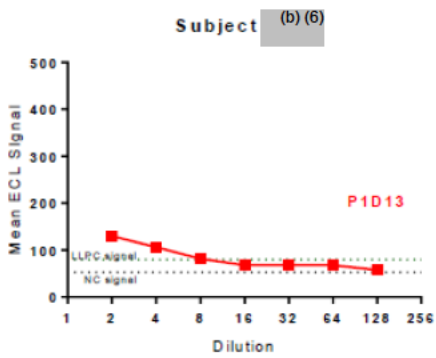
Figure 11-7: Anti-G-CSF Antibody Titer (ECL Signal) Titration Curves

Reliable Assessments

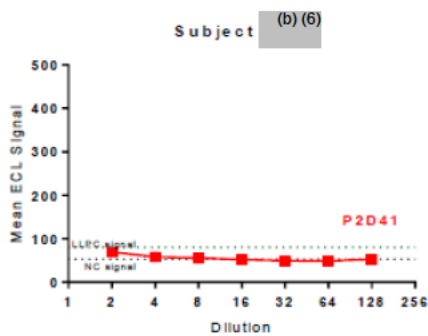
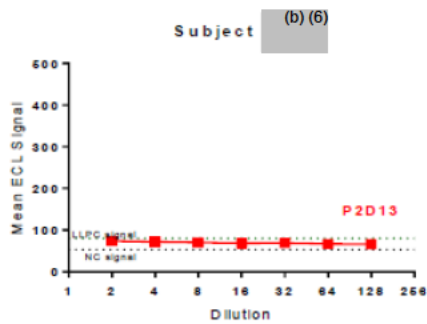
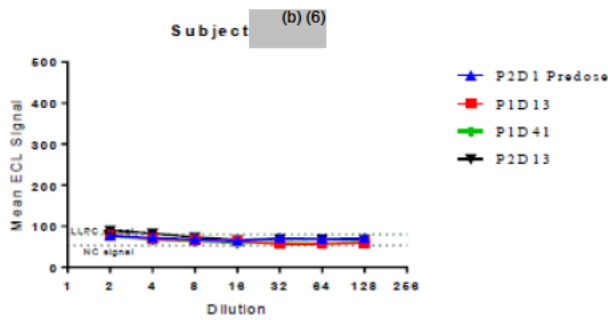
CHS 1701 arm



Neulasta arm



Unreliable titers-three subjects all in the CHS 1701 arm



Reviewer comments

The titers that are classified as unreliable have low ECL value are close to or within the baseline. Thus I agree that the titer data form these three CHS 1701 are subjects is unlikely to provide reliable information about anti-G-CSF titer. Therefore, reliable titers show a low absolute incidence: 2 in CHS-1701 vs. 1 in US-Neulasta

Coherus position on observed anti-G-CSF titers is the following:

p 77 of the CHS-1701-4 study report

<\\cdsesub1\evsprod\BLA761039\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\chs-1701-04>

The transient profile of anti-G-CSF antibody titers further supports the conclusion that the difference in ADA incidence between the CHS-1701 and Neulasta groups is driven by non-neutralizing, low (<4) titer, PEG-reactive ADA. An ADA titer of 4 in the ADA assay regardless of specificity for G-CSF or PEG corresponds to ≤ 200 ng/mL of the polyclonal anti-G-CSF antibody positive control and to approximately 200 ng/mL of the anti-PEG monoclonal antibody positive control used in the ADA assay. In comparison, a normal healthy person could carry anti-PEG IgG and IgM antibodies in $\mu\text{g/mL}$ quantities (Chen et al. Analytical Chemistry, 2016, **88**, pp. 10661–10666). Therefore, it is unlikely that anti-pegfilgrastim antibodies with titers <4 are clinically relevant, as anti-PEG antibodies affect efficacy, PK, and/or safety of pegylated products at much higher titers (Hershfield et al. Arthritis Research & Therapy 2014, **16**, R63 ; Leesch et. al J. Clin Pharmacol. 2016 **46**, pp.747-757).

Reviewer comments

I agree with Coherus' overall position, as they have met the co-primary endpoint of no treatment emergent NAbs, and found only low absolute incidence of anti-G-CSF titers. Thus from an immunogenicity standpoint, there appears to be no important differences between CHS-1701 and US-Neulasta.

IV. Attachment

Validation Report for Neutralizing Antibody Assay:

Testing Strategy

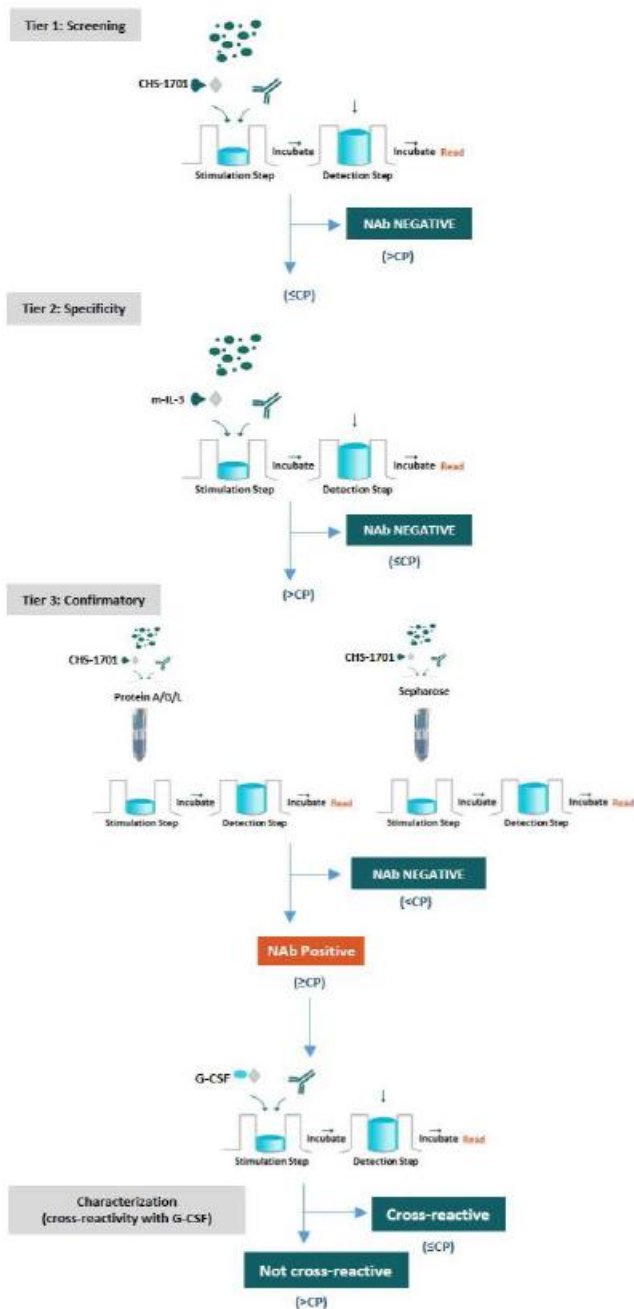
The NAb assay was developed and validated by (b) (4). A three tiered strategy is used to detect and characterize NAb. Samples are first tested in a CHS-1701 based NAb screening assay. Samples that screened positive are sequentially tested by a IL-3 based specificity assay and a Protein A/G/L immunodepletion confirmatory assay. All three assays are cell based assays using the M-NFS-60 cell line, which is dependent on G-CSF for cell growth. Addition of CHS-1701 or US-licensed Neulasta in the test system results in cell proliferation, while the presence of neutralizing antibodies inhibits pegfilgrastim-induced cell proliferation. IL-3 can also stimulate M-NFS-60 cell growth, which is the base for the specificity assay.

Based on the proposed three tier system, samples are considered positive for NAb against pegfilgrastim if they meet all three criteria:

4. inhibit CHS-1701 induced proliferation
5. do not inhibit mIL-3 induced proliferation
6. the inhibitory signal can be eliminated with Protein A/G/L treatment

In addition, all samples positive for NAb against pegfilgrastim will be tested in a cross reactivity assay, where samples are assessed for their ability to neutralize G-CSF. The NAb analysis scheme is shown in the following Table 1.

Figure 1. Neutralizing Antibody Assay Tiers Analysis Scheme



Reviewer’s Comments:

The 3 tiered testing strategy is similar to one used in the NAb assay developed by (b) (4) in the original BLA. At that time, we communicated with the sponsor through an IR (sent on Dec 7, 2016) that we were concerned that this three tiered approach may underestimate the neutralizing antibody positive rate (in other words, it may give a high false negative rate). For

example, a sample with strong neutralizing response in the CHS-1701 based proliferation assay may show modest positive signal in the IL-3 based assay, and thus be scored as negative. Analyzing testing results of the clinical samples from all three assays may help evaluate the strategy. In the original BLA, the sponsor only submitted the final NAb rate, which is 0 in both CHS-1701 and US-Neulasta treated groups, we requested the sponsor to submit the total number of tested clinical samples and positive rate by the CHS-1701 (screening) and IL-3 (confirmatory) based assays.

The current submission did not include clinical immunogenicity testing results; a similar comment will be communicated to the sponsor regarding the 3 tiered strategy.

Method Description

In the CHS-1701 based screening assay, plasma samples are pre-incubated with or without a fixed concentration of CHS-1701(stimulator) for 55±15 min at 37°C in a microtiter plate. M-NFS-60 cells are added to the wells and incubated for 46-48 hours at 37°C/5%CO₂. Proliferation of the M-NFS-60 cells is measured using Cell-Titer Glo ® (Promega) on a micro plate reader. The signal is recorded as Lum unit.

The mIL-3 based specificity assay, the G-CSF based cross activity assay and the protein A/G/L immunodepletion confirmatory assay all have a similar design to the CHS-1701 based screening assay except for the cell growth stimulator used for the assay (mIL-3 and G-CSF) or sample pre-treatment (immunodepeltion).

In the mIL-3 based specificity assay, plasma samples are pre-incubated with a fixed concentration of mIL-3 (instead of CHS-1701). The specific assay is used to determine whether the neutralizing activity detected in the screening assay is specific to CHS-1701 or due to non-specific growth inhibition. Plasma samples which contain neutralizing antibodies that are specific to CHS-1701 (and therefore inhibit cell growth in the CHS-1701 based screening assay) are expected not to inhibit cell growth in the mIL-3 based specificity assay.

In the protein A/G/L immunodepletion confirmatory assay, plasma samples are pre-treated with Protein A/G/L to remove antibodies before proceeding to the CHS-1701 screening assay. The purpose of the immunodepletion is to confirm that the signal observed in the screening assay is indeed due to immunoglobulins (IgG or IgM).

In the G-CSF cross activity assay, plasma samples are pre-incubated with a fixed concentration of Recombinant Glycosylated G-CSF (instead of CHS-1701). The G-CSF cross activity assay is used to determine whether the detected NAb (to pegfilgratim) also able to neutralize the activity of G-CSF in vitro. During assay development, it was determined that anti-PEG antibodies can specifically neutralize the activity of CHS-1701 in the NAb assay, but do not neutralize the activity of G-CSF.

The total volume of the assay mixture in the plate well was kept at 100 µL with minimum required dilution (MRD) at 1:40 and the final concentration of CHS-1701 at 60 pg/mL, mIL-3 at 50 pg/mL, or GCSF at 15 pg/mL.

Reviewer's Comments:

The assay format is acceptable. The inclusion of G-CSF cross activity assay is recommended per OBP immunogenicity working group internal discussion (it was communicated to the sponsor during the BPD type 2 meeting held on 11/29/2017) as the interference of anti-PEG antibody on the NAb assay has been reported in other pegfilgrastim biosimilar submissions.

Essential Reagents and Concentration

The essential reagents are listed in the following reviewer generated Table:

Reagent	Source	Lot or Cat Number	Reviewer's Comments:
NFS-60 cells	(b) (4)	(b) (4)	Culture was limited between 6 and 21 days in culture after thawing for all assay validation. See data in Question 3 .
CHS-1701	Coherus BioSciences	Lot# 2372-119	
US-Neulasta	Amgen	Lot#1057373, #1059900	
G-CSF (Recombinant Glycosylated G-CSF made in HEK cells)	(b) (4)	(b) (4)	Used in G-CSF cross activity assay as stimulator.
mIL-3	(b) (4)	(b) (4)	Used in the specificity study as stimulator.
Anti-PEG IgM	(b) (4)	(b) (4)	Used in the development study.
Anti-G-CSF (Monoclonal antibody)	(b) (4)	(b) (4)	Used as Positive Control in the assay validation and suitability control.
Protein A/G/L	(b) (4)	(b) (4)	
Sepharose beads	(b) (4)	(b) (4)	

Control Samples used in the assay validation are provided in the following Table 4:

Table 4. Control Summary Table

Assay Control	Composition	Purpose	When used
NC	Cells + plasma	To monitor cellular response in the absence of inducer	All assays
DC	Cells + plasma + CHS-1701	To monitor cellular response in the presence of CHS-1701	Screening and confirmatory assays
SC	Cells + plasma + mIL-3	To monitor cellular response in the presence of mIL-3	Specificity assay
EC	Cells + plasma + G-CSF	To monitor cellular response in the presence of G-CSF	Cross-reactivity assay

DC = drug control; EC = endogenous control; G-CSF = granulocyte-colony stimulating factor; mIL-3 = mouse interleukin 3; NC = noninduced control; SC = specificity control

Concentrations of the positive controls (monoclonal anti-G-CSF antibody) are listed in the following Table 5

Table 5. List of Positive Controls Evaluated in Validation

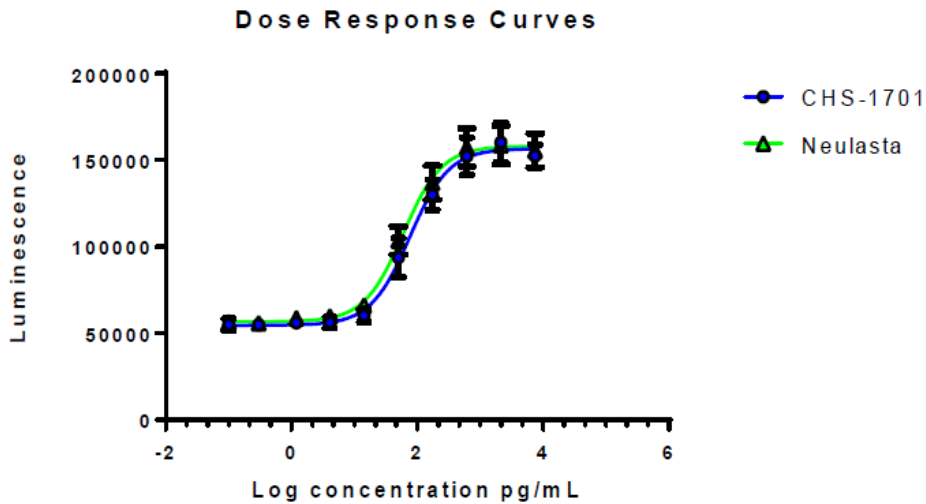
Positive Control	Concentration in ng/mL
HPC	2000
MPC	500
LPC	250
LLPC	150
L2PC	300
L3PC	320
L4PC	400

HPC = high positive control; LPC = low positive control; LLPC = lower low positive control; MPC = mid positive control

Dose Response Curve

Comparison between CHS-1701 and US-Neulasta

Dose response curves of CHS-1701 and Neulasta from 7500.0 to 0.01pg/mL were compared. A total of 8 independently prepared dose-response curves for were run in parallel by 2 analysts over 2 days (see Figure below). All curves yielded an F probability value of $p > 0.05$, indicating a parallel response between the two drugs (sponsor's claim). No statistical difference was observed between the EC50 values of the two drugs (one-way ANOVA).



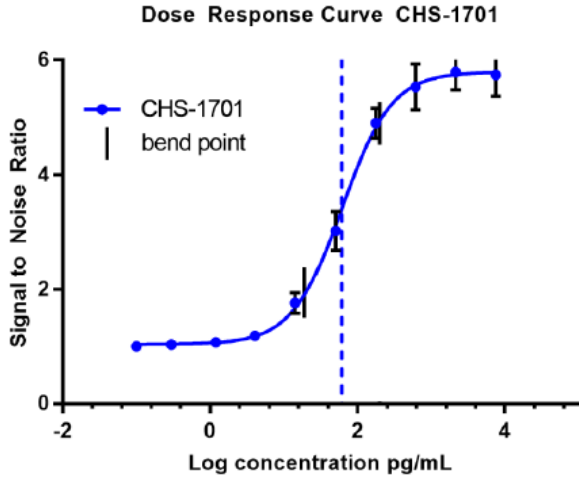
Reviewer's Comments:

The dose response is comparable that the CHS-1701 can be used as stimulator in the NAb screening assay to evaluate the neutralizing antibody in samples from CHS-1701 and US-Neulasta treated subjects.

Dose response curves for CHS-1701, mL-3 and G-CSF

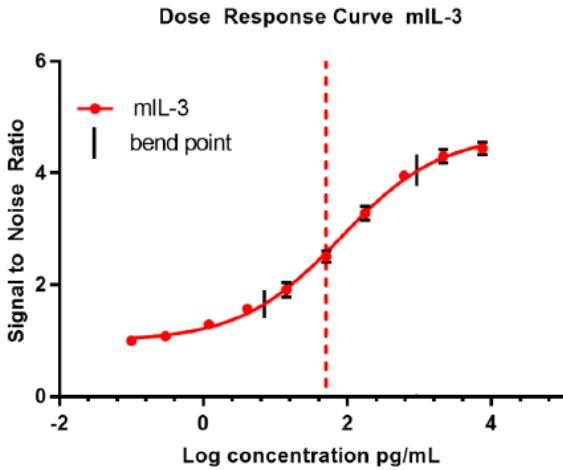
The concentrations of CHS-1701, mL-3, and G-CSF used in the respective screening, specificity and cross-reactivity assays were in the middle of the linear range of the respective dose-response curves shown in the following Figure 3-5.

Figure 3. Dose Response Curve for CHS-1701-induced Proliferation of NFS-60 Cells



Results are presented as mean and SD for 6 independent runs for CHS-1701. Signal to noise ratio represents the Lum over NC Lum value. The dotted line represents the selected concentrations for CHS-1701. Bend points define the upper and lower limits of the linear range and were calculated using the average curve parameters from the 6 CHS-1701 dose response curves

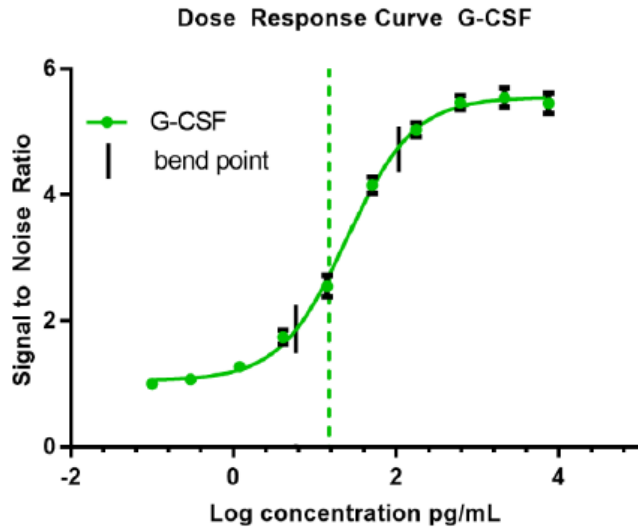
Figure 4. Dose Response Curve for mIL-3-induced Proliferation of NFS-60 Cells



mIL-3 = mouse interleukin 3

Results are presented as mean and SD for 3 independent runs for mIL-3. Signal to noise ratio represents the Lum over NC Lum value. The dotted line represents the selected concentrations for mIL3. Bend points define the upper and lower limits of the linear range and were calculated using the average curve parameters from the 3 mIL-3 dose response curves.

Figure 5. Dose Response Curve for G-CSF-induced Proliferation of NFS-60 Cells



Reviewer’s Comments:

The concentrations of the stimulators (CHS-1701, mIL-3 and G-CSF) are acceptable per guidance that neutralization assay should be performed at therapeutic protein product concentrations that are on the linear range of the curve.

Cut Point Determination

Assay cut points were determined using commercially obtained plasma samples (validation cut points) and predose study plasma samples (in-study cut points).

In the screening, specificity and cross activity assays, the sample signals (Lum) were normalized according to the following formula to account for potential endogenous stimulator and plate-to plate variability. The results for all positive control samples were normalized using the same formula.

$$\text{Normalized Response} = \frac{\text{Sample LUM with inducer}}{\text{Sample LUM without inducer}} \div \frac{\text{NC Pool LUM with inducer}}{\text{NC Pool LUM without inducer}}$$

For the confirmatory assay, a percent inhibition was calculated for each sample using the following formula:

$$\%INH_{AGL-Sepharose} = \left[\frac{\text{Sample LUM w/Protein AGL} - \text{Sample LUM w/Sepharose}}{\text{Sample LUM w/Protein AGL}} \right] \times 100$$

I summarized the statistical analysis and results in the following table:

		Number of serum samples	Number of assays	Number of analysts	Total number of sample values	Number of outliers	Statistical Method for cut point determination (detail below the table)	Cut point value
Screening Assay (CHS-1701)	Commercial sourced plasma	32	3	2	96	6	Cut points were calculated from the log transformed NormLum using parametric method at 1% false positive rate. Analytical and biological outliers were excluded from the cut point calculation.	0.9
	Pre-dose subjects	40	4	2	160	23		0.76
Specificity Assay (mIL-3)	Pre-dose subjects	40	4	2	160	9		0.818
Cross Activity Assay (G-CSF)	Pre-dose subjects	40	4	2	160	3		0.827
Confirmatory Assay (Protein A/G/L Immuno-depletion)	Commercial sourced plasma	32	3	2	96	3	Cut points were calculated from the %INH using parametric method at 1% false positive rate after outlier exclusion.	12.5%
	Pre-dose subjects	20	1	1	20	1	No statistical difference between the mean and variance of the commercial and in-study datasets.	Confirmed the suitability of the cutpoint determined from commercial plasma

Statistical Method

The distribution of ANOVA conditional residual values from the model was evaluated to identify ‘analytic’ statistical outliers as values above the 75th quartile plus 1.5 times the interquartile range or below the 25th quartile minus 1.5 times the inter-quartile range. Outliers identified by this criterion were removed and the model was re-fit until no outlying value was detected.

The distribution of individual sample best linear unbiased predictor (BLUP) values was then examined to identify samples as ‘biologic’ statistical outliers. All values for individual samples identified as biologic outliers were removed and the statistical analysis was repeated until no further outliers were present.

Normality and skewness assessment was conducted to determine the statistical method, parametric or nonparametric, to be used for the cut point calculation.

Reviewer’s comment:

The experimental design and statistical analysis used for cut point calculation is acceptable. The cut points for the above assays are appropriately defined and acceptable.

Assay Precision

Assay precision was calculated using the following expression:

$$\% CV = \frac{\text{Standard deviation of individual measurements}}{\text{Mean of individual measurements}} \times 100$$

The inter-assay precision assessment was performed over 6 to 16 plates by 3 analysts over 3 days. The %CV of the NormLum (for the positive controls) or Lum (for NC, DC, SC, and EC) ranged from 4.2% to 14.0%.

Assessment of intra-assay precision for positive controls and negative controls included a minimum of 3 determinations of the HPC, MPC, LPC, LLPC, NC, DC, SC, and EC run in a single assay, over 3 plates. The %CV of the NormLum (for the positive controls) or Lum (for the other controls) for each control ranged from 2.5% to 13.2%.

Inter- and intra assay precision of positive controls in the cross-reactivity (G-CSF) assay: %CV of the NormLum (for the positive controls) ranged from 6.5% to 15.5% and 2.3% to 2.9% for inter- and intra assay precision, respectively.

Reviewer's Comments:

The assay precision is acceptable.

Assay Sensitivity

Sensitivity was assessed by evaluating 12 independent serial dilutions of a 10,000 ng/mL solution of the positive control in neat plasma. Assay sensitivity was defined as the interpolated value at which a 4-parameter logistic curve fit of the positive control titration crossed the cut point. Sensitivity is at 44.1ng/ml and 137.0ng/mL on average for the cut point of 0.90 (validation cut point) and 0.76 (in study cut point), respectively. Assay sensitivity for C-GSF cross activity assay was determined the similar way at 42.6ng/mL.

Reviewer's Comment: *The assay sensitivities are acceptable.*

Concentration of LPC is determined by

- LLPC = assay sensitivity using validation cut point + $(t_{0.01, df} \times SD) = 44.1 + (2.718 \times 27.3) = 118 \text{ ng/mL}$ ----the sponsor selected LLPC at 150ng/mL
- LPC level = assay sensitivity using validation cut point + $(t_{0.01, df} \times SD) = 137 + (2.718 \times 46.8) = 264 \text{ ng/mL}$ --- the sponsor selected LLPC at 250ng/mL

Reviewer's Comments:

The concentration of LLPC and LPC are appropriate.

Specificity

Specificity was confirmed by evaluating the impact of human IgG antibodies, anti-GCSF positive control and anti-PEG antibody on the screening and specificity assay. These antibodies were spiked into pooled plasma at final assay concentrations of 2000, 500, 250, and 150 ng/mL and tested in the screening and specificity assays. Results are summarized by the reviewer in the following Table:

Spike in	Screening assay	Specificity assay
Commercial IgG	No inhibition	No inhibition
Anti-G-CSF PC	Show inhibition	No inhibition
anti-PEG antibodies	Show inhibition	Not tested

Reviewer's Comments:

The results are as expected that commercial human IgG does not interfere with the screening or the specificity assay. However, anti-PEG antibody can interfere with the screening assay which causes false positive result, shown in Table 23.

Table 23. Anti-PEG Antibody

Concentration ng/mL	GenScript Anti-PEG in CHS-1701 induced cells (NormLum)
0 (DC)	1.000
150	0.887
250	0.851
500	0.772
2000	0.471

DC = drug control; NormLum = normalized value; PEG = polyethylene glycol

It was shown during assay development that some anti-PEG antibodies could specifically inhibit the CHS-1701-induced cell proliferation, without affecting mL-3-induced or GCSF-induced cell proliferation.

Reviewer's Comments:

The assay specificity is appropriately evaluated.

Selectivity

Individual lots of normal human plasma, 10 commercially obtained individual normal human plasma samples, were spiked with the positive control at the 0, 250, 500, 1000, and 2000 ng/mL levels and tested in the CHS-1701 NAb screening test. Results are shown in the Table 24 and 25. Validation cut point 0.9 was used to score the samples.

Table 24. Selectivity in Normal Individual Plasma Samples (Run 26)

	Unspiked (0 ng/mL)	NAb Result	Spiked at 250 ng/mL	NAb Result	Spiked at 2000 ng/mL	NAb Result
(b) (6)	0.918	Neg	0.636	Pos	0.525	Pos
	1.118	Neg	0.808	Pos	0.585	Pos
	1.116	Neg	0.816	Pos	0.598	Pos
	1.024	Neg	0.751	Pos	0.577	Pos
	1.110	Neg	0.797	Pos	0.581	Pos
	1.052	Neg	0.712	Pos	0.532	Pos
	0.864	Neg*	0.634	Pos	0.527	Pos
	1.004	Neg	0.735	Pos	0.555	Pos
	1.045	Neg	0.748	Pos	0.540	Pos
	0.889	Neg*	0.707	Pos	0.511	Pos

*= negative in confirmatory assay; Neg = negative; Pos = positive

Table 25. Selectivity in Normal Individual Plasma Samples (Run32)

	Unspiked (0 ng/mL)	NAb Result	Spiked at 500 ng/mL	NAb Result	Spiked at 1000 ng/mL	NAb Result
(b) (6)	0.839	Neg*	0.470	Pos	0.468	Pos
	1.000	Neg	0.616	Pos	0.567	Pos
	1.068	Neg	0.663	Pos	0.601	Pos
	1.056	Neg	0.646	Pos	0.568	Pos
	0.965	Neg	0.588	Pos	0.526	Pos
	0.873	Neg*	0.510	Pos	0.478	Pos
	0.680	Neg*	0.452	Pos	0.414	Pos
	0.800	Neg*	0.537	Pos	0.453	Pos
	0.860	Neg*	0.523	Pos	0.469	Pos
	0.789	Neg*	0.491	Pos	0.454	Pos

*= negative in confirmatory assay; Neg = negative; Pos = positive

Reviewer's Comments:

Using the in study cut point of 0.76, the assay scored 7 out of 10 individual plasma spiked with 250ng/mL PC, and 10 out of 10 spiked with 500ng/mL PC. The assay selectivity in normal human plasma sample is acceptable (in terms of adequate sensitivity in individual plasma samples).

I noticed that the NormLum of unspiked individual samples ranges from 0.680-1.118. In the Statistical Report 2017-63, the 40 drug naïve in study samples ranges from ~0.3-1.1 (Table 2 below). The higher end the ranges is ~1.1 (close to 1) which can be due to assay variation. However, the lower end of the ranges is far from 1, it is unclear how some of the unspiked individual samples show very low NormLum value that can be scored positive in the screening assay. These can potentially be samples with endogenous stimulator. In the proposed testing strategy, these samples would be tested positive in the NAb screening assay and subject to subsequent specificity and confirmatory assay. Therefore, it is unlikely to cause false positive result.

Table 2: Listing of Normalized Response Values for Human Plasma Samples in the Presence of CHS-1701

Group	Subject	Set 1	Set 2	Set 3	Set 4
A	(b) (6)	0.919	0.880	1.034(a)	1.020
A		0.995	0.983	1.015	1.062
A		0.919	0.916	0.914	0.939
A		0.901	0.889	0.913	0.925
B		1.013	1.016	1.073	1.126
B		0.832	0.856	0.963	0.950
B		0.864	0.869	0.927	0.985
B		0.953	0.997	1.084	1.078
C		0.887	0.913	1.016	1.043
C		0.958	0.985	1.042	1.028
C		0.982	1.030	1.057	1.077
C		0.997	1.175(a)	1.112	1.105
D		1.095	1.063	1.130	1.090
D		0.807	0.781	0.797	0.803
D		0.269(b)	0.259(b)	0.320(a)	0.402(a)
D		0.975	1.068	1.079	1.058
E		0.956	1.054	0.965	1.096
E		0.931	0.931	0.867	0.909
E		0.728(b)	0.721(b)	0.614(a)	0.711(b)
E		0.770	0.820	0.633(a)	0.825
F		1.158	1.026	1.118	1.086
F		1.040(a)	0.893	0.886	0.872
F		0.953	0.914	1.029	0.978
F		0.462(a)	0.717	0.791	0.741
G		0.724(a)	0.953(a)	0.827	0.837
G		0.990	0.879	0.966	0.915
G		1.087	0.982	1.040	1.049
G		0.756(b)	0.706(b)	0.694(b)	0.713(b)
H		1.164	1.132	1.117	1.180
H		0.900	0.812	0.829	0.865
H		0.996	0.981	1.011	1.017
H		0.501(a)	0.583(b)	0.591(b)	0.591(b)
I		1.063	1.097	1.156	1.090
I		0.962	1.026	1.027	0.978
I		0.931	0.935	1.004	0.929
I		1.030	1.071	1.095	0.998

Five moderately hemolyzed samples (approximately 140-275 mg/dL hemoglobin), and 5 visually lipemic samples, were spiked with the positive control at the 0, 250, 500, 1000, and 2000 ng/mL levels and tested in the CHS-1701 NAb screening test. The results are shown in the following Table 27 and 28.

Table 27. Selectivity in Hemolyzed Individual Plasma Samples (Run 32)

	Unspiked (0 ng/mL)	NAb Result	Spiked at 500 ng/mL	NAb Result	Spiked at 1000 ng/mL	NAb Result
(b) (6)	1.073	Neg	0.676	Pos	0.559	Pos
	1.076	Neg	0.743	Pos	0.587	Pos
	0.917	Neg	0.772	Pos	0.598	Pos
	1.098	Neg	0.758	Pos	0.634	Pos
	1.266	Neg	0.783	Pos	0.682	Pos

Neg = negative; Pos = positive

Table 28. Selectivity in Lipemic Individual Plasma Samples (Run 26)

	Unspiked (0 ng/mL)	NAb Result	Spiked at 250 ng/mL	NAb Result	Spiked at 2000 ng/mL	NAb Result
(b) (6)	0.941	Neg	0.688	Pos	0.399	Pos
	0.983	Neg	0.758	Pos	0.425	Pos
	0.919	Neg	0.738	Pos	0.443	Pos
	0.938	Neg	0.818	Pos	0.448	Pos
	0.972	Neg	0.849	Pos	0.483	Pos

Neg = negative; Pos = positive

Reviewer's Comments:

Limited number of hemolyzed and lipemic samples were tested. The NormLum of the PC spike in hemolyzed and lipemic samples are slightly higher than the individual normal plasma samples shown in [Table 24](#) and [Table 25](#) above. Based on the current data, the impact of sample condition on assay sensitivity is inconclusive. The sponsor may need to include additional samples to test the impact.

Drug Tolerance

The sponsor evaluated the ability of the assay to detect NAb in the presence of circulating drug and established drug tolerance limits for the assay. The result is provided in the following Table 29

Table 29. Drug Tolerance for CHS-1701 and Neulasta

CHS-1701						Neulasta					
HPC (2000 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave	HPC (2000 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave
38.4	1.091	1.155	1.080	1.116	1.110	38.4	1.084	1.124	1.095	1.123	1.106
19.2	0.835	0.840	0.833	0.820	0.832	19.2	0.857	0.844	0.852	0.864	0.854
9.6	0.629	0.652	0.638	0.639	0.639	9.6	0.641	0.655	0.649	0.654	0.650
4.8	0.540	0.532	0.533	0.541	0.536	4.8	0.540	0.545	0.536	0.536	0.539
2.4	0.488	0.494	0.494	0.486	0.490	2.4	0.487	0.502	0.492	0.486	0.492
1.2	0.468	0.470	0.467	0.458	0.466	1.2	0.467	0.469	0.464	0.465	0.466
0	0.468	0.479	0.461	0.474	0.470	0	0.457	0.474	0.469	0.483	0.471
MPC (500 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave	MPC (500 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave
38.4	1.352	1.337	1.349	1.321	1.340	38.4	1.384	1.308	1.358	1.330	1.345
19.2	1.193	1.218	1.200	1.214	1.206	19.2	1.256	1.231	1.240	1.200	1.232
9.6	0.960	0.957	0.953	0.951	0.955	9.6	0.952	0.960	0.944	0.954	0.952
4.8	0.746	0.741	0.728	0.714	0.732	4.8	0.733	0.721	0.710	0.701	0.716
2.4	0.551	0.570	0.572	0.577	0.567	2.4	0.583	0.582	0.544	0.566	0.569
1.2	0.490	0.492	0.488	0.479	0.487	1.2	0.493	0.498	0.486	0.491	0.492
0	0.560	0.590	0.569	0.590	0.577	0	0.587	0.603	0.604	0.601	0.599

LPC (250 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave	LPC (250 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave
38.4	1.469	1.444	1.493	1.508	1.479	38.4	1.476	1.464	1.555	1.586	1.520
19.2	1.328	1.387	1.363	1.367	1.361	19.2	1.339	1.364	1.424	1.413	1.385
9.6	1.158	1.181	1.152	1.182	1.168	9.6	1.168	1.162	1.167	1.201	1.175
4.8	0.894	0.930	0.904	0.864	0.898	4.8	0.867	0.912	0.922	0.905	0.901
2.4	0.663	0.682	0.668	0.665	0.669	2.4	0.643	0.658	0.699	0.693	0.673
1.2	0.551	0.555	0.551	0.530	0.547	1.2	0.529	0.544	0.579	0.561	0.553
0	0.665	0.672	0.678	0.691	0.677	0	0.684	0.689	0.704	0.703	0.695
LLPC (150 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave	LLPC (150 ng/mL)	Norm Lum 1	Norm Lum 2	Norm Lum 3	Norm Lum 4	Ave
38.4	1.425	1.483	1.503	1.443	1.464	38.4	1.507	1.570	1.545	1.412	1.508
19.2	1.334	1.356	1.357	1.360	1.352	19.2	1.394	1.395	1.469	1.240	1.375
9.6	1.234	1.245	1.226	1.201	1.227	9.6	1.194	1.267	1.271	1.214	1.236
4.8	0.968	1.011	0.929	0.933	0.960	4.8	0.938	0.951	0.997	0.906	0.948
2.4	0.730	0.724	0.704	0.709	0.717	2.4	0.701	0.707	0.750	0.680	0.710
1.2	0.551	0.562	0.551	0.548	0.553	1.2	0.570	0.571	0.588	0.532	0.565
0	0.761	0.762	0.768	0.759	0.763	0	0.746	0.785	0.794	0.798	0.781

HPC = high positive control; LPC = low positive control; LLPC = lower low positive control; MPC = mid positive control; NormLum = normalized value

Note: The cells highlighted in blue generated a signal above the validation cut point (0.900).

Neutralizing antibody at 500 ng/mL can be detected in the presence of 4.8 ng/mL of CHS-1701 or US-Neulasta. Neutralizing antibody at 250 or 150 ng/mL can be detected in the presence of 2.4 ng/mL of either drug.

Reviewer's Comments:

According to the clinical pharmacology reviewer Sarah Schrieber, the level of CHS-1701 or US-Neulasta in the subjects from the CHS-1701-04 study (immunogenicity study) are lower than LOQ (of the PK assay, 0.15ng/mL) at the time points when the immunogenicity samples were taken. The results presented above indicate that expected plasma concentrations of CHS-1701 and US-Neulasta are not expected to interfere with the detection of 150ng /ml of NAb in this assay. The assay drug tolerance is acceptable.

Stability

Stability of positive control samples (HPC and LLPC) were prepared in pooled human plasma and subjected to free-thaw (9 cycles), room temperature for 5 hours, 2-8°C for 25 hours before tested in the CHS-1701 screening assay. All storage samples showed %CV ≤10.2% when compared to base value (Lum).

Reviewer's Comments:

The sample stability is acceptable.

Sample Analysis Plate Acceptance Criteria

Assay acceptance criteria are listed in the following Table 40-44.

Table 40. All assays acceptance criteria

Criteria	Acceptance Criteria
Cell viability	≥ 96 %
Cells	To be used between Day 6 and Day 21 after vial thawing
Lum of the NC, DC, EC, or SC	Must have a %CV ≤20%
PC	All set of PCs run twice in duplicate for each plate must pass all acceptance criteria Mean NormLum of each antibody control duplicate set (HPC) (LPC) and (LLPC if applicable) must have a %CV ≤20%.
All controls	Both replicate set of each control must pass all acceptance criteria

Table 41. Screening Assay Acceptance Criteria

Criteria	Acceptance Criteria
DC/NC	≥ 1.8
PC in CHS-1701 induced cells	Mean NormLum of the HPC must be lower than the mean NormLum of the LPC in CHS-1701 induced cells Mean NormLum of the LLPC must be lower or equal to the validation cut point 0.900 Mean NormLum of the LPC must be lower or equal to the in-study cut point 0.760

Table 42. Specificity Assay Acceptance Criteria

Criteria	Acceptance Criteria
SC/NC	≥ 1.8
PC in mIL-3 induced cells	Mean NormLum of the HPC in mIL3 induced cells must be greater than 0.818

Table 43. Confirmatory Assay Acceptance Criteria

Criteria	Acceptance Criteria
DC/NC	≥ 1.8
PC in CHS-1701 induced cells (not treated with Protein AGL or sepharose)	Mean NormLum of the HPC must be lower than the mean NormLum of the LPC in CHS-1701 induced cells
	Mean NormLum of the LPC must be lower or equal to the in-study cut point 0.760
Inhibition %	DC % inhibition $< 12.5\%$
	HPC % inhibition $\geq 12.5\%$ for each set of PC run in duplicate
	LPC % inhibition $\geq 12.5\%$ for each set of PC run in duplicate

Table 44. Cross-Reactivity Assay Acceptance Criteria

Criteria	Acceptance Criteria
EC/NC	≥ 1.8
PC in G-CSF induced cells	Mean NormLum of the HPC must be lower than the mean NormLum of the LLPC in GCSF induced cells
	Mean NormLum of the LLPC must be lower or equal to the in-study cut point 0.827

The lower limit of the normalization control, DC/NC, SC/NC and EC/NC, were based on the formula: $\text{mean} - (t_{0.01,df} \times \text{SD})$. The data from the validation runs were used to calculate the limit to be 0.8, 1.6 and 1.9 respectively. The sponsor applied the lowest normalizing control values obtained during assay validation (1.8) to all three normalizing controls.

Reviewer's Comments:

The normalizing control can be considered a negative control for monitoring the cell response to stimulator. The assay suitability control is acceptable.



Frederick
Mills

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Haoheng
Yan

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Joslyn
Brunelle

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 17 September 2018
To: Administrative File, **STN 761039/0-RESUB-57**
From: Monica Commerford, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV
Through: Reyes Candau-Chacon, Ph.D. Acting Quality Assessment Lead,
CDER/OPQ/OPF/DMA/BIV
Subject: Review of Final Response to the Complete Response letter dated 9 June 2017 for
BLA 761039/0 to support a new Biologics Licensing Application
Applicant: Coherus BioSciences, Inc.
US License: 2023
Product: CHS-1701 (Proposed name: UDENYCA, a proposed biosimilar to US licensed
Neulasta)
Dosage: Pre-filled syringe, subcutaneous liquid solution for injection (6 mg/0.6 mL)
Indication: Decrease incidence of infection manifested by febrile neutropenia in patients
receiving myelosuppressive anti-cancer drugs
Facilities: KBI Biopharma, Inc.
2500 Central Ave.
Boulder, CO 80301
(FEI: 3011326133)
Receipt Date: 3 May 2018
Action date: 3 November 2018

Recommendation for Approvability: The drug substance section of BLA 761039/0 is
recommended for approval, as amended, from a microbial control and product quality microbiology
perspective.

Review Summary

Coherus BioSciences, Inc. has submitted this Response to the Complete Response letter sent by the
FDA on 9 June 2017 to support the licensure of Biological License Application (BLA) 761039/0, for
CHS-1701 to be used in patients receiving myelosuppressive anti-cancer drugs associated with a

clinically significant incidence of febrile neutropenia to decrease infection manifested by febrile neutropenia. The drug substance (DS) is manufactured at KBI Biopharma, Inc., in Boulder, CO (FEI: 3011326133). The drug product (DP) is manufactured at (b) (4) in (b) (4) (FEI: (b) (4)). The amendment to BLA 761039 (CHS-1701) was submitted on 3 May 2018. The application contains CMC information in an eCTD format. The original BLA was submitted on 9 August 2016, a Complete Response letter was sent by the FDA on 9 June 2017.

REVIEW NARRATIVE



Conclusion

- I. The drug substance section of BLA 761039/0 is recommended for approval, as amended, from a microbial control and product quality microbiology perspective.
- II. The non-microbial aspects of the BLA should be reviewed by the OBP reviewer.
- III. A pre-license inspection was conducted at KBI BioPharma on September 5 – 7 and 9 – 12, 2018 by OPF/DMA (Scott Nichols), OBP (Ralph Bernstein), and ORA (Jamie Dion). A five-item FDA Form 483, Inspectional Observations, was issued. Refer to Panorama for the current compliance status of the facility.

FDA Requests for Information (dated 5 July 2018)

- 1. In regards to the routine CHS-1701 drug substance (DS) shipping conditions:

(b) (4)



- 2. The “Analytical Procedures – Endotoxin” document in Section 3.2.S.4.2 indicates that the

(b) (4)



FDA Requests for Information (dated 31 July 2018)

- 1. Report the drug substance endotoxin release specification as EU/mL to align with the units of the drug product endotoxin release specification and update sections 3.2.S.4.1 and 3.2.S.4.5 of the BLA accordingly.

Administrative File: 761039.0.BLA.DS.resubmission.57.9.17.2018.docx



Monica
Commerford
(Markovski)

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Reyes
Candau-Chacon

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.

QAL: Reyes Candau-Chacon, Ph.D.

BLA: 761039/0

Applicant: Coherus BioSciences, Inc.

US License Number: 2023

Submission Reviewed: Original 351(k) BLA resubmission-57

Product: CHS-1701 (UDENYCA™)

Indication: 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

Dosage Form: Single use, pre-filled syringe for subcutaneous injection (6 mg/0.6 mL) with a safety needle device

Manufacturing Site: (b) (4)

FEI# (b) (4)

FDA Receipt Date: May 3, 2018

Action Date: November 3, 2018

Conclusion and Approvability Recommendation

The drug product portion part of this BLA is recommended for approval from a sterility assurance and product quality microbiology perspective.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description

0056	05/03/18	BLA Resubmission
0063	07/27/18	IR Response
0063	08/14/18	IR Response

Reviewer comment: The original BLA was reviewed in the memo uploaded and archived in Panorama on May 5, 2018. This memo reviews only the drug product complete response items and additional comments communicated to the sponsor in the Complete Response (CR) letter. Refer to the BLA review memo in Panorama for the drug product (DP) microbiology CR items and additional comments for the applicant.

Drug Product

Complete Response Comments

Microbiology Question 5:

(b) (4)



Conclusion

- I. The BLA was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.

III. One inspection follow-up item was identified and is listed below:

i.

(b) (4)



DP Microbiology Information Requests Sent:

Date: 7/5/18

Microbiology Question 7

(b) (4)





Jessica
Hankins

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Reyes
Candau-Chacon

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Recommendation: Complete Response

**BLA 761039
Review 1
June 7, 2017**

Drug Name/Dosage Form	CHS-1701/injection
Strength/Potency	6mg/0.6mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
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
Applicant/Sponsor	Coherus

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (DS)	Ying-Xin Fan	OBP/DBRR-IV
Drug Product (DP)	Jacek Cieslak	OBP/DBRR-IV
Analytical Similarity	Jacek Cieslak	OBP/DBRR-IV
Immunogenicity Assays	Haohang Yan	OBP/DBRR-IV
Immunogenicity Data	Fred Mills	OBP/DBRR-IV
Business Regulatory Process Manager	Keith Olin	OPQ/OPRO
Facilities	Marion Michaelis, Peter Qiu	OPF/DIA
Microbiology	Monica Commerford (DS), Jessica Hankins (DP), Reyes Candau-Chacon (QAL), Patricia Hughes	OPF/DMA
Application Technical Lead	Joslyn Brunelle	OBP/DBRR-IV
Acting Review Chief	Joel Welch	OBP/DBRR-IV
Division Director	Gibbes Johnson	OBP/DBRR-IV

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Beatrice Kallungal Natasha Kormanik	OHOP/DHP
Cross-disciplinary Team Lead	Nicole Gormley	OHOP/DHP
Medical Officer	Bindu Kanapuru	OHOP/DHP
Pharm/Tox	Michael Manning, Chris Sheth	OHOP/DHP
Clinical Pharmacology	Olanrewaju Okusanya, Sarah Schrieber	OTS/OCF
Statistics	Jingjing Ye, Lei Nie	OTS/OB
CMC Statistics	Meiyu Shen, Tsong Yi	OTS/OB/DBVI
Biosimilar Policy	Carla Lankford, Sue Lim, Leah Christl	OND/TBBS

- a. Names
 - i. Company Code: CHS-1701
 - ii. Non-Proprietary: To be determined (pegfilgrastim-xxxx)
 - iii. CAS registry number 208265-92-3
 - iv. Compendial Name: PEGylated Granulocyte-Colony Stimulating Factor (G-CSF), pegfilgrastim
 - v. OBP systematic name:
CONJ: RPROT P09919 (CSF3_HUMAN); PEG [CHS-1701]

- b. Pharmacologic category: Leucocyte Growth Factor

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	August 9, 2016
Amendment 2 (update per BPD Type 4 comments)	August 12, 2016
Amendment 4 & 5 (DS manufacturing schedule, details)	September 12, 2016; September 20, 2016
Amendment 6 & 7 (Response to filing deficiencies)	October 5, 2016
Amendment 12 (DP manufacturing schedule)	November 4, 2016
Amendment 14 (DS manufacturing schedule update)	November 7, 2016
Amendment 15 (DS manufacturing schedule)	November 14, 2016
Amendment 16 (Response to 74 day letter, Micro Info)	November 21, 2016
Amendment 17 (Analytical Similarity Assessment Info)	November 28, 2016
Amendment 22 (Micro Info)	December 15, 2016
Amendment 26 (Micro Info)	January 6, 2017
Amendment 29 (CDRH Info)	January 13, 2017
Amendment 32 (CDRH Info)	January 19, 2017
Amendments 33 & 34 (Micro & OBP Info)	January 30, 2017
Amendment 37 (OBP Info)	February 24, 2017
Amendment 40 (OBP Info)	March 21, 2017
Amendment 42 (Facilities Info)	April 3, 2017

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	Type III		(b) (4)	3	N/A	
	Type III		3	N/A		
	Type III		3	N/A		
	510(k)		3	N/A		
	Type II		3	N/A		
	Type V		3	N/A		
	Type V		3	N/A		
	Type III		3	N/A		

		(b) (4)			
(b) (4)	Type III		3	N/A	

¹ Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available; 6 – Other (explain under "Comments")

² Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CDRH ODE	December 19, 2016	completed	Adequate	Keith Marin/ Alan Stevens
CDRH OC	November 18, 2016	completed	Adequate	Rakhi Dalal/Francisco Vicenty

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Pharmaceutical Quality, CDER, has completed review of BLA 761039 for CHS-1701 manufactured by Coherus. The information submitted in this application is not sufficient to support a conclusion that CHS-1701 is highly similar to US-licensed Neulasta or that the manufacture of CHS-1701 is well-controlled. OPQ is recommending a Complete Response be issued to Coherus. Refer to the action letter for specific details regarding these deficiencies. The action letter will serve as the final version of the deficiencies identified in review of this 351(k) BLA. The deficiencies are noted below.

b. Summary of Complete Response issues

The following deficiencies were identified regarding manufacturing processes and control strategy for drug substance and drug product:

- Release and stability specifications
 - Insufficient information to support Reverse phase chromatography (RPC) method B
 - Approach to establishing specifications is not adequate
 - Missing data on impurities
 - Insufficient control for (b) (4)
 - For DS, specification and method validation for host cell protein assay is inadequate
- Stability data and expiry
 - Post-approval stability protocol is inadequate
 - Missing data on impurities
 - Insufficient information to support expiry
- Description of manufacturing process (DS only)
 - Missing process parameter(s) to control (b) (4)
 - Insufficient data to support (b) (4)
 - In-process testing lacks controls (b) (4)
 - Revise in-process testing of (b) (4) to include rejection limits
 - Inadequate (b) (4)
 - Missing information for routine DS shipping
- Description of Manufacturing Process (DP only)
 - Unclear disposition status of lots upon failure of the (b) (4) test
- Control of critical steps
 - Criticality assignment of process parameters is not justified

- Inadequate endotoxin control
- Control of Material (DS)
 - Stability testing for cell banks is inadequate
 - Insufficient detail for [REDACTED] (b) (4) process
 - Missing risk assessment for leachables/extractables for material that comes into contact with product contact
 - Certificates of analysis for critical reagents are missing
- Process Validation (DS)
 - Missing data on impurities
 - Missing clearance data for [REDACTED] (b) (4)
 - [REDACTED] (b) (4) qualification protocol lacks sufficient monitoring of product quality and microbial control
 - Shipping validation is inadequate
- Process Validation (DP)
 - Missing data to support homogeneity
 - Insufficient data for media fill validation
 - Insufficient data to support [REDACTED] (b) (4)
 - Insufficient data to support [REDACTED] (b) (4)
- Characterization
 - Forced degradation studies are incomplete
 - Missing data on subvisible particles 2-10 um
- Reference standard
 - Missing data to support stability of current reference standards
 - Reference standard qualification protocol is inadequate
- Container Closure System
 - Freeze/thaw studies are missing potency
 - Provide update for ongoing studies to assess the compatibility of prefilled syringe with CHS-1701, including leachables, [REDACTED] (b) (4), and [REDACTED] (b) (4)

The following deficiencies were identified during the evaluation of analytical similarity between CHS-1701 and US-Neulasta:

- The side-by-side forced degradation studies between CHS-1701 and US-licensed Neulasta did not include an assessment of potency
- Potency data for US-licensed Neulasta lot 1054829 used in the clinical immunogenicity study CHS-1701-04 was not provided

CR items associated with the review of the immunogenicity assays and the consult for clinical immunogenicity data are provided in separate reviews and not described here.

c. Draft Complete response letter language

3.2.R.1 Analytical Similarity Assessment

1. Adequate physicochemical and functional assessment of degradation profiles of CHS-1701 and US-licensed Neulasta should be performed to provide a direct comparison of the proposed biosimilar and the reference product. However, you did not evaluate the potency of CHS-1701 and US-licensed Neulasta in the forced degradation study included in the analytical similarity assessment and you did not demonstrate that potency of both products is affected to similar extent when subjected to forced degradation conditions. Provide CHS-1701 and US-licensed Neulasta potency data of samples subjected to forced degradation conditions.
2. You used US-licensed Neulasta lot 1054829 in the CHS-1701-04 clinical study, but you did not include this lot in the Tier 1 analyses of potency due to material limitations. You stated that limited supply of this material has been returned from the clinical site and potency testing for this lot “can be submitted to the BLA upon Agency’s request”. Provide potency data for US-licensed Neulasta lot 1054829.

General CMC CR Comments

Drug Substance (DS) & Drug Product (DP) Release and Stability Specifications





d. Benefit/Risk Considerations

The proposed biosimilar CHS-1701 has been evaluated and compared to US-licensed Neulasta using a variety of structural, physicochemical, and functional assays. A total of 13 lots of CHS-1701 Drug Product and 22 lots of US-Neulasta were evaluated in the analytical similarity assessment. A tiered approach was used when comparing both product and the tier assignment was based on the criticality risk ranking and method capabilities. Table A below lists the analytical methods and their corresponding tier assignments.

Biological Function	Attribute	Method	Tier
Efficacy and immunogenicity	Primary structure (including amino acid sequence and disulfide structure)	Peptide map by Glu-C digest with LC-MS/MS	NA ^a
Efficacy	Biological activity (percent potency)	Proliferative bioassay	1
Efficacy	Protein content (mg/mL)	Protein Content by UV	1
Efficacy	Receptor binding (K _D)	SPR	2
Efficacy	Molar mass (kDa)	SEC-MALS	2
Efficacy	Mass (Mw) of PEG conjugate (kDa)	SEC-MALS	2
Efficacy	PEG polydispersity (Pd)	SEC-MALS	2
Efficacy	PEG polydispersity (Pd)	LC-MS	3
Efficacy and immunogenicity	HMW species (including dimer/diPEG, oligomers) (percent area)	SEC-MALS	2
Efficacy and immunogenicity	HMW species (including dimers/diPEG, and oligomers)	SDS-PAGE	3
Efficacy and immunogenicity	unPEGylated filgrastim	SEC	3
Efficacy and immunogenicity	Clips	SEC	3
Efficacy and immunogenicity	Clips	SDS-PAGE	3
Efficacy	diPEGylated species (percent area)	CEC	2
Efficacy and immunogenicity	Total oxidized species (percent area)	RPC	2
Efficacy and immunogenicity	Total deamidated species (percent area)	RPC	2
Efficacy and immunogenicity	Partially reduced species	RPC	3
Efficacy and immunogenicity	Norleucine misincorporation	RPC	3
Immunogenicity	SVPs $\geq 2 \mu\text{m}$ (total counts/mL)	MFI	2
Efficacy	Intact mass and PEG linker analysis	LC-MS	3 ^b
Efficacy and immunogenicity	unPEGylated N-terminus	Edman degradation	3
Efficacy and immunogenicity	free PEG	SDS-PAGE with iodine stain	3
Efficacy and immunogenicity	Secondary/tertiary structure	CD, 2D NMR, DSC, fluorescence, HDX	3
Efficacy	Extinction coefficient	SEC-UV-RI	3
Immunogenicity	HCPs	ELISA by Cygnus kit	3
Immunogenicity	Total protein pattern, including all impurities and HCPs	2D gels with silver stain	3
Efficacy and immunogenicity	Size profile: Sedimentation Behavior	AUC	3
Efficacy and immunogenicity	Charge profile	IEF gel	3
Immunogenicity	Clarity	Turbidimetry	3
Immunogenicity	Color	Visual inspection	3

Tier 1 includes assays that evaluate the clinically relevant mechanism(s) of action with a high level of precision and accuracy. Tier 1 attributes are potency and protein concentration; statistical equivalence testing was performed to demonstrate similarity, except for primary structure, where an identity match was confirmed.

Tier 2 contains assays with lower risk ranking, specifically those measuring attributes that impact clinical function only indirectly, those with lower levels of precision, or those measuring species present in low abundance. Similarity for these attributes was assessed based on quality ranges. One sided ranges were used for the following attributes: High Molecular Weight species, unPEGylated species and PEG polydispersity by SEC-MALS, total oxidized and deamidated species by reverse phase chromatography (RPC), diPEGylated species by cation exchange chromatography (CEC), and subvisible particles. Two sided ranges were defined for the following attributes: molar mass, mass of PEG conjugate, and receptor binding.

Tier 3 contains attributes that are evaluated based on qualitative results or attributes of low criticality. Similarity was assessed by comparisons of images or graphical representations of the raw data. No statistical analysis was performed for tier 3 attributes due to the qualitative nature of the data.

The categorization of attributes and corresponding analytical methods are appropriate and a sufficient number of lots is included to perform meaningful review of data. Overall, the purity is similar between CHS-1701 and US-licensed Neulasta, with US-licensed Neulasta containing slightly higher product related variants due to the age of the material. The data provided would not preclude a determination that CHS-1701 is highly similar to US-licensed Neulasta. However, a final conclusion if the data support such a demonstration cannot be made at this time. The following limitations are noted:

The CR letter contains comments regarding missing data that are necessary to make a determination of highly similar:

- The side-by-side forced degradation studies between CHS-1701 and US-licensed Neulasta did not include an assessment of potency
- Potency data for US-licensed Neulasta lot 1054829 used in the clinical immunogenicity study CHS-1701-04 was not provided

Furthermore, there is residual uncertainty with respect to biosimilarity after evaluation of immunogenicity between CHS-1701 and US-licensed Neulasta based on the reviews by F. Mills and H. Yan. To assess comparative immunogenicity of CHS-1701 versus US-Neulasta, Coherus conducted Study CHS-1701-04, a parallel arm study in healthy volunteers who were treated with two doses, 6 weeks apart, of either CHS-1701 (n=122) or US-Neulasta (n=120). The design of this clinical study was appropriate to assess immunogenicity. Assessment of anti-drug antibody (ADA) incidence revealed a higher incidence for CHS-1701 relative to US-Neulasta (9.8% vs 5.8%, which yields a 95% confidence 1-sided upper exact upper limit of 10.16%). The incidence of treatment emergent persistent anti-GCSF antibody is also higher in the CHS-1701 arm compared to the US-Neulasta arm (11.5% vs 7.5%). The observed difference in incidence rates at or above the 10% threshold creates residual uncertainty regarding biosimilarity of CHS-1701 to US-Neulasta. Differences need to be considered in the context of

other factors that may affect safety and efficacy, such as titer, persistence, and whether ADA bind the PEG or G-CSF parts of CHS-1701.

Coherus reported zero incidence of neutralizing antibody (NAb) in both CHS-1701 and US-Neulasta treatment arms; however, the neutralizing assay is not adequate due to issues related to assay precision, assay design, cut point determination, and assay sensitivity. Coherus submitted a second NAb assay validation report on January 18, 2017; the second assay was also assessed to be inadequate. Since neither Nab assay is adequate, the application lacks clinical data to assess whether the ADA positive samples have the ability to neutralize C-GSF activity. Therefore, the similarity assessment for immunogenicity is incomplete and additional immunogenicity data are needed to reduce residual uncertainty regarding the biosimilarity of CHS-1701 to US-Neulasta.

The following deficiencies related to immunogenicity are listed in the CR letter:

- Provide additional information to address the differences in ADA rates between CHS-1701 and US-Neulasta treatment arms. Differences need to be considered in the context of other factors that may affect safety and efficacy, such as titer, persistence, and whether ADA bind the PEG or G-CSF parts of CHS-1701. Depending on the information provided, further clinical studies may be needed to provide assurance that the difference in ADA rates between CHS-1701 and US-Neulasta treatment groups do not have a clinically meaningful impact on safety and efficacy.
- Revise and Revalidate the Neutralizing assay
- Test all samples confirmed positive for ADA with the revised Neutralizing assay

II. Summary of Quality Assessments

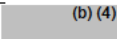
A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below lists the critical quality attributes (CQAs) for CHS-1701. CQA's are monitored and controlled during release and stability testing. The approach that Coherus used to establish the acceptance criteria for release and stability testing is not appropriate. The CR letter includes a comment to re-evaluate and provide justification for the acceptance criteria for release and stability testing.

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other – Deficiencies included in the CR letter
Potency	Efficacy	Intrinsic to the molecule	(b) (4)	Approach to establishing specifications is not appropriate
HMW species including Dimers, Oligomers, diPEG <i>(Product related variants)</i>	Efficacy and Immunogenicity	Formed during manufacturing process and storage		Acceptance criteria for dimer/diPEG is not specified; Approach to establishing specifications is not appropriate
Oxidation <i>(Product related variants)</i>	Efficacy and Immunogenicity. Oxidized species demonstrate reduced potency.	Formed during manufacturing process and storage		Did not provide adequate information to support RPC Method B for release and stability testing; Approach to establishing specifications is not appropriate

Deamidation <i>(Product related variants)</i>	Efficacy and immunogenicity	Formed during the manufacturing process and storage	(b) (4)	RPC method does not contain acceptance criteria for deamidated species
diPEGylated species <i>(Product related variants)</i>	Bioavailability	Formed during pegylation step		Approach to establishing specifications is not appropriate
Double size PEG species <i>(Product related variants)</i>	Bioavailability	Formed during pegylation step		Unclear whether acceptance criteria for (b) (4) include double size PEG; Approach to establishing specifications is not appropriate
Non-pegylated species <i>(Product related variants)</i>	Bioavailability	Unreacted during pegylation step		
Clips and	Efficacy and	Formed during the		

truncations <i>(Product related variants)</i>	Immunogenicity	manufacturing process and storage		(b) (4)
Reduced species <i>(Product related variants)</i>	Efficacy and Immunogenicity	Formed during  (b) (4) 		

B. CHS-1701 Drug Substance Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 provides a summary of critical quality attributes (CQAs) that are derived from the drug substance manufacturing process.

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other – Deficiencies included in the CR letter
Host Cell Proteins (HCP)	Safety and Immunogenicity	(b) (4)	(b) (4)	Method validation missing data for accuracy, precision, specificity Revise acceptance criteria for release testing
DNA	Safety and Immunogenicity	(b) (4)		
Endotoxin (contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.		(b) (4)

				(b) (4)
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	(b) (4)	
Protein concentration	Efficacy (dosing)	Final formulation occurs on drug substance		
(b) (4) (b) (4)	Stability	Final formulation occurs on drug substance		(b) (4)
Leachables from (b) (4)	Safety	Entire process		
(b) (4)	Safety	(b) (4))		

			(b) (4)
(b) (4)	Safety	(b) (4))	
m-PEG aldehyde	Safety	PEGylation	
(b) (4)	Safety	(b) (4)	
(b) (4)	Safety	(b) (4)	
Kanamycin	Safety	Fermentation	

(b) (4)	Safety	(b) (4)	(b) (4)	
(b) (4)	Safety	(b) (4)		Missing information on clearance and/or risk assessment based on worst case exposure levels

a. Description

PEGylated G-CSF consists of a PEG molecule linked to recombinant methionyl human granulocyte colony stimulating factor (referred to as Coherus r-met-Hu-G-CSF). The total molecular weight is approximately 39 kDa.

Coherus r-met-Hu-G-CSF is the human G-CSF sequence with an additional methionine on the amino terminus. It is produced in *E.coli*, is non-glycosylated, and is a single polypeptide chain with a total of 175 amino acids and has an approximate molecular weight of 19 kDa.

PEG molecule (approximately 20kD) is attached by a stable covalent amide bond to the N-terminal methionine of r-met-Hu-G-CSF.

b. Mechanism of action

G-CSF is a haematopoietic growth factor that regulates the production of neutrophils within the bone marrow. Activity is initiated by binding to the G-CSF receptors on cells of myeloid lineage, such as granulocytic precursors and mature neutrophils. G-CSF stimulates growth and differentiation of granulocytic precursor cells, shortens the transit time of developing granulocytes, and facilitates the migration of the mature cells into the peripheral blood. This results in a rapid induction and sustained elevation in absolute neutrophil counts (ANC) in blood, which is a direct measure of in vivo activity. The pegylation increases the size of the protein, which in turn reduces renal clearance and increases the half-life of the protein.

c. Potency Assay

The potency is assessed using a cell based proliferation assay with the NFS-60 cell line. NFS-60 is a murine myeloblastic cell line that expresses the G-CSF receptor and is dependent on G-CSF for growth and maintenance of viability. Cells are grown in a 96 well plate. Proliferation is measured by a colorimetric assay using Thiazolyl Blue Tetrazolium Bromide (MTT); MTT is a yellow tetrazole that is reduced to purple formazan in living cells. The amount of formazan can be measured using a spectrophotometer and is directly proportional to the number of living cells. Biological activity is reported relative to reference material. The CR letter includes a comment that the approach to establishing specifications for release and stability testing is not adequate.

d. Reference material(s)

The sponsor has primary reference standards to both unpegylated (169A14-02 pre-PEG RS) and pegylated G-CSF (169A14-02 PEG RS); however, information to support stability of the current primary reference standards was not provided. In addition, the qualification protocol for future reference standards is not acceptable for the following reasons:

- Acceptance criteria are not adequate
- Insufficient information on the statistical assessment
- Insufficient information to ensure control of potency
- Insufficient information to assess calibration against international standards

These deficiencies are included in the CR letter.

e. Critical starting materials or intermediates

(b) (4)



f. Manufacturing process summary

(b) (4)



**g. Container closure**

Drug substance is stored in (b) (4)

Information on extractables was provided and assessed as low risk to impact product quality. In addition, the sponsor initiated a leachable study on the drug substance container closure. The Agency requested updated information for the leachable study as an additional comment.

h. Dating period and storage conditions

The sponsor initially proposed (b) (4) month shelf-life for drug substance stored at (b) (4) °C and ultimately planned to establish (b) (4) month shelf-life with ongoing stability study.

After simple stability update, the sponsor provided 18-24 months of real-time stability data (b) (4) for four primary registration batches. In addition, three batches are included as supportive with 12-15 months of stability data.

However, the stability data does not contain sufficient information to assess impurities. In addition, the sponsor implemented a new reverse phase chromatography (RPC) method in the middle of the stability study and the application lacks bridging data for RPC Methods A and B. Therefore, insufficient information is provided to support proposed drug substance expiry. Furthermore, the proposed post-approval stability protocol is inadequate. These deficiencies are included in the CR letter.

C. Drug Product [Established Name] Quality Summary

Table 3 provides a summary of the drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other – Deficiencies listed in the CR letter
Sterility	Safety, Purity, and Efficacy (due to degradation or modification of the product)	Contamination could be introduced throughout DP manufacturing or storage	(b) (4)	Missing information to support sterility, including (b) (4)
Container Closure Integrity Testing (CCIT)	Safety	May be impacted by storage conditions		
Endotoxin (Contaminant)	Safety and Purity	Contamination could be introduced throughout DP		

		manufacturing	(b) (4)	
Protein concentration	Efficacy (dosing)	(b) (4)		
Polysorbate 20	Stability	(b) (4)		(b) (4)
Volume in container	Efficacy (dosing)	Manufacturing process		
Clarity, Color, Visible particles	Efficacy and Safety			
pH	Stability	Formulation		
Osmolality		Formulation		
Particulate matter	Safety and Immunogenicity	Container Closure System (CCS)		Missing characterization for subvisible particles in the range of 2-10 µm

Peptide mapping	Efficacy	Product Identity test per CFR 610.14	(b) (4)	
(b) (4)	Safety	Container Closure System (CCS)		Provide update for (b) (4) study
(b) (4)	Safety	Container Closure System (CCS)		Provide update for (b) (4) compatibility study
Leachables/extractables	Safety	Manufacturing equipment and CCS		Provide update for leachables study
Device functionality tests	Safety and Efficacy	Container Closure System (CCS)		

- a. Strength: 6mg/0.6 mL
Single use, pre-filled syringe (PFS) for subcutaneous injection

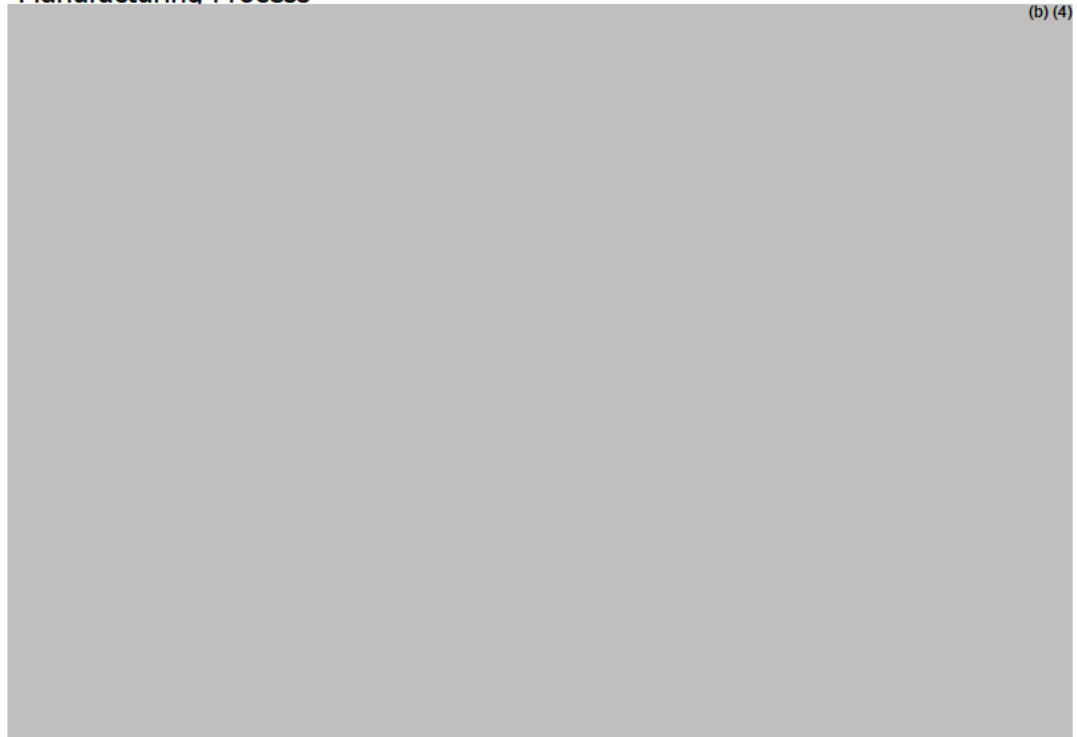
The data submitted by the applicant support a demonstration that the proposed presentation of CHS-1701 has the same strength as the respective presentation of US-licensed Neulasta. The strength of both products, in mass in a container closure and mass per volume, is statistically equivalent, which supports the demonstration of same strength.

- b. Summary of Product Design
CHS-1701 was developed to be a biosimilar to US-licensed Neulasta. It has the same route of administration, dosage form, and strength as the reference product.

- c. List of Excipients
(b) (4), (b) (4) sorbitol, (b) (4) polysorbate 20, pH 4.0

- d. Reference material(s)
The same reference material is used for DS and DP

- e. Manufacturing Process



- f. Container Closure

The drug product container closure is a (b) (4) glass syringe barrel (b) (4) rubber plunger stopper and 29 1/2 gauge needle. In addition, there is a needle safety device (b) (4)

The following deficiencies are included in the CR letter:

- Provide updated results for ongoing container closure studies, including (b) (4) and leachables studies
- Freeze/thaw study did not include an evaluation of potency

g. Expiration Date & Storage Conditions

(b) (4) 36 months at 2-8°C

The sponsor initially proposed (b) (4) month shelf-life for drug product stored at 2-8°C and ultimately plans to establish 36 month shelf-life with ongoing stability study. After simple stability update, the sponsor provided 18-24 months of real-time stability data (2-8°C) for four primary registration batches. Additional batches are included as supportive with 12 months of stability data.

However, the stability data does not contain sufficient information to assess impurities. In addition, the sponsor implemented a new reverse phase chromatography (RPC) method in the middle of the stability study and the application lacks bridging data for RPC Methods A and B. Therefore, insufficient information is provided to support proposed drug product expiry. Furthermore, the proposed post-approval stability protocol is inadequate. These deficiencies are included in the CR letter.

h. List of co-packaged components – not applicable

D. Biopharmaceutics Considerations- Not applicable

E. Novel Approaches/Precedents-None

F. Any Special Product Quality Labeling Recommendations-None

G. Environmental Assessment

In Module 1, Coherus is requesting a categorical exclusion under 21 CFR 25.31 from the need to prepare an environmental assessment.

Reviewer comment: The claim of categorical exclusion is accepted.

H. Establishment Information

OVERALL RECOMMENDATION: Approve Facilities					
DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug Substance Manufacturing, Release and Stability Testing	KBI Biopharma, Inc., Boulder, CO	079582679/ 3011326133		VAI Summary of nine observations: - Instruction for defining where a batch begins was not clearly defined. - Annual GMP training lacked comprehensive GMP subject matter. -Storage of CHS-170 bulk drug substance, materials control, Standard Operating Procedure instruction and quality oversight were found to lack instruction or were inadequate in several areas.	Approve

Drug Substance Release and Stability Testing	(b) (4)		Approve based on profile		Approve
DRUG PRODUCT					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER		INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Drug Product Manufacturing Drug Product Release Testing	(b) (4)			VAI Summary of three observations: (b) (4)	Approve

				(b) (4)	
Drug product release and stability testing	(b) (4)		Approve based on profile		Approve
Drug Product Release and Stability Testing	KBI Biopharma, Inc., Boulder, CO	079582679/ 3011326133		VAI Summary of nine observations: - Instruction for defining where a batch begins was not clearly defined. - Annual GMP training lacked comprehensive GMP subject matter. -Storage of CHS-170 bulk drug substance, materials control, Standard Operating Procedure instruction and quality oversight were found to lack instruction or were inadequate in several areas.	Approve

Assembly of the Safety Device Labeling and Packaging	(b) (4)		Approve based on profile		Approve
Combination Product – Medical Device Manufacturer	Coherus BioSciences, Inc., Redwood City, CA	078502849/3009682611		NAI	Approve
Functional performance testing of the safety device for batch release and stability	(b) (4)		Approve based on profile		Approve

I. Facilities

The inspection of the drug substance manufacture and testing facility, KBI Biopharma, Inc. (KBI), was conducted from December 5-9, 2016 by CDER/OPQ. A nine-item 483 was issued to the firm at the closeout meeting. The initial recommendation was “withhold”; this was downgraded to VAI after review of the firm’s responses to nine observations on the 483. The facility was approved based on the inspectional assessment which included review of the firm’s corrections to the nine observations.

The inspection of the drug product manufacturing and testing facility, (b) (4) (b) (4) was conducted (b) (4) by CDER-DIA and was classified VAI. The facility was approved based on the inspectional assessment.

The inspection of the medical device manufacturer Coherus BioSciences, Inc. was conducted March 13-16, 2017 by San Francisco FDA District Office and was classified NAI.

For additional information see the Facilities Review: Division of Inspectional Assessment.

J. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved: None
- ii. Outstanding review issues/residual risk: See CR comments in section Ic
- iii. Future inspection points to consider:
The determination to re-inspect the KBI DS facility will be made at the time of BLA resubmission by the applicant following the complete response.

b. Drug Product

- i. Protocols approved: None
- ii. Outstanding review issues/residual risk: See CR comments in section Ic
- iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material		X	
7.	Non-Mammalian Cell Substrate/Source Material	X		
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity		X	
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		

14.	Other _____		X	
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (FDA-2017-P-2528)	X		
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)			
18.	SPOTS (Special Products On-line Tracking System			
19.	USAN Name Assigned			
20.	Other _____			
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation	X	
23.		Process	X	
24.		Analytical Methods	X	
25.		Other	X	
26.	Other QbD Elements		X	
27.	Real Time Release Testing (RTRT)		X	
28.	Parametric Release in lieu of Sterility Testing		X	

29.	Alternative Microbiological Test Methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial Analytical Procedures	Drug Product	X	
32.		Excipients		X
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin		X
35.		Novel		X
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other _____		X	



Joslyn
Brunelle

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Comments: thanks

Memorandum of Review

STN:	BLA761039
Subject:	Immunogenicity Review: Assay and Immunogenicity Clinical Data
Submission Date:	September 28, 2016
Review/Revision Date:	May 1, 2017
Primary Reviewer:	Haoheng Yan, MD, PhD (assays) Product Quality Reviewer, OPQ/OBP/DBRR IV Fred Mills, PhD (clinical immunogenicity data) Staff Scientist, OPQ/OBP/DBRR IV
Secondary Reviewer:	Joslyn Brunelle, PhD Team Leader, OPQ/OBP/DBRR IV
Tertiary Reviewer:	Joel Welch, PhD Acting Review Chief, OPQ/OBP/DBRR IV
Consults:	Immunogenicity
Applicant:	Coherus
Product:	CHS-1701, PEGylated G-CSF, proposed biosimilar to US-licensed Neulasta
Indications:	Decreasing the incidence of infection in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Action Due Date:	June 9, 2017

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I. Summary Basis of Recommendation:

- a. **Recommendation:** We do not recommend approval of this 351(k) BLA application for CHS-1701 (Udenyca) as a biosimilar to US-licensed Neulasta for the reasons listed in section II. Deficiencies to be conveyed to the sponsor.
- b. **Justification:** To assess comparative immunogenicity of CHS-1701 versus US-Neulasta, Coherus conducted Study CHS-1701-04, a parallel arm study in healthy volunteers who were treated with two doses, 6 weeks apart, of either CHS-1701 (n=122) or US-Neulasta (n=120). The design of this clinical study was appropriate to assess immunogenicity. Assessment of anti-drug antibody (ADA) incidence* revealed a higher incidence for CHS-1701 relative to US-Neulasta (9.8% vs 5.8%, which yields a 95% confidence 1-sided upper exact upper limit of 10.16%). The incidence of treatment

emergent persistent anti-GCSF antibody is also higher in the CHS-1701 arm compared to the US-Neulasta arm (11.5% vs 7.5%). The observed difference in incidence rates creates residual uncertainty regarding similarity of CHS-1701 to US-Neulasta. Coherus reported zero incidence of neutralizing antibody (NAb) in both treatment arms; however, the neutralizing assay (from which the results of NAb are derived from) is not adequate due to issues related to assay precision, assay design, cut point determination, and assay sensitivity. On Jan 18, 2017(mid-cycle), Coherus submitted a second NAb assay validation report which is also deemed inadequate after a complete review. Upon receiving the second NAb assay, FDA had suggested that Coherus should not test clinical samples using the second NAb assay until FDA determines whether the assay is adequate. Since neither Nab assay is adequate, the application does not contain reliable NAb data. Therefore, the FDA cannot conduct a complete immunogenicity assessment.

*Coherus reached agreement with the FDA during a teleconference held on August 31, 2015, that the ADA incidences are calculated using treatment emergent, confirmed and persistent ADA with titer $\geq$ 1.

II. Deficiencies to be conveyed to the sponsor:

We recommend that you request a meeting to discuss your approach to addressing the immunogenicity related CR Comments 1-3.

1. In Amendment 41(received March 21, 2017), for treatment emergent persistent antibodies with a titer $\geq$ 2, you report an ADA incidence of 9.8% in the CHS-1701 arm and an incidence of 5.0% in the US-Neulasta arm. FDA identified an additional subject ^{(b) (6)} as positive in the US-Neulasta arm, which makes the ADA incidence 5.8%. Coherus conducted statistical analysis of ADA incidence yielding a 1-sided upper exact upper limit of 10%, while the FDA performed independent analysis of your data and obtained a 1-sided upper exact limit of 10.97%.

We note that in the FDA communication to Coherus on June 18, 2015, the FDA stated that “if the upper bound of the 95% 1-sided confidence interval of the difference between ADA confirmed positive rates between CHS-1701 and US-licensed Neulasta is 10%, the study may be considered adequate to rule out clinically meaningful difference in ADA confirmed positive response between CHC1701 and US-licensed Neulasta.”

Based on the June 18, 2015 communication, a difference of < 10% by itself, may not be sufficient to demonstrate no clinically meaningful differences. This is because differences need to be considered in the context of other factors that may affect safety and efficacy, such as titer, persistence, and whether ADA bind the PEG or G-CSF parts of CHS-1701. The observed difference in incidence rates at or above the 10% threshold creates residual

uncertainty regarding similarity of CHS-1701 to US-Neulasta. Provide additional information to address this concern. Depending on the information provided, further clinical studies may be needed to provide assurance that the difference in ADA rates between CHS-1701 and US-Neulasta treatment groups do not have a clinically meaningful impact on safety and efficacy.

2. You did not provide data on anti-G-CSF antibody titers for patients confirmed positive for anti-G-CSF antibodies. You also did not provide data for the incidence of neutralizing antibodies. Lack of these two pieces of information creates uncertainty about whether the difference in ADA incidence rates indicates a difference in factors impacting safety and efficacy. To address this concern provide the following:
 - (a) anti-G-CSF titers for anti-G-CSF positive samples together with time courses for evolution of anti-G-CSF titers
 - (b) Since our original discussions regarding neutralizing antibody testing, the Agency has found that anti-PEG ADA can be neutralizing. We recommend that you test all confirmed positive samples in your neutralizing antibody assay.
3. You provided validation reports for two neutralizing antibody (NAb) assays. The first Nab assay was submitted with the original BLA on August 9, 2016, and the second Nab assay was submitted in an amendment on January 18, 2017. Both of the NAb assays in their respective current status are inadequate and will not allow for meaningful evaluation of NAb in clinical samples. The reasons are listed below. To resolve the lack of adequate neutralizing assay, submit a fully validated NAb assay, including the assay validation report and the test method standard operational protocol.

You can revise one of the two NAb assays submitted to the BLA or develop a new NAB assay. In either case, refer to the FDA draft guidance of “Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Product, April 2016” for recommendation on assay validation.

The FDA has the following comments regarding neutralizing antibody assay (b) (4) submitted in the original BLA on August 9, 2016:

- 1) The CHS-1701 based screening assay shows excessively high intra- and inter-assay variability (%CV). For example, (b) (4). Due to the high variability of the assay, the validation data generated are deemed unreliable. In addition, you did not provide intra-assay precision for negative control samples (referred as BTS samples using pooled human plasma in the submission).
- 2) In the information request dated December 7, 2016, the Agency asked Coherus to provide the justification or additional data to support using the plating concentration (b) (4)

(b) (4)



Revise the concentrations of CHS-1701 so that it is in the linear range of the dosing curve. In addition, revise the concentration of mIL-3 used in the mIL-3 based confirmatory assay so that it yields an outcome similar to that of the CHS-1701.

- 3) The condition of the M-NFS-60 cells, including passage number, cell density, and cell viability, may affect the cellular response to CHS-1701 and mIL-3. However, you have not provided developmental data to support these cell related parameters specified in the assay validation report. Provide data to support these key assay parameters used in the assay, including an evaluation of cellular response to CHS-1701 and mIL-3 (dosing curves) when cells at the low, middle, and high range of the specified passage numbers, cell density, and cell viability. Include sufficient runs to demonstrate the reproducibility of the responses.

4)



(b) (4)

To address this concern, provide information showing that your NAb assay can sensitively detect NAb if they are present.

- 5) For the mIL-3 based confirmatory assay, the confirmatory assay cut-point factor was determined by statistical methods to be 0.726 using a parametric method, and 0.817 using a non-parametric method. The statistical methods used to determine the cut point factor is acceptable. However, it appears that Coherus decided not to use either of the statistically

determined cut point factors, but arbitrarily picked cut-point factor of 0.829 from the CHS-1701 based screening assay to be the cut point factor of the mIL-3 based confirmatory assay. Arbitrarily determined cut points are not acceptable. Assay cut points should be experimentally determined with appropriate statistical methods. To address this concern select a cut-point determined using a solid scientific rationale.

- 6) For the immunodepletion confirmatory assay, the cut point factor was arbitrarily determined to be 0.829. Arbitrarily determined cut points are not acceptable. The cut points should be experimentally determined with appropriate statistical methods. Determine the cut point for the immunodepletion confirmatory assay by using a minimum of 30 individual plasma samples tested in the immunodepletion assay on at least 3 different days by at least two analysts. To address this concern select a cut-point determined using a solid scientific rationale.
- 7) The assay cut points were determined from commercially obtained normal human plasma. Processing and storage of plasma can impact assay performance. To ensure that cut-points are appropriate for the specific study population, the cut-points need to be verified using plasma samples from treatment-naive study subjects. Provide the data confirming the sensitivity and cut-point of your CHS-1701 based screening assay, mIL-3 based confirmatory assay, and immunodepletion confirmatory assay with samples collected and handled the same way as study samples.
- 8) You state that sample stability was considered acceptable “(b) (4))”.
Your approach is insensitive for the detection of sample degradation (antibody reactivity). Revise the stability acceptance criteria to be based on the comparison of the sample RLU level.

The FDA has the following comments regarding the neutralizing antibody assay ((b) (4)) submitted on January 18, 2017:

- 1) The drug concentrations used in the NAb assays are (b) (4)

This indicates the cell growth may be insensitive to the neutralizing effect of anti-drug antibody in the current test method. In order to optimize the assay sensitivity, revise the concentrations of CHS-1701 and mIL-3 so that they are in the linear range of the dosing curves.

- 2) [REDACTED] (b) (4)
- These data indicate that there might be endogenous stimulators in these plasma samples ([REDACTED] (b) (6)). Consequently, the assay is less sensitive to detect neutralizing antibody in samples with endogenous stimulators. Provide a plan to identify, test, and interpret data for samples with endogenous stimulator(s) which would interfere with the assay. Alternatively, re-design and re-validate an assay to address this issue. [REDACTED] (b) (4)
- 3) The condition of the M-NFS-60 cells, including passage number, cell density, and cell viability, may affect the cellular response to CHS-1701 and mIL-3. However, you have not provided developmental data to support these cell related parameters specified in the assay validation report. Provide data to support these key assay parameters used in the assay, including an evaluation of cellular response to CHS-1701 and mIL-3 (dosing curves) when cells at the low, middle, and high range of the specified passage numbers, cell density, and cell viability. Include sufficient runs to demonstrate the reproducibility of the responses.
- 4) You initially determined a preliminary low positive control (LPC) using a statistical method, which leads to the rejection of an assay run 1% of the time (Table 6 in Appendix I). This approach and the concentration of LPC at 631.6ng/mL are acceptable. However, you later increased the concentration of LPC to 1000ng/mL based on the data in Table 7 in Appendix I. The later approach and LPC at 1000ng/mL are not acceptable because the purpose of LPC is to verify that the assay is running as expected. Based on the PC titration curve (Figure 2 in Appendix I), 1000ng/mL (of PC) is at mid-point of the linear range of the curve; therefore, 1000ng/mL is not appropriate to be LPC because it will not adequately demonstrate that the assay is performing as expected.
- 5) The statistical method used to determine the screening cut point (SCP) and confirmatory cut point (CCP) underestimates data variance, which may increase the risk of false positive detection in both assays. Specifically, the outlier exclusion is calculated on each batch rather than two batches together and cut point calculation is based on the mean

value of the two batches rather than the individual value. We recommend that you revise the statistical method used for cut point determination and recalculate the SCP and CCP.

- 6) The SCP and the CCP were determined from commercially obtained normal human plasma. Processing and storage of plasma can impact assay performance. In order to ensure that cut-points are appropriate for the specific study population, the cut-points need to be verified using plasma samples collected and handled in the same way as study samples. Provide the data confirming the sensitivity and cut points of your assay.
- 7) Based on the data reported in Table 11A and 11B of Appendix I for hemolyzed and lipemic plasma interference, it appears that sample hemolysis may increase the risk of false positive detection in the neutralizing assay. Provide a plan to analyze hemolyzed serum samples.
- 8) The current acceptance criteria for Negative Control (NC), Variation Control (VC), and Positive Control (PC) samples require only half of the controls to be within the acceptance range. Specifically, (b) (4)
. Such plate acceptance criteria do not provide adequate control across the entire plate. Revise the plate acceptance criteria to require both sets of NC, VC and PC controls to be within the acceptance range.
- 9) You did not provide assay precision for NC samples. Report intra- and inter-assay precision for NC according to the FDA draft guidance Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016.

III. Review

- Unless otherwise noted, figures and tables in the review were adapted or copied directly from the submission.
- The review sequence of the individual aspect of the assay validation may not follow the exact sequence in the submission.
- The “guidance” cited in the review refer to “FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016”
<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf>

Assay Validation Review Summary

The sponsor developed an ADA binding assay and two neutralizing assays. The ADA binding assay consists of an ECL based screening assay and a confirmatory assay based on cold competition with unlabeled drug product. The neutralizing assays are based on assessing the

neutralizing activity using M-NFS60 cells that proliferates in response to pegylated G-CSF. The ADA binding assay is deemed adequate. However, neither of the neutralizing assays is adequate.

Information Requests and Amendments

The following information requests were sent during the review of the immunogenicity assays and data.

IR1: for ADA assay, sent on 11/18/2016

IR2: for NAb assay 1, sent on 12/7/2016

IR3: for ADA assay and clinical immunogenicity data, sent on 12/23/2016

IR4: for ADA assay and clinical immunogenicity data, sent on 2/10/2017

IR5: for ADA assay and clinical immunogenicity data, sent on 2/22/2017

The immunogenicity related amendments are listed in the following Table:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment 18	November 29, 2016
Amendment 19	December 5, 2016
Amendment 23	December 16, 2016
Amendment 25	December 23, 2016
Amendment 27	January 10, 2017
Amendment 30	January 13, 2017
Amendment 31	January 18, 2017
Amendment 36	February 16, 2017
Amendment 38	February 28, 2017
Amendment 39	March 15, 2017
Amendment 41	March 21, 2017

Validation Report for Anti-drug Antibody Binding Assay:

The sponsor uses a two tiered strategy to detect anti-drug antibody (ADA). Samples are first tested in an ADA binding screening assay. Samples that screened positive were tested by confirmatory assays and a titer assay. There are four confirmatory assays, including confirmatory assay for anti-CHS-1701, anti-US-Neulasta, anti-GCSF and anti-PEG. Titers are reported for confirmed positive samples (confirmed for anti-CHS-1701 or anti-US-Neulasta).

The CHS-1701 based screening assay is an electrochemiluminescence (ECL) based bridging assay. In brief, human plasma samples are incubated in a mixture of biotinylated CHS-1701 and ruthenylated (SULFO-TAG™) CHS-1701 to form “biotinylated CHS-1701: anti-drug antibody : ruthenylated (SULFO-TAG™) CHS-1701” complex. This complex is then added to a streptavidin coated plate and allowed to bind. After washing, the detection agent was added to the complex, and the luminescence signal is read by a plate reader.

The sponsor also developed a similar US-Neulasta screening assay using biotinylated US-Neulasta and ruthenylated US-Neulasta. However, this assay was not used in testing clinical

samples, it was used during assay validation to compare results with the CHS-1701 based screening assay.

Reviewer's Comments:

The Sponsor uses a tiered approach to evaluate ADA as recommended in the guidance.

Essential Reagents and Concentration

- Positive Control (PC): Anti-G-CSF rabbit polyclonal antibody, abcam ab9691
Anti-PEG rabbit polyclonal antibody, abcam ab51257
- Normal human plasma: K₂EDTA, (b) (4)
- Negative Control (NC): referred as Blank Test Sample (BTS) which is pooled human plasma purchased from (b) (4)
- G-CSF: Coherus Batch/Lot No: 1701-DS-104

Screening Cut Point Determination

Fifty different lots of normal human plasma (25 males and 25 females) were analyzed on 3 runs performed by 2 different analysts using a balanced design. Each plasma lot was tested in duplicate and the average of the 2 corresponding measurements was used in the data analysis.

Reviewer's Comment

The sponsor did not provide a clear description of the statistical method used to determine the cut points. The Agency sent IR on 11/18/2016 and 12/23/2016 requesting additional information and clarification. The following review for screening cut point (SCP) and confirmatory cut point (CCP) determination is based on the information from the original submission and the responses to the IR received on 11/29/2016 and 1/10/2017.

The sponsor conducted outlier exclusion first. Outlier were identified and removed by calculating the Z-score using the formula of Standardized ECL value = (ECL value – Mean) / SD for each data point. The resulting values for the individual plasma lots (50 data points) were used to detect up to 3 outliers via a sequential process, using iteratively one-sided 90%, 95%, and 99% upper confidence bounds of the 95th percentile.

After outlier removal, the original plasma lots data were used to determine the SCP. Shapiro-Wilk's test (significance level at 10%) was used to evaluate the data normality for each run (3 runs in total). Based on the data normality for each run, the cut points for each run were calculated using parametric or non-parametric method. Screening cut point was targeted at 5% false positive rate. It appears that the sponsor calculated the screening cut point factor (SCPF) for each run using the formula of $[SCPF_{run} = SCP_{run}/\text{signal of } NC_{run}]$, and the overall SCPF = the average of the $SCPF_{run}$. SCPF is referred as correction factor (CF) by the sponsor.

The SCPF were determined to be 1.214 for CHS-1701 based assay and 1.199 for US-Neulasta based assay. The sponsor decided to use the value of 1.199 as a “conservative” approach.

In the clinical sample analysis, the plate $SCP = 1.199 \times \text{the mean of } NC_{plate}$. NC is referred as blank, blank TS or PHP (pooled human plasma) by the sponsor.

Reviewer's Comment

The statistical method used to determine the cut points are not acceptable for the following reasons:

- 1. Because the outlier analysis was conducted using the mean value of the 50 individual sample, this outlier exclusion approach neglected potential analytical outliers.*
- 2. Only 3 outliers are allowed to be excluded, while the real outliers may be more than 3.*
- 3. It is not clear why the 3 sequential outlier exclusion approach use three different criteria, respectively, at one-sided 90%, 95%, and 99% upper confidence bounds of the 95th percentile.*
- 4. The significance level of Shapiro-Wilk's test is commonly set at 5%, not 10%.*
- 5. Only the CHS-1701 based screening assay was used in testing clinical samples, it is unjustified to use the SCP determined for another assay (the US-Neulasta based assay) as the SCP for the CHS-1701 based assay.*

In one of comments in the initial information request sent on 11/18/2016, the Agency requested the sponsor to confirm the SCP in pre-doses clinical samples.

In the response received on 12/05/2016, the sponsor provided ECL value obtained in the screening assay from the pre-dose samples of the 268 subjects, and the correspondent mean ECL value of the NC_{plate} from the clinical immunogenicity study CHS-1701-04.

Reviewer comment:

The reviewer performed the following statistical calculation:

- 1. Identified and excluded outliers using the outlier box-plot method described in Shankar et al.2008. All samples that meet the following criteria are excluded as outlier: samples that are above the 75th percentile (Q3) plus 1.5 times the inter-quartile range (Q3-Q1) and samples that are below the 25th percentile (Q1) minus 1.5 times inter-quartile range. Twenty seven (27) samples are identified as outliers.*
- 2. Using the screening cut point factor of 1.199 determined by the sponsor, 31/268 (11.6%) samples are screened positive (after outlier exclusion). Although the in study false positive rate is higher than the targeted 5%, it is within the guidance recommendation of 90% one-sided lower confidence interval for the 95th percentile of the negative control population. Therefore, the screening cut point factor of 1.199 is acceptable.*

Confirmatory Cut Point Determination

The same 50 lots individual human plasma used for SCP determination was used in confirmatory cut point (CCP) determination. To determine the confirmatory cut points, excess amount of drug (CHS-1701, US-Neulasta, or G-CSF at 10µg/mL, PEG at 20µg/mL) were added to individual samples before running the CHS-1701 based screening assay. The unspiked and spiked samples were then tested in duplicate in 3 runs performed by 2 different analysts. An inhibition of the samples mean ECL value in the presence of CHS-1701 or US-Neulasta was calculated as follows:

$$\% \text{ Signal Inhibition} = 100 (1 - [\text{spiked sample mean ECL} / \text{unspiked sample mean ECL}]).$$

The same statistical approach as the SCP was applied for the CCP of the individual lots of human plasma, except the CCP was calculated using the % signal inhibition instead of the ECL in the screening assays. The process of excluding outliers was performed in order to detect up to 1 outlier, using the 1-sided 90% upper confidence bound of the 99.9th percentile. The CCP was targeted at 0.1% false positive rate. The determination of the CCPs for CHS-1701, US-Neulasta, and PEG followed this statistical approach. The Sponsor reported that the % signal inhibition is (b) (4) % for LLPC (b) (4) % for HPC (b) (4)

Reviewer's Comments:

The statistical methods used to determine the CCP (for CHS-1701, US-Neulasta, PEG) are not acceptable for the following reasons:

- 1. Only 1 outlier is allowed to be excluded.*
- 2. Only the positive outliers are allowed to be excluded.*
- 3. The method to exclude outliers at 99.9th percentile for DCCP is not recommended as it can be very sensitive to the extreme values present in the dataset, and consequently fewer outliers are identified.*
- 4. The significance level of Shapiro-Wilk's test is commonly set at 5%, not 10%.*
- 5. The Agency recommended the sponsor to target false positive rate for the confirmatory cut points at 1% instead the 0.1% used by the Sponsor. (Advice letter sent on Aug 28,2015)*

The sponsor used a different statistical approach to determine the CCP for G-CSF. The information of the statistical method for determining the CCP for G-CSF is in the assay validation report amendment 1 (submitted in the original BLA submission). The statistical report is conducted by (b) (4) (page 52-75 out of 89 total pages in report). Total of 150 data points (% inhibition, 50 lots x 3 runs) were included in the analysis. Analytical outliers were identified using the criteria of any values above the 75th quartile plus 1.5 times the interquartile range or below the 25th quartile minus 1.5 times the inter-quartile range. Biological outliers were examined by applying the same criteria (as for the analytical outliers) on individual sample best linear unbiased predictor (BLUP) values. Three (3) analytical outliers were identified and excluded from further analysis. No biological outlier was identified. The normality assumption was confirmed by the Shapiro-Wilk test for the distribution of the % Signal Inhibition values ($p = 0.241$), therefore parametric method was used to determine the CCP for G-CSF at 12.3% targeting 1% false positive rate.

Reviewer's Comments:

The statistical method used for determine the CCP for G-CSF is appropriate and the cut point of 12.3% is acceptable. In the information request sent on Dec 23,2016, the Agency communicated to the sponsor that the statistical methods used for determine the CCP for CHS-1701, US-Neulasta and PEG are inappropriate, with detailed reasons. We pointed out that the statistical method used for determine the CCP for G-CSF confirmatory assay is appropriate and suggested Coherus use the same approach to determine the CCP for CHS-1701, US-Neulasta, and PEG confirmatory assays.

The sponsor recalculated the confirmatory cut point following the Agency’s request and recommendation. The sponsor submitted the re-calculated cut points in the following Table (Response received on 1/10/2017):

Table 1: Drug Competition Cut Points (Re-analysis of Validation Data)

Description	Units	FPER	Parametric Estimate	Non-parametric Estimate
CHS-1701	% inhibition	1.0%	21.85%	22.40%
		0.1%	28.43%	NR
Neulasta	% inhibition	1.0%	15.84%	17.05%
		0.1%	20.73%	NR
PEG	% inhibition	1.0%	11.59%	11.36
		0.1%	14.98%	NR

FPER= False Positive Error Rate

NR=Not Reported: The non-parametric cut point at the 0.1% FPER was not performed due to the small sample size.

At 1% false positive rate, CCP for CHS-1701 is 21.85%, 15.84% for US-Neulasta and 11.59% for PEG.

Reviewer’s Comment

After reviewing the statistical reports (No. 2016CP062A and No. 2016CP062B), CCPs for CHS-1701(21.85%), US-Neulasta (15.84%), and PEG (11.36%) are acceptable. The OBP immunogenicity working group has previously reached consensus that for the pegfilgrastim biosimilar programs, sponsors can confirm with the biosimilar, CHS-1701 in this case. If sample confirms positive using the CHS-1701 confirmatory assay, then subsequently the sample will be confirmed with G-CSF and PEG confirmatory assays in order to identify the targets of the ADA. Coherus approach was to confirm with both CHS-1701 and US-Neulasta confirmatory assays, sample confirmed positive by either of the assays are scored as confirmed positive, regardless whether the subject (patient) was treated with CHS-1701 or US-Neulasta. To be consistent with other pegfilgrastim biosimilar applications, the Agency communicated with the Sponsor that sample scoring will be based on data from CHS-1701 confirmatory assay regardless whether the subject (patient) was treated with CHS-1701 or US-Neulasta.

Assay Precision

Anti-G-CSF and anti-PEG PC samples (LLPC, LPC, MPC, and HPC) were assayed in triplicate, each 1 in duplicate on each plate, for a total of 6 plates performed by 2 analysts. LLPC (low low positive control)=200ng/mL, LPC (low positive control)=300ng/mL, MPC (medium positive control)=6000ng/mL, HPC (high positive control)=20,000ng/mL. Sample ECL was used to evaluate %CV. The %CV from all PCs are less than 25%. All ECL values of all the PC samples are greater than the plate SCP.

Reviewer’s Comment

The assay precision is acceptable. However, the reviewer noticed that at the LLPC level of 200ng/mL (anti-GCSF), the ECL values are at least two times higher than the plate SCP which indicates the selected level of LLPC is much higher than the assay sensitivity (framed in red by the reviewer). See further discussion in Assay Sensitivity.

Table 7: Intra- and Inter-Assay Precision of the Positive Controls: Anti-G-CSF with CHS-1701 Tagged Reagents
Testing Facility Study No. 20029114

	Plate	Date Analyzed	Intra-Assay Precision											Inter-Assay Precision			
			ECL Value 1	ECL Value 2	ECL Value 3	ECL Value 4	ECL Value 5	ECL Value 6	Mean ECL Value	StDev	CV%	CV% < 25?	Mean	STDEV	CV%	CV% < 25?	
HPC (20,000 ng/mL)	MV1	21 Mar 2013	10250	9936	7857	7964	7614	8213	8639.0	1146.890	13	Yes	7928.7	1030.512	13	Yes	
	MV3	21 Mar 2013	9039	9399	9052	8787	8014	8529	8803.3	483.894	5	Yes					
	MV5	23 Mar 2013	9137	8962	8302	8685	8030	7496	8435.3	615.868	7	Yes					
	MV28	02 Apr 2013	8590	8264	6463	6680	5987	6645	7104.8	1058.567	15	Yes					
	MV42	04 Apr 2013	7133	7380	7053	6987	6257	7019	6971.5	377.519	5	Yes					
MV44	05 Apr 2013	8373	8400	7451	7264	7005	7115	7618.0	616.884	8	Yes						
MPC (6000 ng/mL)	MV1	21 Mar 2013	3479	3394	3300	2906	2666	2717	3077.0	357.635	12	Yes	2764.5	382.396	14	Yes	
	MV3	21 Mar 2013	3132	3303	3114	3044	2740	2835	3028.0	207.020	7	Yes					
	MV5	23 Mar 2013	2990	3061	3137	3107	2846	2725	2977.7	161.485	5	Yes					
	MV28	02 Apr 2013	3021	3132	2230	2112	2105	2017	2436.2	501.832	21	Yes					
	MV42	04 Apr 2013	2698	2599	2546	2645	2281	2309	2513.0	176.394	7	Yes					
MV44	05 Apr 2013	2820	2705	2529	2511	2382	2384	2555.2	175.788	7	Yes						
LPC (300 ng/mL)	MV1	21 Mar 2013	229	228	245	222	210	209	223.8	13.467	6	Yes	213.9	24.541	11	Yes	
	MV3	21 Mar 2013	240	238	249	260	239	239	244.2	8.750	4	Yes					
	MV5	23 Mar 2013	219	230	236	243	216	220	227.3	10.764	5	Yes					
	MV28	02 Apr 2013	217	219	170	162	157	174	183.2	27.636	15	Yes					
	MV42	04 Apr 2013	208	198	196	201	188	197	198.0	6.542	3	Yes					
MV44	05 Apr 2013	218	219	203	210	201	192	207.2	10.496	5	Yes						
LLPC (200 ng/mL)	MV1	21 Mar 2013	170	172	170	159	150	161	163.7	8.548	5	Yes	157.9	18.660	12	Yes	
	MV3	21 Mar 2013	186	187	186	185	172	177	182.2	6.178	3	Yes					
	MV5	23 Mar 2013	173	173	176	168	158	157	167.5	8.167	5	Yes					
	MV28	02 Apr 2013	159	164	122	127	120	117	134.8	20.971	16	Yes					
	MV42	04 Apr 2013	154	151	144	140	146	137	145.3	6.439	4	Yes					
MV44	05 Apr 2013	161	168	150	150	145	150	154.0	8.649	6	Yes						

Summary	Response
CV% within 25% at each PC level for Intra-Assay Precision	Yes
CV% within 25% at each PC level for Inter-Assay Precision	Yes

	MV1	MV3	MV5	MV28	MV42	MV44	Mean	STDEV	CV%
Mean BTS	52.333	58.364	52.917	53.250	43.250	47.083	51.200	5.290	10
PSCP	62.747	69.978	63.447	63.847	51.857	56.453	61.388	6.342	10

Assay Sensitivity

The assay sensitivity was set at the LLPC (200 ng/mL in neat plasma), based on the observation that precision of LLPC met assay precision criteria and LLPC consistently produced a positive signal (i.e. >SCP).

Reviewer’s Comment

The approach used to determine assay sensitivity is inappropriate. Per guidance, ADA assay sensitivity is defined as the lowest concentration at which the positive control antibody(ies) consistently produces either a positive result or ECL value equal to the SCP. Based on the precision data, the assay sensitivity is probably much lower than 200ng/mL for anti-GCSF. The reviewer estimate the sensitivity to be lower than 100ng/mL based on the ECL trend seen in the Table 7 above. Despite that the ADA assay sensitivity at 200ng/mL or lower is acceptable, the reviewer is concerned about the level of low positive control selected for system suitability control. A low positive control at the level just slightly above the sensitivity of the assay is essential to ensure that the sensitivity of the assay is consistent. Per guidance, the low positive system suitability control should be designed to fail in 1% of the runs (fail=below plate SCP). To ensure the low positive control at 200ng/mL for anti-GCSF is appropriate, we requested the Sponsor to confirm the real sensitivity of the assay. In the teleconference with the sponsor on

11/30/2016, the Agency suggested the sponsor submit ECL value from further dilutions of PC (lower than 200ng/mL).

In the response submitted on Dec 23, 2016, the sponsor assessed the precision of the anti-G-CSF and anti-PEG positive controls at 100, 50, and 25ng/mL. Intra-assay and inter-assay precision were assessed in 3 plates, by 2 analysts on two different days. The data are provided in the following Tables:

Table 4: Intra-Assay Precision of the Positive Controls: Anti-G-CSF

	Plate	ECL Value 1	ECL Value 2	ECL Value 3	ECL Value 4	ECL Value 5	ECL Value 6	Mean ECL Value	PSCP	Mean ECL >PSCP	StDev	CV%	CV% < 25?
Anti-G-CSF (100 ng/mL)	MD85	98	94	90	89	93	89	92.0	86.628	Yes	3.545	4	Yes
	MD86	94	87	95	91	98	96	94.0	84.802	Yes	3.937	4	Yes
	MD92	88	94	88	92	83	89	89.0	73.439	Yes	3.795	4	Yes
Anti-G-CSF (50 ng/mL)	MD85	85	79	82	83	85	82	83.0	86.628	No	2.251	3	Yes
	MD86	78	76	84	83	82	82	81.0	84.802	No	3.125	4	Yes
	MD92	75	78	73	77	72	75	75.0	73.439	Yes	2.280	3	Yes
Anti-G-CSF (25 ng/mL)	MD85	83	74	72	74	77	73	76.0	86.628	No	4.037	5	Yes
	MD86	77	73	75	76	81	77	77.0	84.802	No	2.665	3	Yes
	MD92	71	68	67	67	65	68	68.0	73.439	No	1.966	3	Yes

Table 6: Intra-Assay Precision of the Positive Controls: Anti-PEG

	Plate	ECL Value 1	ECL Value 2	ECL Value 3	ECL Value 4	ECL Value 5	ECL Value 6	Mean ECL Value	PSCP	Mean ECL >PSCP	StDev	CV%	CV% < 25?
Anti-PEG (100 ng/mL)	MD85	119	124	118	121	113	117	119.0	86.628	Yes	3.724	3	Yes
	MD86	117	109	110	114	121	116	115.0	84.802	Yes	4.506	4	Yes
	MD92	70	71	65	67	67	68	68.0	73.439	No	2.191	3	Yes
Anti-PEG (50 ng/mL)	MD85	93	94	90	90	85	84	89.0	86.628	Yes	4.082	5	Yes
	MD86	83	87	91	80	83	85	85.0	84.802	Yes	3.817	4	Yes
	MD92	61	63	61	66	62	61	62.0	73.439	No	1.966	3	Yes
Anti-PEG (25 ng/mL)	MD85	85	87	86	83	79	80	83.0	86.628	No	3.266	4	Yes
	MD86	75	80	77	72	77	74	76.0	84.802	No	2.787	4	Yes
	MD92	59	59	57	62	57	60	59.0	73.439	No	1.897	3	Yes

The %CV for inter-assay precision are below 25% for both anti-GCSF and anti-PEG antibodies at all tested concentrations.

Reviewer's Comment:

Based on the results submitted in the response, the assay sensitivity is between 50 to 100ng/mL for anti-GCSF, and between 100 to 200ng/mL for anti-PEG. Therefore, setting the LLPC at 200ng/mL for anti-GCSF is too high to ensure the sensitivity and reliability of the assay throughout the runs. However, the reviewer considered the following two factors and concluded that the selected concentration of LLPC, although not ideal, provided sufficient control for the assay runs. The factors include 1) that the current screening cut point generates around 11-12% false positive results, the ideal SCP (5% false positive) is higher than the current one. 2) FDA

has traditionally recommended sensitivity of 250-500ng/mL, the LLPC provide control that the assay can reliably detected ADA at 200ng/mL.

Drug Tolerance

The sponsor evaluated the ability of the assay to detect ADA in the presence of circulating drug (CHS-1701 or US-Neulasta) and established drug tolerance limits for the assay. The result is provided in the following Table 13 and 14:

Table 13: Drug Tolerance with CHS-1701
Testing Facility Study No. 20029114

Assay ID		MV51		
Assay Date		12 Apr 2013		
PSCP		55.154		
Mean Blank TS		46.000		
PC Concentration	Drug Concentration	Mean ECL	% Difference	Mean ECL > PSCP
HPC (20,000 ng/mL)	10 µg/mL	67.0	-99	Yes
	5 µg/mL	96.5	-99	Yes
	1 µg/mL	384.5	-96	Yes
	0.5 µg/mL	777.0	-92	Yes
	0.1 µg/mL	3882.5	-59	Yes
	0 µg/mL (Unspiked Reference)	9562.5	N/A	N/A
LPC (300 ng/mL)	10 µg/mL	51.0	-80	No
	5 µg/mL	52.0	-79	No
	1 µg/mL	66.5	-73	Yes
	0.5 µg/mL	75.0	-70	Yes
	0.1 µg/mL	110.5	-56	Yes
	0 µg/mL (Unspiked Reference)	249.5	N/A	N/A
LLPC (200 ng/mL)	10 µg/mL	47.5	-72	No
	5 µg/mL	49.0	-71	No
	1 µg/mL	56.5	-67	Yes
	0.5 µg/mL	68.0	-60	Yes
	0.1 µg/mL	90.0	-47	Yes
	0 µg/mL (Unspiked Reference)	169.0	N/A	N/A

Summary	Response
HPC: The highest drug concentration that results in the mean ECL value of PC samples >PSCP	10 µg/mL
LPC: The highest drug concentration that results in the mean ECL value of PC samples >PSCP	1 µg/mL
LLPC: The highest drug concentration that results in the mean ECL value of PC samples >PSCP	1 µg/mL

Table 14: Drug Tolerance with Pegfilgrastim
Testing Facility Study No. 20029114

		Assay ID	MV52	
		Assay Date	12 Apr 2013	
		PSCP	59.450	
		Mean Blank TS	49.583	
PC Concentration	Drug Concentration	Mean ECL	% Difference	Mean ECL > PSCP
HPC (20,000 ng/mL)	10 µg/mL	72.5	-99	Yes
	5 µg/mL	102.0	-99	Yes
	1 µg/mL	471.0	-95	Yes
	0.5 µg/mL	985.5	-90	Yes
	0.1 µg/mL	4641.5	-55	Yes
	0 µg/mL (Unspiked Reference)	10237.5	N/A	N/A
LPC (300 ng/mL)	10 µg/mL	56.0	-78	No
	5 µg/mL	58.5	-78	No
	1 µg/mL	71.5	-73	Yes
	0.5 µg/mL	85.0	-67	Yes
	0.1 µg/mL	119.5	-54	Yes
	0 µg/mL (Unspiked Reference)	260.0	N/A	N/A
LLPC (200 ng/mL)	10 µg/mL	57.5	-73	No
	5 µg/mL	56.0	-73	No
	1 µg/mL	67.5	-68	Yes
	0.5 µg/mL	73.0	-65	Yes
	0.1 µg/mL	99.0	-53	Yes
	0 µg/mL (Unspiked Reference)	210.0	N/A	N/A

Summary	Response
HPC: The highest drug concentration that results in the mean ECL value of PC samples >PSCP	10 µg/mL
LPC: The highest drug concentration that results in the mean ECL value of PC samples >PSCP	1 µg/mL
LLPC: The highest drug concentration that results in the mean ECL value of PC samples >PSCP	1 µg/mL

Reviewer's Comment:

According to the clinical pharmacology reviewer Sarah Schrieber, the level of CHS-1701 or US-Neulasta in the subjects from the CHS-1701-04 study (immunogenicity study) are lower than LOQ (of the PK assay, 0.15ng/mL) at the time points when the immunogenicity samples were taken. To understand the sensitivity of the assay in the presence of drug, the sponsor determined the amount of drug that could be present in plasma and still allow for the detection of 200ng/ml, 300ng/ml and 20,000 ng/ml of ADA. The results presented above indicate that expected drug plasma concentration is not expected to interfere with the detection of 200ng/ml of ADA in this assay. In addition, the level of drug tolerance is comparable between CHS-1701 and US-Neulasta. Overall, assay sensitivity in the presence of on-board drug is acceptable.

Titer Determination

All Samples that screened positive are evaluated for titer determination. The sponsor states that samples are titrated using a 2-fold serial dilution scheme until the level of sensitivity is reached (200ng/mL). The final titer reported is the highest dilution factor that produces a mean ECL value > mean G-CSF LPC (200ng/mL, titer cut point) of the plate. For samples with ECL

value above the SCP, but below the titer cut point, the sample titer is reported as “no titer”. Because the minimum required dilution MRD is 2 (1 fold dilution) in the screening assay, titer of “1” is assigned to samples with the highest dilution factor determined to be the MRD. Therefore, the available titers are “no titer, 1, 2, 4, 8, 16...” Titers are only reported for confirmed positive samples.

Reviewer’s Comment

It is noted that the current titer assay reports the titer against pegfilgrastim, it does not differentiate the specificity for anti-GCSF or anti-PEG.

The Sponsor’s approach to determine the titer cut point is not acceptable. Per Guidance, titers are defined as the maximal dilution where a sample gives a value above the SCP. The sponsor arbitrarily set the titer cut point as the ECL level of 200ng/mL, which is more than 2 times of the ECL level of the screening cut point. In the information requests sent on 11/18/2016 and 12/23/2016, and during the teleconference on 11/30/2016, the Agency communicated with the Sponsor that under the proposed titer definition, clinical samples within a considerable range of low titers will be under-reported.

In the response received on 1/10/2017, the Sponsor revised the titer cut point factor to be 1.5. The plate titer cut point = 1.5 x the mean of NC_{plate}. To support the titer cut point, the Sponsor provided dilution curves for anti-G-CSF positive controls and titer precision data.

Reviewer’s Comment

After reviewing the dilution curve in relation to the proposed titer cut point, as well as the titer precision data, the proposed titer cut point = 1.5 x the mean of NC_{plate} is deemed acceptable.

In the information requests sent on 11/29/2016 and 2/28/2017, the Agency requested the Sponsor to factor in MRD when calculating the sample titer. The titer should be reported as multiples of 2, such as 2, 4, 8, 16 and extending to higher dilutions as necessary. The lowest titer should be MRD (which is 2) instead of “no titer”. In response, the Sponsor replaced the “no titer” with “<2”, titer “1” with “2”, titer “2” with titer “4” and so on..

Reviewer’s Comment

Considering the titer reporting mainly serves the purpose of comparing the titer over time for a subject, the relative value (e.g. day 7 vs day 42) is more important than the absolute value, the response is acceptable.

Stability

Stability of positive control samples (anti-GCSF at 20,000ng/mL, 300ng/mL, and 200ng/mL) were prepared in pooled human plasma and subjected to free-thaw (7 cycles), -20°C for 1 year, or -80°C for 1 year before tested in the CHS-1701 screening assay. Upon the end point of each

condition, the samples were tested in the titer assay. The titers of each sample are within $\pm$ one 2-fold dilution for all analyses.

Reviewer's Comment

The anti-GCSF positive control is stable under the studied conditions.

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 [REDACTED] (b) (4)

The following assay parameters are reviewed during the inspection and through review of the response to observations.

Hemolyzed Plasma

Inspector comment: [REDACTED] (b) (4)

Selectivity

Inspector comment: [REDACTED] (b) (4)

Reviewer's Comment

The ADA assay detect antibodies against the two moieties of the drug, G-CSF and PEG, with higher sensitivity and selectivity for the antibodies against G-CSF than the PEG. We take this into consideration when reviewing the clinical data.

Validation Report for Neutralizing Antibody Assay 1:

Method

[REDACTED] (b) (4)

Review of clinical immunogenicity results

BLA 761039 CHS-1701 PEG G-CSF biosimilar for treatment of neutropenia Review of clinical immunogenicity results

From: Frederick C. Mills, Ph.D., Staff Scientist, Division IV, OBP, OPQ, CDER, FDA
To: Joslyn Brunelle, Ph.D., Team Lead, Division IV, OBP, OPQ
Subject: Clinical immunogenicity data
Sponsor: Coherus

Executive Summary

Coherus has developed CHS-1701 as a proposed biosimilar to the reference product, US-Neulasta (pegfilgrastim), which is a PEG conjugated (pegylated) G-CSF for treatment of neutropenia. To assess comparative immunogenicity of CHS-1701 versus US-Neulasta, Coherus conducted Study CHS-1701-04, a parallel arm study in healthy volunteers who were treated with two 6mg doses either CHS-1701 or US-Neulasta on Day 1 and Day 41; there were approximately 120 volunteers in each arm. Blood samples for antibody testing were taken at Predose, 13, 27 and 41 days after each dose.

Assessment of confirmed ADA incidence revealed a higher incidence for CHS-1701 relative to US-Neulasta. FDA calculated a rate of 9.8% for the CHS-1701 arm and 5.8% for the US-Neulasta arm, yielding a 95% confidence 1-sided upper exact upper limit of 10.97%. Coherus' calculations were very similar, giving an incidence in CHS-1701 arm of 9.8% and 5.0% for the US-Neulasta arm, yielding a 1-sided upper exact upper limit of 10 %.

In the FDA communication to Coherus on June 18, 2015, the FDA stated that

“if the upper bound of the 95% 1-sided confidence interval of the difference between ADA confirmed positive rates between CHS-1701 and US-licensed Neulasta is 10%, the study may be considered adequate to rule out clinically meaningful difference in ADA confirmed positive response between CHC1701 and US-licensed Neulasta.”

Based on this communication, a difference of $\leq 10\%$ by itself, may not be sufficient to demonstrate no clinically meaningful differences. This is because differences need to be considered in the context of other factors that may affect safety and efficacy, such as titer, persistence, and whether ADA bind the PEG or G-CSF parts of CHS-1701.

The Sponsor provided data provided for ADA reactivity with the G-CSF and PEG moieties. These data suggest that there is no important difference in these specific reactivities between the CHS-1701 and Neulasta arm. ADA titers are also similar, but a specific measurement for titers of anti-GCSF antibodies were not provided. The Sponsor's neutralizing antibody assay are not acceptable, and thus there is no information on the incidence of neutralizing antibodies. Overall, there is uncertainty about whether the difference in ADA incidence rates indicates a difference in

factors impacting safety (lack of anti-G-CSF antibody titer data) as well as efficacy (lack of neutralizing antibody data). Until this information is available, there is concern that CHS-1701 poses an increased risk relative to US-Neulasta for both safety and efficacy.

In summary, The Agency is recommending CR.

The CR comment will ask that Coherus will provide additional information to provide assurance that the difference in ADA rates between CHS-1701 and US-Neulasta treatment groups do not have a clinically meaningful impact on safety and efficacy. We note that additional clinical studies may be needed.

In addition, we request that Coherus provide anti-G-CSF titers for anti-G-CSF positive samples together with time courses for evolution of anti-G-CSF titers.

Since original discussions with Coherus regarding neutralizing antibody testing, the Agency has found that anti-PEG ADA can be neutralizing. We recommend that test all confirmed positive samples in your neutralizing antibody assay, and not just confirmed G-CSF positive samples.

Background (from the CTD introduction)

G-CSF is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

CHS-1701(UDENYCA) has been developed by Coherus as a biosimilar to the reference product, Neulasta® (pegfilgrastim). CHS-1701 is a covalent conjugate of recombinant human G-CSF and PEG. The G-CSF moiety is a 175 amino acid cytokine produced in E. Coli. To manufacture CHS-1701, a 20 kD PEG molecule is covalently bound to the N-terminal methionyl residue of G-CSF. The average molecular weight of pegfilgrastim is approximately 39 kD.

The CHS-1701 drug product is provided as a single use prefilled syringe in a 1 mL syringe to deliver 0.6 mL. Similar to Neulasta (US), each prefilled syringe contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

Trial design and criterion for biosimilarity

Study CHS-1701-04 was conducted in healthy volunteers who were treated with two doses of 6 mg CHS-1701 or US-Neulasta on Day 1 and Day 41, with approximately 120 volunteers in each arm. Blood samples for antibody testing were taken at Predose, 13, 27 and 41 days after each dose.

In a communication to Coherus on June 18, 2015, the FDA stated that

“ if the upper bound of the 95% 1-sided confidence interval of the difference between ADA confirmed positive rates between CHS-1701 and US-licensed Neulasta is 10%, the study may be considered adequate to rule out clinically meaningful difference in ADA confirmed positive response between CHC1701 and US-licensed Neulasta.” Furthermore, in the teleconference held between Coherus and the FDA on August 31, 2015, agreement was reached that the clinically meaningful immunogenicity endpoint (subject scored as antibody positive) would be:

Treatment-emergent confirmed positive persistent (≥ 2 time points) with titer ≥ 1 in P1 and P2 or in P2, where P1 is the period after the first dose, and P2 is the period after the second dose.

During the BLA review, Coherus revised titer cutpoint and titer calculation upon FDA request. Under current calculation, Titer ≥ 2 means assay signal is greater than assay titer cut point which is comparable to the level of 50-100ng/ml of positive control (MRD=2). Samples with signal between the assay screening cutpoint and assay titer cutpoint are scored as titer <2 .

FDA advice regarding cutpoints and titer

FDA Request for Information dated 10 February 2017:

In the amendment received January 10, 2017, your new confirmatory cutpoints at a 1% false positive rate for inhibition by CHS-1701 (21.85%), US-Neulasta (15.84%), PEG (11.59%), and G-CSF (12.3%) are acceptable. For the purpose of ADA rate calculation in the CHS-1701 and US-Neulasta treated groups, the score of the positive samples should be based upon the CHS-1701 confirmatory assay with your re-determined CHS-1701 (21.85%) cutpoint. In addition, provide the following information:

b. Since some samples that were initially scored negative may now be positive using the CHS-1701 confirmatory assay with the new cut point; these samples will also need to be tested in the anti-PEG and anti-G-CSF confirmatory assays. Provide the results from the samples that need re-testing or provide an estimate of the time that will be required for re-testing in the anti-PEG and anti-G-CSF confirmatory assays. When you have the results, update the Excel spreadsheets you provided on January 10, 2017.

c. Identify all subject IDs that are confirmed positive with the new CHS-1701 assay cutpoint and indicate whether these subjects are confirmed positive for anti-PEG and/or anti-G-CSF.

FDA Request for Information Dated 22 Feb 2017:

1. In the amendment received January 10, 2017, you revised the titer cut point factor (CPF) to 1.5 and submitted Excel spreadsheet with the recalculated titer using the CPF of 1.5. The Agency agrees that the CPF of 1.5 is acceptable. However, we have the following comments regarding your anti-drug antibody (ADA) titer results:

- a. The Excel spreadsheets report the lowest titer as “no titer” and the next lowest titer as “1”. This titer calculation does not follow FDA Draft Guidance: Assay Development for Immunogenicity Testing of Therapeutic Proteins 2016, which states that “the minimum required dilution (MRD) should be factored in the calculations of titers and provided when reporting titers”. Therefore, for the confirmed positive samples with screening assay results

below the CPF, the titer should be reported as MRD, which is 2 for your current ADA assay. Since you used 2-fold serial dilution in the titer assay, the titer should be reported as multiples of 2, such as 2, 4, 8, 16 and extending to higher dilutions as necessary. Recalculate ADA titer for your samples according to this guidance and update the Excel spreadsheets you provided on January 10, 2017.

Led to titer < 2 considerations as stated above under...

b. The Agency notes that your new Titer CPF may require further dilution of some samples (e.g. sample with current titer of ">16"). Provide the results from the samples that need further dilution or provide an estimate of the time that will be required for re-testing in the titer assay. When you have the results, update the Excel spreadsheets you provided on January 10, 2017.

Coherus provided these updated data in their February 28, 2017 submission

2. On February 16, 2017, you provided rates and numbers of subjects with confirmed positive and persistent anti-drug antibodies (ADA) in Table (*designated as appendix-a1-chs-1701.xls and appendix-a2-neulasta.xls*). The Agency is confirming the rates and numbers you reported with the data found in the Excel spreadsheets you provided. In order to confirm your conclusions regarding incidence rates, clarify whether results from the P2 predose samples were counted in your analyses as part of treatment period P1 or P2.

Coherus responded that the P2 predose samples were counted as part of P2.

3. Based on results provided in Table 1, the Agency would like to understand the evolution of the immune response in antibody positive subjects, including all the confirmed positive subjects in the CHS-1701 and US-Neulasta treated groups. Provide graphical plots of time courses (P1day 0, 13, 27, 41, P2day 0, 13, 27, 41) for titer, anti-G-CSF positivity, and anti-PEG positivity. You should provide a separate plot for each individual confirmed positive subject. These plots should include data from subjects who were pretreatment positive (P1predose). In addition to these plots from individual subjects, you should also combine the titer data into one plot for all subjects treated with CHS-1701 and one plot for all subjects treated with US-Neulasta.

Coherus provided these time course plots, and the combined titer plots for CHS 1701 and Neulasta treated subjects are provided below in the section on ADA titers. Visual representations of time courses for GSF positive samples are Attached in Appendix 3, and similar representations for time courses of PEG positive samples are attached in Appendices 4 and 5.

ADA Incidence

Coherus responded to the Agency Information requests, including Excel spreadsheets with the final measurements of ADA incidence, including additional information to specify ADA titers and whether ADA are specific to anti-GCSF and/or anti-PEG for each subject.

FDA reviewer (Fred Mills) independently analyzed the data provided by Coherus in the amendment dated February 28, 2017.

For this analysis, I extracted sampling times for each subject and the associated YES/NO confirmed anti-CHS-1701 antibody status for each sampling time from the Sponsor's Excel

tables for immunogenicity results submitted February 28, 2017 (appendix-a1-chs-1701.xlsx for the CHS-1701 arm, and appendix-a2-neulasta.xlsx for the US-Neulasta arm) and placed these values into two new Excel tables for the CHS-1701 and US-Neulasta arms. These analyses are found as attached Appendices 1 and 2, and the analysis is explained verbally below.

Using nested IF statements, the sampling times and their associated YES/NO values were sorted to bring all the YES/NO values for a given sampling time into one Excel column, with each row of an Excel table corresponding to a given subject. Numerical values were assigned to YES/NO status as YES=1, and NO, NA, or blank=0. These values were then summed across the row for each subject, and scores of 1 were placed in a column if there were positives at 1 or more time points in the P1 period and a single positive time point in P2 ($P1 \geq 1 + (P2=1)$), corresponding to one of the agreed criteria for persistent antibodies. The YES/NO scores for P2 were also summed, and a value 1 was placed in another column if there were ≥ 2 positive time points in P2 ($P2 \geq 2$), corresponding to the second agreed criterion for persistent antibodies. The values in each of these two columns were summed to give a $P1 \geq 1 + (P2=1)$ total, and a P2 total, and these two totals were then added together to give an incidence that included subjects who were pre-treatment positive.

Two additional columns were generated to obtain the incidence of treatment-emergent antibodies. In one column a score for each subject was set to 1 if the $P1 \geq 1 + (P2=1)$ score was 1 and the subject was not pre-treatment positive ($P1_{\text{predose}} = \text{NO}$), while the score was set to 0 if the $P1 \geq 1 + (P2=1)$ score was 1, but the subject was pre-treatment positive ($P1_{\text{predose}} = \text{YES}$). Similarly, in an adjacent column a score was set to 1 if $P2 \geq 2 = 1$ and the subject was pre-treatment negative ($P1_{\text{predose}} = \text{NO}$), while the score was set to 0 if the $P2 \geq 2$ score was 1, but the subject was pre-treatment positive ($P1_{\text{predose}} = \text{YES}$). The scores in each of these two treatment emergent columns were summed separately, and then added together to give an incidence of treatment emergent antibodies. For the CHS-1701 arm the treatment-emergent incidence was $16/122=13.1\%$, while for the Neulasta arm, the treatment emergent incidence was $9/120=7.5\%$.

Finally, to assess the incidences according to the agreed criterion that persistence be defined by two or more time points with titer ≥ 2 , subjects who did not meet this criterion were excluded from the treatment emergent totals. For the CHS-1701 arm, subjects (b) (6) did not meet this criterion, yielding a total of 12 subjects with two or more time points that had a titer ≥ 2 , yielding a rate of $12/122=9.8\%$. For the Neulasta arm, subjects (b) (6) had only a single titer >2 , and were thus not classified as persistent, so there were 7 subjects who met the titer ≥ 2 criterion, for an incidence rate or $7/120=5.8\%$.

The reviewer analysis included one subject in the Neulasta arm (subject (b) (6)) who was not counted in the Coherus analysis. In addition, in the CHS-1701 arm Subject (b) (6) was ADA positive at P1D41 with a titer < 2 , and on P2D41 with a titer=2, so this subject was included in our analysis for "Treatment Emergent Persistent" but as mentioned above was excluded from "Treatment Emergent persistent w/titer ≥ 2 " because there was only one titer ≥ 2 , and thus this subject did not meet the criterion for persistent ADA

As seen in the tables below, inclusion of subject (b) (6) in the Neulasta arm makes only a small difference in the % incidence and the 1-sided upper limit. The 1-sided upper confidence limits for both the Incidence data by FDA and the Incidence data by Coherus were calculated by Jingjing Ye, Statistical Reviewer, CDER

Incidence data by FDA

	Treatment emerging, persistent	1-sided Upper Limit (Exact)	Treatment emerging, persistent w/ titer ≥2	1-sided Upper Limit (Exact)
CHS-1701	16/122 (13.1%)	12.6%	12/122 (9.8%)	10.16%
US-Neulasta	9/120 (7.5%)		7/120 (5.8%)	

Incidence data by Coherus

	Treatment emerging, persistent	1-sided Upper Limit (Exact)	Treatment emerging, persistent w/ titer ≥2	1-sided Upper Limit (Exact)
CHS-1701	16/122 (13.1%)	>12.3%	12/122 (9.8%)	10.97%
US-Neulasta	8/120 (6.7%)		6/120 (5.0%)	

Reviewer comments

There is an approximate two-fold difference in confirmed, treatment emergent antibody incidence between CHS-1701 and US-Neulasta treated subjects, which yields a 1-sided upper exact confidence limit greater than 10%. This result places the ADA incidence beyond the threshold for biosimilarity, provided by the FDA in the June 18,2015 communication to Coherus, in which the FDA stated that

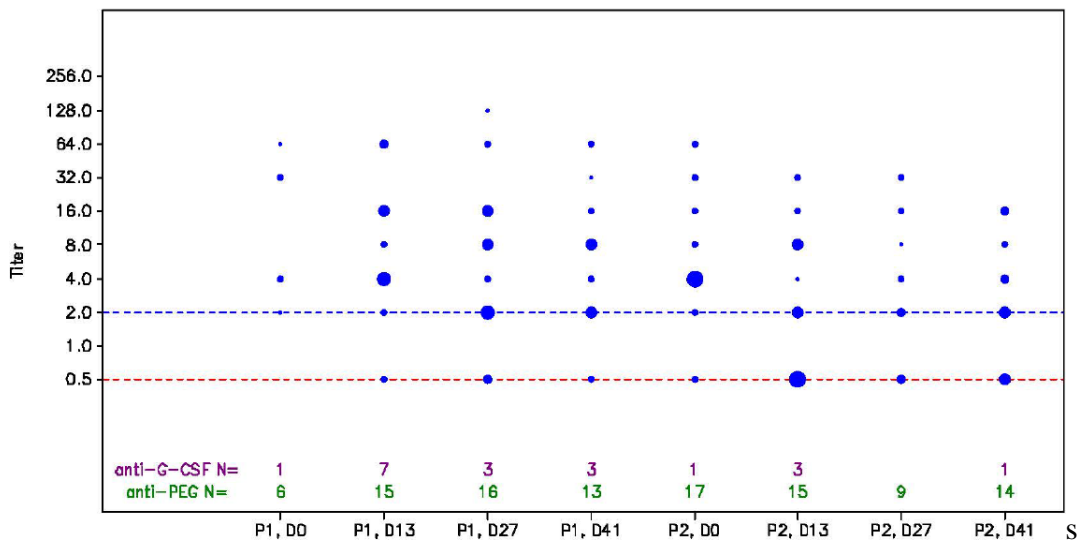
“ if the upper bound of the 95% 1-sided confidence interval of the difference between ADA confirmed positive rates between CHS-1701 and US-licensed Neulasta is 10%, the study may be considered adequate to rule out clinically meaningful difference in ADA confirmed positive response between CHS-1701 and US-licensed Neulasta.”

The wording of the FDA’s advice, as per the highlighted “may be considered adequate” clause, indicates that additional factors can be considered in assessing biosimilarity besides a 10% difference. On one hand, this indicates that a difference of >10% may not absolutely rule out biosimilarity if other, mitigating factors are considered. However, in this case there is limited understanding of the CHS-1701 vs. Neulasta difference, since neither titers of anti-GCSF antibodies nor the incidence of neutralizing antibodies have been measured. Lack of these two pieces of information creates uncertainty about whether the difference indicates a difference in factors impacting safety (lack of anti-GCSF antibody titer data) as well as efficacy (lack of neutralizing antibody data). Until this information is available, there is concern that CHS-1701 poses an increased risk relative to Neulasta for both safety and efficacy.

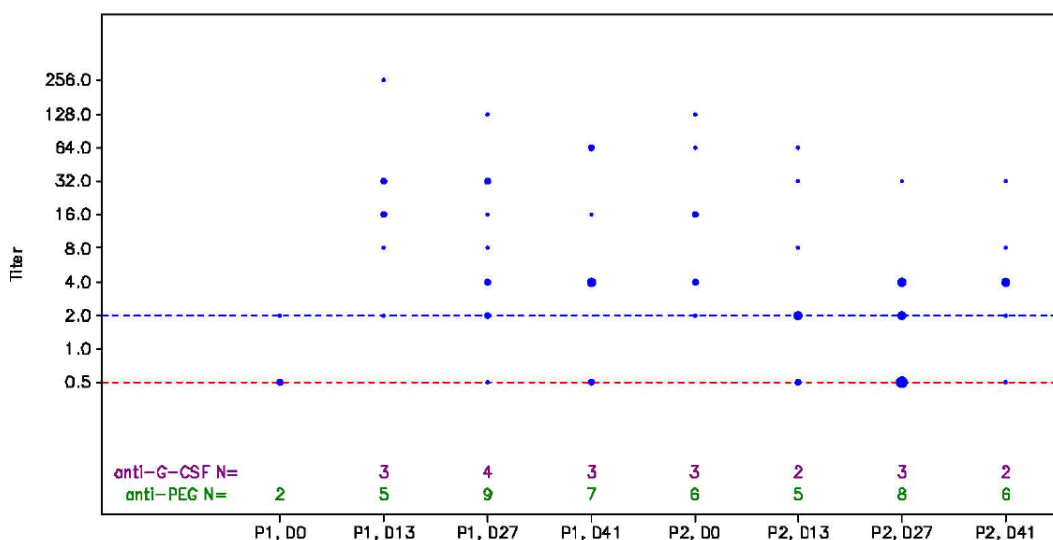
ADA titers

As per FDA request, the Sponsor provided graphical presentations of titers for individual confirmed positive patients (data not shown), as well as combined titer data for the CHS-1701-04 immunogenicity study; titer data for both CHS-1701 and US-Neulasta arms can be found in the following two graphs. Note that the size of circles at a given time point indicates the number of subjects with a given titer at that time point, so that larger circles indicate more subjects with a given titer, and small circles indicate few subjects with a given titer.

CHS-1701 arm



US-Neulasta arm



Reviewer comments

Examination of the combined ADA titer plots, as well as the individual titer plots, indicates general similarity in time courses between CHS-1701 and US Neulasta arms of the clinical study, with a trend toward declining titers over time.

Anti-G-CSF and Anti-Peg ADA incidence

Using the data submitted to the FDA on March 21, 2017, FDA calculated the following treatment emergent anti-G-CSF incidence rates: 14 out of 122 for CHS 1701 and 9 out of 120 for US-Neulasta. This data includes subjects who had anti-GCSF positive sample at any sampling time, excluding pre-treatment positive subjects. Appendix 3 (Table from Haoheng Yan) provides a visual representation of the anti-GCSF incidence for each treatment emergent subject. Similarly, Appendix 4 shows the treatment emergent anti-PEG incidence across time points for each subject in the CHS-1701 arm, while Appendix 5 shows the corresponding anti-PEG incidence in the US-Neulasta arm.

Reviewer comments

The CHS-1701 and US-Neulasta G-CSF tables look generally similar, but with fewer anti-G-CSF positive samples in the US-Neulasta arm. There is one Neulasta subject (b)(6) showing more persistence (all time points subsequent to the predose sample) than any of the CHS-1701 subjects.

Appendices 4 and 5 indicate similar courses of anti-PEG responses for the CHS-1701 and US-Neulasta arms, with 21.3 % of CHS-1701 treated patients showing at least one treatment emergent anti-PEG time point, and 23.2% of US-Neulasta treated patients showing one or more positive time points. For both CHS-1701 and US-Neulasta, the anti-PEG responses diminish over time in a similar progression, so that there were 9/122 positive = 7.3% positive subjects at the CHS-1701 P2D41 sampling, and 5/120=4.2% anti-PEG positives at the corresponding US-Neulasta P2D41 time point, which is the last sampling time point in the study. Overall, the

existing data indicates no obvious differences in anti-GCSF and anti-PEG responses between CHS-1701 and US-Neulasta treatments.

However, it should be noted that the Sponsor has only assessed titers for antibodies to the entire pegfilgrastim molecule (either CHS1701 or Neulasta) and has not measured specific titers for either anti-GCSF or anti-PEG responses. It would be more informative to have data for titers for ADA specific to anti-GCSF. A difference in anti-GCSF titers between CHS-1701 and US-Neulasta arms would suggest a potential difference in safety profiles via increased reactivity with endogenous GCSF.

Neutropenia

There were reports of neutropenia in both the immunogenicity study (CHS-1701-04) and the confirmatory crossover PK/PD study (CHS-1701-05). These reports are summarized in the following April 7, 2017 communication from Bindu Kanapuru, Clinical Reviewer for BLA 761039.

1. Study CHS-1701-04 (Immunogenicity)- No lab testing for neutrophils.

In the ADSL dataset Three (3) subjects in the CHS-1701 group and 2 additional subjects in the Neulasta group (all of whom were eligible for the study and were randomized, dosed, and completed.

Period 1) had ANC's at Day -1 of Period 2 below the $1.7 \times 10^9/L$ minimum (all Grade 2 neutropenia) that precluded redosing per protocol. Subjects (b) (6) (received CHS-1701) and subject (b) (6) (Neulasta) had positive ADA. (**BK Table 1**)

Subject	Treatment	Screening ANC	Completed Period 1	Period 1 Day 41/ Period 2 Day -1 ANC	Discontinuation category
(b) (6)	CHS-1701	$1.73 \times 10^9/L$	yes	$1.15 \times 10^9/L$	Protocol deviation
	CHS-1701	$3.10 \times 10^9/L$	yes	$1.30 \times 10^9/L$	Physician decision
	Neulasta	$2.00 \times 10^9/L$	yes	$1.20 \times 10^9/L$	Withdrawal by subject
	Neulasta	$4.68 \times 10^9/L$	yes	$1.28 \times 10^9/L$	Protocol deviation
	CHS-1701	$1.11 \times 10^9/La$	yes	$1.25 \times 10^9/L$	Protocol deviation

Reviewer comments

In a subsequent conversation with Dr. Kanapura, I clarified that the ANC data for the 5 subjects cited in the table immediately above (BK Table 1-my designation) was obtained because these individuals did not meet the study inclusion for the Lower Limit of Normal (LLN) of 1.7×10^9 neutrophils/liter. Dr. Kanapura noted that 1.7×10^9 is a high LLN, and

the actual measured values for these subjects, which were in the range $1.15-1.3 \times 10^9/L$, are not alarming. Otherwise, there are no ANC values for Study CHS-1701-04.

2. Study CHS 1701-05 (Confirmatory PK/PD). Lab testing included neutrophils. The numbers were very small for LLN and this was a cross over study. Attached is the table. (**BK Table 2**)

AVISIT	CHS-1701	Neulasta Dose 1	Neulasta Dose 2
Baseline	N=96 1(1.0)	N=111 5 (4.5)	N=78 4 (5.1)
Day 13	N=93 6 (6.5)	N=110 5 (4.5)	N=76 4 (5.3)

The following (*additional*) subjects were listed as not meeting ANC criteria for dosing in ADSL. Of these three received Neulasta in period 1 and 3 CHS-1701 and did not receive the period 2 dose. Two subjects received Neulasta in period 1 and period 2 but could not receive period 3 dose. 2 subjects who received Neulasta in period were ADA positive and 1 CHS -1701 period 1 subject was ADA positive.

Subjects (b) (6)

Reviewer comments

*In a subsequent conversation with Dr. Kanapuru, I clarified that the 8 subjects listed above are those that discontinued study CHS-1701-05. They are different from the subjects who completed the study, but who had lab ANC values less than the LLN of 1.7×10^9 at sometime during the study, as per Dr. Kanapuru’s second table (**BK Table 2-my designation**). In addition, Dr. Kanapuru stated that more extensive work would be required to extract the ANC values for neutropenia from the clinical reports for Study CHS-1701-05. However, Dr. Kanapuru did note that there were no safety signals for infections in either CHS-1701 or US-Neulasta arms of Studies CHS-1701-04 and CHS-1701-05, supporting the view that although neutropenia did occur to a limited extent, it was of a mild nature so that it did not impact subjects’ ability to fight infection. Therefore, I suggest that the ANC values for the incidents of neutropenia were likely in the “mild” range of $1-1.5 \times 10^9/L$ where risk of infection is minimal (<https://en.wikipedia.org/wiki/Neutropenia>)*

Appendix 3 G-CSF positive samples CHS-1701 and US-Neulasta arms

CHS-1701		P1D0	P1D13	P1D27	P1D41	P2D0	P2D13	P2D27	P2D41
CHS-1701 14/122 11.5%	(b) (6)	-	+	+	+	-	+	-	-
	(b) (6)	-	+	-	+	+	+	-	-
	(b) (6)	-	+	+	-	-	-	-	-
	(b) (6)	-	-	-	-	-	+	-	-
	(b) (6)	-	+	+	-	-	-	-	-
	(b) (6)	-	+	-	+	-	-	-	-
	(b) (6)	-	-	-	-	-	-	-	+
	(b) (6)	-	+	-	-	-	-	-	-
	(b) (6)	-	+	-	-	-	-	-	-
	(b) (6)	-	-	-	-	-	+	-	-
	(b) (6)	-	-	-	-	-	-	-	+
	(b) (6)	-	-	-	+	-	-	-	-
	(b) (6)	-	+	-	-	-	-	-	-
	(b) (6)	-	+	-	-	-	-	-	-
(b) (6)	+	+	-	-	-	-	-	-	
(b) (6)	+	-	-	-	-	-	-	-	
US-Neulasta		P1D0	P1D13	P1D27	P1D41	P2D0	P2D13	P2D27	P2D41
US-Neulasta 9/120 7.5%	(b) (6)	-	+	+	+	+	+	+	+
	(b) (6)	-	+	+	+	+	-	-	-
	(b) (6)	-	+	+	-	-	-	+	+
	(b) (6)	-	-	+	+	+	+	+	-
	(b) (6)	-	+	-	-	-	-	-	-
	(b) (6)	-	+	-	-	-	-	-	-
	(b) (6)	-	+	-	-	-	-	-	-
	(b) (6)	-	-	-	+	-	-	-	-
	(b) (6)	-	+	-	-	-	-	-	-

Appendix 5 PEG positive samples US-Neulasta arm

Neulasta	P1D1predose	P1D13	P1D27	P1D41	P2D1predose	P2D13	P2D27	P2D41
(b) (6)		+	+	+	+	+	+	+
		+	+		+	+	+	+
			+	+	+	+	+	+
		+	+	+	+	-	+	
		+	+	+	+	-	-	
		+	+	+	+	-	+	-
		+	+	+	+	-		
		+	+		+	-		
		+	+	+				+
		+	+	+	+		-	
		+	+	-	+	-		
		+	-	+	+	-	-	-
		+	-	+	+	-	-	-
		+				+	-	+
		-		-	-			
		-	+		+			
		-	-	+	+	-	-	
		+	+		-			
		+	-	+	-			-
		+						
		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
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		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
		+	-		-	-	-	-
		-	-	+	-			

US Neulasta
PEG positive
subjects
28/120=23.2%



Frederick
Mills

Digitally signed by Frederick Mills
Date: 5/23/2017 09:22:22AM
GUID: 508da6da0002654d90868d9b6af4ed79



Joslyn
Brunelle

Digitally signed by Joslyn Brunelle
Date: 5/22/2017 04:10:25PM
GUID: 508da6da000265eafdde3cc7507da20b



Joel
Welch

Digitally signed by Joel Welch
Date: 5/23/2017 09:43:50PM
GUID: 508da6dc0002673d83d264d81364d6cf



Haoheng
Yan

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Date: 5/23/2017 01:43:27PM
GUID: 54e4d29c0006b60003d1272740430bcc

BLA STN 761039

Product USAN name: TBD

CHS-1701

Manufacturer: Coherus BioSciences

Reviewer (Drug Substance): Ying-Xin Fan, Ph.D.

Team Leader: Joslyn Brunelle, Ph.D.

**Office of Biotechnology Products
Division of Biotechnology Review and Research IV**

OBP CMC Review Data Sheet

1. **BLA#:** STN 761039
2. **REVIEW DATE:** April 28, 2017
Revision Date: May 3, 2017
3. **PRIMARY REVIEW TEAM:**
 - Medical Officer:** Nicole Gormley, Clinical Team Leader
Bindu Kanapuru, Clinical Reviewer
 - Pharm/Tox:** Chris Sheth, Team Leader
Michael Manning, Reviewer
 - Product Quality Team:** Joslyn Brunelle, Product Quality Team Leader and
Application Technical Lead
Ying-Xin Fan, Drug Substance Reviewer
Jacek Cieslak, Drug Product and Analytical Similarity Reviewer
Haoheng Yan, Immunogenicity (assays)
Frederick Mills, Immunogenicity (clinical data)
 - BMT or Facilities:** Reyes Candau-Chancon, Microbiology Team Leader
Jessica Hankins, Drug Product Microbiology Reviewer
Monica Commerford, Drug Substance Microbiology Reviewer
Marion Michaelis, Facilities
 - Clinical Pharmacology:** Sarah Schrieber, Pharmacology Team Leader
Lanre Okusanya, Pharmacology Reviewer
 - Statistics:** Meiyu Shen and Yi Tsong, CMC Statistics Team Leader
Tianhua Wang, CMC Statistics
 - OBP Labeling:** Not finalized
 - RPM:** Natasha Kormanik and Beatrice Kallungal
4. **MAJOR GRMP DEADLINES**
 - Filing Meeting** September 28, 2016
 - Mid-Cycle Meeting:** January 17, 2017
 - Wrap-Up Meeting:** May 10, 2017
 - Primary Review Due:** May 5, 2017
 - Secondary Review Due:** May 12, 2017
 - CDTL Memo Due:**
 - PDUFA Action Date:** June 9, 2017
5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
BPD Type 4 Meeting	August 8, 2016
Filing Meeting	September 28, 2016
Information Request #1 (DS and DP)	November 29, 2016
Mid-cycle Meeting	January, 17, 2017
Information Request #2 (DS and DP)	February 16, 2017
Information Request #3 (DS and DP)	March 15, 2017
Planning Meeting	April 28, 2017
Wrap-up Meeting	May 10, 2017

6. **SUBMISSION(S) REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
Original	August 9, 2016
Amendment 2 (update per BPD Type 4 comments)	August 12, 2016
Amendment 4 & 5 (DS manufacturing schedule, details)	September 12, 2016; September 20, 2016
Amendment 6 & 7 (Response to filing deficiencies)	October 5, 2016
Amendment 12 (DP manufacturing schedule)	November 4, 2016
Amendment 14 (DS manufacturing schedule update)	November 7, 2016
Amendment 15 (DS manufacturing schedule)	November 14, 2016
Amendment 16 (Response to 74 day letter, Micro Info)	November 21, 2016
Amendment 17 (Analytical Similarity Assessment Info)	November 28, 2016
Amendment 22 (Micro Info)	December 15, 2016
Amendment 26 (Micro Info)	January 6, 2017
Amendment 29 (CDRH Info)	January 13, 2017
Amendment 32 (CDRH Info)	January 19, 2017
Amendments 33 & 34 (Micro & OBP Info)	January 30, 2017

Amendment 37 (OBP Info)	February 24, 2017
Amendment 40 (OBP Info)	March 21, 2017
Amendment 42 (Facilities Info)	April 3, 2017

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Udenyca
- b. Non-Proprietary/USAN: To be determined
- c. CAS name:
 - Colony-stimulating factor (human), 3-hydroxypropyl-N-methionyl-, 1-ether with a-methyl-w- hydroxypoly (oxy-1,2-ethanediyl)
 - CAS registry number: 208265-92-3
- d. Common name: Pegylated G-CSF
- e. INN Name:
- f. Compendial Name:
- g. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [CHS1701]
- h. Other Names: CHS-1701

8. **PHARMACOLOGICAL CATEGORY:** Leukocyte growth factor

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:** 6 mg/0.6 mL (cell proliferation potency assay)

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

12. **REFERENCED MASTER FILES:**

DMF # Type	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b) (4)	Yes	None
			Yes	None
			Yes	None

13. INSPECTIONAL ACTIVITIES

The pre-license inspection of the KBI Biopharma, Inc. drug substance manufacturing site in Boulder, CO, was conducted from December 5th to December 9th, 2016 and was classified VAI. The inspection team consisted of Monica Commerford, Ph.D. (OPQ/OPF/DMA – Lead), Diane Raccasi (ORA), Marion Michaelis (OPQ/OPF/DIA), Michele Dougherty, Ph.D. (OPQ/OBP), Ying-Xin Fan, Ph.D. (OPQ/OBP), and Andrea Franco, Ph.D. (OPQ/OBP).

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

15. PRECEDENTS

None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Joel Welch, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV	<i>Captured in Panorama</i>
Joslyn Brunelle, Ph.D. Team Leader and Application Technical Lead Division of Biotechnology Review and Research IV	<i>Captured in Panorama</i>
Ying-Xin Fan, Ph.D. Primary Reviewer (Drug Substance) Division of Biotechnology Review and Research IV	<i>Captured in Panorama</i>

B. CC Block

Recipient	Date
Clinical Division BLA RPM	
Division of Biotechnology Research and Review IV File/BLA STN 761039	

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SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

I do not recommend approval of this 351(k) BLA application for CHS-1701 as a biosimilar to US-licensed Neulasta from the Drug Substance quality perspective because of the deficiencies listed below.

II. List Of Deficiencies To Be Communicated

The following deficiencies were identified regarding manufacture and control of Drug Substance:

1. Description of Manufacturing Process

- a)  (b) (4)
- b)
- c)
- d)
- e)

- f)  (b) (4)

2. Control of Material

- a)  (b) (4)
- b)
- c)
- d)

3. Control of Critical Steps and Intermediates

-  (b) (4)

4. Process Validation

- a)  (b) (4)
- b)
- c)
- d)

5. Characterization

Incomplete data for potency evaluation in the forced degradation study

6. Control of CHS-1701 Drug Substance (Also reflected in the review by J. Cieslak)

- a) Insufficient information regarding the change in reverse phase chromatography (RPC) method over the course of development from Method A (or compendial method) to Method B (or commercial method):
 - i. Data to compare Method A and B was not provided
 - ii. Insufficient data to support proposed RPC specifications
 - iii. No acceptance criteria for deamidated species by RPC
 - iv. Insufficient information regarding Method B sensitivity to detect and quantify oxidized species
 - v. Incomplete method validation for RPC Method B (robustness and accuracy)
 - vi. Lack of information to specify which RPC method (A or B) was used in studies supporting BLA application
 - b) Inadequate approach to establish specifications for purity methods
 - c) Missing data for impurity peaks and chromatograms for purity methods including RPC, SEC, and CEC
 - d) Inconsistency information on impurities measured by SEC
 - e) Inappropriate acceptance criterion for host cell protein in unPEGylated product
 - f) Missing information in the method validation report for the ELISA for Host Cell Proteins (accuracy, precision, specificity)
7. Reference Standards (RS) or Materials
- a) Inadequate information for future reference standard qualification
 - i) Inappropriate acceptance criteria for purity of PEGylated RS tested by RPC, SEC, and CEC
 - ii) Insufficient information for the statistical method used for the comparability assessment of future and current RS lots
 - iii) Lack of information on approach to the assignment of potency as 100% for future RS
 - iv) Lack of information on procedure for the potency calibration against the international standards
 - b) Insufficient information for RS retest
8. DS Stability
- a) Exclusion of CEC method in post-approval stability protocol for Drug Substance
 - b) Missing data for impurity peaks from RPC, SEC, and CEC analyses in the stability data
 - c) Insufficient stability data to support the proposed DS expiry periods
9. Additional comments not considered as CR deficiencies
- a) Poor quality of the BLA
 - b) Clarification that no more than (b) (4)
 - c) Revision of the operation (b) (4)
 - d) No data/report provide for MCB, WCB, EOPCBs testing
 - e) Clarification of long term strategy for establishing a secondary reference standard
 - f) Advise for qualification of new lots of ELISA kit used for Drug Substance release

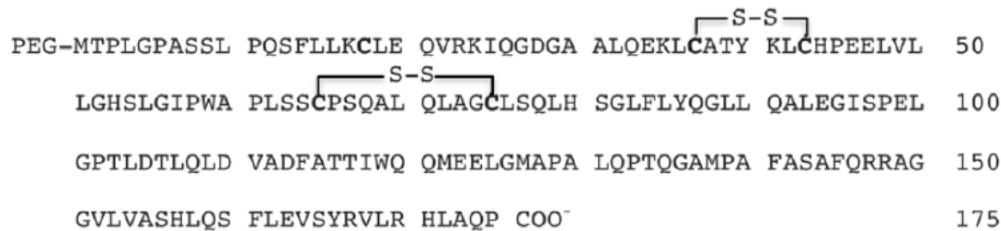
DESCRIPTION OF DRUG SUBSTANCE

S. DRUG SUBSTANCE (DS)

3.2. S.1.2 Structure

The active component of CHS-1701 (UDENYCA, pegfilgrastim-^{(b) (4)}) is a covalent conjugate of recombinant methionyl human G-CSF (referred as to Coherus r-met-Hu-G-CSF) and monomethoxypolyethylene glycol (PEG). The amino-acid sequence for G-CSF is shown in Figure 1 below:

Figure 1: Amino Acid Sequence for Coherus r-met-Hu-G-CSF



Coherus r-met-Hu-G-CSF is expressed in ^{(b) (4)} *E. coli* cells. Compared to the human derived G-CSF, *E. coli* manufactured Coherus r-met-Hu-G-CSF has an additional amino-terminal methionine and the single chain polypeptide is not glycosylated. The G-CSF moiety is a single chain 175 amino-acid polypeptide with a theoretical molecular weight of 18799 Da. The G-CSF molecule contains five cysteine residues, four of which form disulfide bonds (between residues 37 and 43; 65 and 75). An approximately 20 kDa PEG group is attached to the amino terminus of G-CSF to form CHS-1701, which has a theoretical molecular weight of 39 kDa.

3.2. S.1.3 General Properties

CHS-1701 is formulated at ^{(b) (4)}. The formulation composition is the same as for the reference product, US-Neulasta. The density of CHS-1701 was determined to be 1.0176 g/mL. The extinction coefficient $\epsilon_{0.1\%}^{280}$ nm used in CHS-1701 concentration measurements is based only on protein weight and measures only the protein (Coherus r-met-Hu-G-CSF) content. An extinction coefficient of 0.86 mg⁻¹ mL cm⁻¹ was assigned to ^{(b) (4)} PEGylated DS. The physicochemical, biological and immunological properties and other relevant properties of CHS-1701 are summarized in Table 3 (copied from the submission).

Table 3: General Properties of pegfilgrastim- (b) (4)

Property	Description
Physicochemical properties	
Physical form	(b) (4)
Color	(b) (4)
Clarity	(b) (4)
pH	(b) (4)
Isoelectric point	Major peak at pI 6.3 (with no quantifiable minor peaks)
Structural characteristics	
Relative molecular weight	Theoretical molecular weight is ~ 39 kDa, This value is consistent with the result of 39.3 kDa by the on-line light scattering analysis (SEC-MALS)
Secondary and tertiary structure (determined by circular dichroism)	Secondary and tertiary structure is consistent with the reference product, Neulasta (US)
Biological properties	
Binding activity (determined by surface plasmon resonance analysis)	Binds to human G-CSF receptor, with a binding affinity constant (K_D) of approximately 90-130 pM
Potency assay (determined by NFS-60 cell proliferation assay)	Biological activity monitored by inducing proliferation of NFS-60 cells (a murine myeloblastic cell line infected with Cas Br-M murine leukemia virus which is dependent on G-CSF for growth). Activity is consistent with the reference product, Neulasta (US)

3.2.S.2 Manufacture

3.2. S.2.1 Manufacturer(s)

(b) (4)



Ying Xin
Fan

Digitally signed by Ying Xin Fan
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Joslyn
Brunelle

Digitally signed by Joslyn Brunelle
Date: 5/23/2017 10:12:55AM
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Joel
Welch

Digitally signed by Joel Welch
Date: 5/23/2017 09:43:31PM
GUID: 508da6dc0002673d83d264d81364d6cf

BLA STN 761039

Product USAN name: TBD

CHS-1701

Manufacturer: Coherus BioSciences

Reviewer: Jacek Cieslak, Ph.D.

Team Leader: Joslyn Brunelle, Ph.D.

**Office of Biotechnology Products
Division of Biotechnology Review and Research IV**

OBP CMC Review Data Sheet

1. **BLA#:** STN 761039

2. **REVIEW DATE:** April 21, 2017
Revision Date: May 3, 2017

3. **PRIMARY REVIEW TEAM:**
 - Medical Officer:** Nicole Gormley, Clinical Team Leader
Bindu Kanapuru, Clinical Reviewer
 - Pharm/Tox:** Chris Sheth, Team Leader
Michael Manning, Reviewer

 - Product Quality Team:** Joslyn Brunelle, Product Quality Team Leader and
Application Technical Lead
Ying-Xin Fan, Drug Substance Reviewer
Jacek Cieslak, Drug Product and Analytical Similarity Reviewer
Haoheng Yan, Immunogenicity (assays)
Frederick Mills, Immunogenicity (clinical data)

 - BMT or Facilities:** Reyes Candau-Chancon, Microbiology Team Leader
Jessica Hankins, Drug Product Microbiology Reviewer
Monica Commerford, Drug Substance Microbiology Reviewer
Marion Michaelis, Facilities

 - Clinical Pharmacology:** Sarah Schrieber, Pharmacology Team Leader
Lanre Okusanya, Pharmacology Reviewer

 - Statistics:** Meiyu Shen and Yi Tsong, CMC Statistics Team Leader
Tianhua Wang, CMC Statistics

 - OBP Labeling:** No labeling review performed
 - RPM:** Natasha Kormanik and Beatrice Kallungal

4. **MAJOR GRMP DEADLINES**
 - Filing Meeting** September 28, 2016
 - Mid-Cycle Meeting:** January 17, 2017
 - Wrap-Up Meeting:** May 10, 2017
 - Primary Review Due:** May 5, 2017
 - Secondary Review Due:** May 12, 2017
 - CDTL Memo Due:**
 - PDUFA Action Date:** June 9, 2017

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date

BPD Type 4 Meeting	August 8, 2016
Filing Meeting	September 28, 2016
Information Request #1 (DS and DP)	November 29, 2016
Mid-cycle Meeting	January, 17, 2017
Information Request #2 (DS and DP)	February 16, 2017
Information Request #3 (DS and DP)	March 15, 2017
Planning Meeting	April 28, 2017
Wrap-up Meeting	May 10, 2017

6. **SUBMISSION(S) REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
Original	August 9, 2016
Amendment 2 (update per BPD Type 4 comments)	August 12, 2016
Amendment 4 & 5 (DS manufacturing schedule, details)	September 12, 2016; September 20, 2016
Amendment 6 & 7 (Response to filing deficiencies)	October 5, 2016
Amendment 12 (DP manufacturing schedule)	November 4, 2016
Amendment 14 (DS manufacturing schedule update)	November 7, 2016
Amendment 15 (DS manufacturing schedule)	November 14, 2016
Amendment 16 (Response to 74 day letter, Micro Info)	November 21, 2016
Amendment 17 (Analytical Similarity Assessment Info)	November 28, 2016
Amendment 22 (Micro Info)	December 15, 2016
Amendment 26 (Micro Info)	January 6, 2017
Amendment 29 (CDRH Info)	January 13, 2017
Amendment 32 (CDRH Info)	January 19, 2017
Amendments 33 & 34 (Micro & OBP Info)	January 30, 2017
Amendment 37 (OBP Info)	February 24, 2017
Amendment 40 (OBP Info)	March 21, 2017

Amendment 42 (Facilities Info)	April 3, 2017

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Udenyca
- b. Trade Name:
- c. Non-Proprietary/USAN: To be determined
- d. CAS name:
 - Colony-stimulating factor (human), 3-hydroxypropyl-N-methionyl-, 1-ether with a-methyl-w- hydroxypoly (oxy-1,2-ethanediyl)
 - CAS registry number: 208265-92-3
- e. Common name:
- f. INN Name:
- g. Compendial Name:
- h. OBP systematic name: CONJ: RPROT P09919 (CSF3_HUMAN); PEG [CHS1701]
- i. Other Names: CHS-1701

8. **PHARMACOLOGICAL CATEGORY:** Leukocyte growth factor

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:** 6 mg/0.6 mL (cell proliferation potency assay)

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	None
			Yes	None
			Yes	None

13. INSPECTIONAL ACTIVITIES

The inspection of the drug product manufacturing and testing facility, (b) (4) was conducted (b) (4) by CDER-DIA and was classified VAI. The facility was approved based on the inspectional assessment.

The inspection of the medical device manufacturer Coherus BioSciences, Inc. was conducted March 13-16, 2017 by San Francisco FDA District Office and was classified NAI.

14. CONSULTS REQUESTED BY OBP

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CDRH ODE	December 19, 2016	completed	Adequate	Keith Marin/ Alan Stevens
CDRH OC	November 18, 2016	completed	Adequate	Rakhi Dalal/Francisco Vicenty

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

☐	Design Space
☐	Design of Experiments
☐	Formal Risk Assessment / Risk Management
☐	Multivariate Statistical Process Control
☐	Process Analytical Technology
☐	Expanded Change Protocol

15. PRECEDENTS

None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Joel Welch, Ph.D. Acting Review Chief Division of Biotechnology Review and Research IV	<i>Captured in Panorama</i>

Joslyn Brunelle, Ph.D. Team Leader and Application Technical Lead Division of Biotechnology Review and Research IV	<i>Captured in Panorama</i>
Jacek Cieslak, Ph.D. Primary Reviewer (Drug Product, Analytical Similarity Assessment) Division of Biotechnology Review and Research IV	<i>Captured in Panorama</i>

B. CC Block

Recipient	Date
Clinical Division BLA RPM	
Division of Monoclonal Antibodies/Therapeutic Proteins File/BLA STN XXXXXX	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

I do not recommend approval of this 351(k) BLA application for CHS-1701 (Udenyca) as a biosimilar to US-licensed Neulasta for the reasons listed below.

II. List Of Deficiencies To Be Communicated

The following deficiencies were identified regarding manufacturing process and control strategy:

1. CHS-1701 drug product specifications
 - a) Insufficient information regarding the reverse phase chromatography (RPC) method that was changed over the course of development from Method A (or compendial method) to Method B (or commercial method):
 - i. Data to bridge Method A and B was not provided
 - ii. Insufficient data to support proposed RPC specifications
 - iii. No acceptance criteria for deamidated species by RPC
 - iv. Insufficient information regarding Method B sensitivity to detect and quantify oxidized species
 - v. Incomplete method validation for RPC Method B (robustness and accuracy)
 - vi. Specify which RPC method (A or B) was used in studies supporting BLA application
 - b) Inadequate approach to establish specifications for purity methods
 - c) Missing chromatograms for purity methods including RPC, SEC, and CEC
 - d) Inadequate description of impurities measured by CEC
2. CHS-1701 drug product process validation
 - a) Missing process validation data for PPQ lot 2372-115
 - b) Inadequate evaluation of critical and non-critical manufacturing process parameters
3. CHS-1701 drug product control
 - a) Insufficient data for subvisible particles in the range 2-10 microns
4. CHS-1701 drug product stability
 - a) Insufficient information to establish product expiry
 - b) Insufficient data to support product potency after freezing

The following deficiency was identified during the evaluation of analytical similarity assessment between CHS-1701 and US-licensed Neulasta:

5. Potency assay was not included in forced degradation studies
6. Potency data for US-licensed Neulasta lot 1054829 was not included

Refer to the Integrated Quality Assessment for detailed Complete Response comments.

III. List Of Post-Marketing Commitments/Requirement

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

V. Primary Container Labeling Review

No labeling review performed at this time.

VI. Review Of Common Technical Document-Quality Module 3.2

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Refer to review by Haoheng Yan

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The CHS-1701 drug product 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 CHS-1701 drug product (DP), in a sterile, clear, colorless, preservative-free isotonic solution. The protein is formulated in (b) (4), (b) (4) sorbitol, and (b) (4) polysorbate 20, pH 4.0. It is provided at a single strength using the same formulation as that of the reference product, US-licensed Neulasta.¹

Each PFS of CHS-1701 contains 10 mg/mL CHS-1701 DP in 0.6 mL solution for injection, designed to deliver a dose of 6 mg. The overfill in the PFS is intended to ensure that the intended therapeutic dose of CHS-1701 DP is delivered in the 0.6 mL injection and reflects the comparable overfill of the PFS units of the reference product, US-licensed Neulasta.

The nominal composition of CHS-1701 drug product, 10 mg/mL, is provided in Table 1.

Table 1: Composition of the Drug Product

Ingredients	Composition per dose		Function	Compendial Reference
	Quantity per syringe	Concentration		
Active				
CHS-1701 DP	6 mg	10 mg/ml	Active substance	In house specification
Excipients				
(b) (4) a	(b) (4) mg	(b) (4)	(b) (4)	Ph. Eur., JP, BP, USP
(b) (4)	(b) (4) mg	(b) (4)	(b) (4)	Ph. Eur., JP, BP, USP
Sorbitol	30 mg	(b) (4)	(b) (4)	Ph. Eur., JP, BP, NF
Polysorbate 20	0.02 (b) (4) mg	(b) (4)	(b) (4)	Ph. Eur., JP, BP, NF
WFI	q.s.	q.s.	(b) (4)	USP, Ph. Eur.

* Total acetate content per syringe is equivalent to 0.35 mg

† Total sodium content per syringe is equivalent to 0.02 mg

Key: q.s. = quantum satis. WFI = Water For Injection

Reviewer comment:

The tables included in this memo were copied/adapted from the BLA submission unless specified otherwise.

¹ US-Neulasta Label. Revised April 2016. Accessed by Drugs@FDA.

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

3.2.R.4 Analytical similarity assessment

Data presented and discussed in this section of the review memo was provided by Coherus in order to attempt to demonstrate that CHS-1701 drug product is highly similar to the reference product, US-licensed Neulasta. To this end, a comparative step wise approach was initiated including extensive structural and functional characterization of the proposed biosimilar and the reference product. This analysis was conducted through a comprehensive analysis and characterization of critical quality attributes.

The sponsor performed this study comparing 13 lots of the proposed biosimilar CHS-1701 to 22 lots of US-licensed Neulasta when evaluating attributes assessed using a Tier 1 statistical method. Smaller number of lots was used when tier 2 and 3 statistical methods were employed. Detailed information regarding the exact number of the proposed biosimilar and the reference product will be provided in the respective section discussing the results of the similarity assessment for each particular method/attribute. Considering the definition of similarity, the goal was to demonstrate that CHS-1701 is highly similar to the reference product notwithstanding minor differences in clinically inactive components. This analytical similarity study is complemented by comparative PK, PD and immunogenicity studies performed to demonstrate that there are no clinically meaningful differences between the two products in terms of safety, purity and potency.

The analytical similarity assessment includes evaluations of primary, secondary, and tertiary structure, as well as product variant profiles, post-translational modifications, impurities, potency, and includes but is not limited to:

- Primary structure, such as amino acid sequence and disulfide bridges
- Higher order structures, including secondary and tertiary structure
- Other potential variations, such as protein deamidation and oxidation
- Chemical modifications, such as PEGylation

Per Agency recommendation, a tiered approach was used when comparing both product and the tier assignment was based on the criticality risk ranking and method capabilities.

The sponsor stated that some attributes have previously been evaluated in smaller analytical similarity studies to establish the quality targets and associated margins. However, for the purpose of the definitive similarity study, all lots were newly analyzed per protocol, with CHS-1701 lots and US-licensed Neulasta lots analyzed in parallel whenever possible. The results reported below stem from the final definitive similarity analyses.

Reviewer comment:

The overall plan to demonstrate analytical similarity between the proposed biosimilar and the reference product using the tiered approach and including the evaluations of primary, secondary, and tertiary structure, product variants, post-translational modifications, impurities, and potency/activity is acceptable. The sponsor stated that the analytical similarity assessment was performed per protocol; however the protocol itself was not included in the BLA application. This is acceptable because the data demonstrating similarity of the proposed biosimilar to the reference product was provided. It is also acceptable not to include initial studies designed to establish the quality targets as long as there is sufficient data provided in the final definitive similarity assessment to make a proper evaluation of the analytical similarity study.

Analytical similarity – lot selection:

The sponsor performed the analytical similarity assessment using 13 DP lots of CHS-1701 excluding 6 DP lots (1701-DP-107, 1701-DP-108, 1701-DP-109, 1701-DP-110, 1701-DP-116, and 1701-DP-121). The reasons for exclusion, as provided by the sponsor upon the Agency request, were that these lots were repeat fills of the parent drug substance lots or fills of pooled DS lots. Therefore, these lots are not considered fully independent lots and were not applicable for use in the analytical similarity studies. In addition to those lots, a toxicology lot was also excluded from the analytical similarity assessment due to the fact that a different manufacturing process was used to produce this lot (the tox lot was still found comparable to the first clinical lot 1-FIN-1501) and the Agency agreed with this plan before the BLA was submitted [refer to IND 115573 Type 2 meeting held on September 29, 2015].

Similarly, not all 22 US-licensed Neulasta lots were included in the assessment of all product quality attributes. The sponsor provided an explanation that in certain cases only limited quantities were available for analytical evaluation of some of the reference product lots acquired early in the development of the similarity program (such as lots 1042866 and 1047431) and two of the lots used in clinical studies (lots 1048834 and 1054829). In these cases, care was taken to ensure inclusion of the limited supply lots in Tier 1 analyses requiring statistical equivalence testing for the demonstration of analytical similarity where possible, although there was insufficient material available for potency assessment of one lot (lot 1054829). At the time of testing, specifically for the 22nd US-licensed Neulasta lot (lot 1054829) care was taken to ensure inclusion of the limited supply batch in Tier 1 analyses, where possible. Analyses requiring quality-range analysis (Tier 2) were performed on all lots where material availability permitted. However, there was insufficient material available for MFI (lot 1042866, 1047431, and 1048834) and receptor binding by SPR (1042866 and 1047431), due to material requirements for these tests. Testing for Tier 3 attributes were performed on a large number of representative lots, but were only included when sufficient quantities of reference product were available after most of the Tier 1 and Tier 2 analyses were performed.

Reviewer comment:

Justifications provided by the sponsor for not using all manufactured proposed biosimilar lots in the analytical similarity assessment are acceptable. The repeat fills of the parent drug substance lots may in fact lead to artificially inflating the number of the proposed biosimilar lots and not truly represent the consistency of the manufacturing process. Moreover, these lots are also labelled as development lots and in some cases may or may not be truly representative of the commercial manufacturing process. It is also understandable, that there are limitations associated with the acquisition of sufficient quantities of the reference product and in some cases that may lead to insufficient quantities of the reference product for testing of quality attributes where significant product quantities are required. The justification for not including all 22 lots of reference product in the analytical similarity assessment is also acceptable.

The sponsor provided qualification reports for all methods used in the analytical similarity assessment. For attributes assessed using a Tier 1 statistical test, potency was assessed using a validated method and protein content was assessed using a characterization method. The qualification report for protein concentration by UV spectrophotometry included an assessment of accuracy, precision, linearity, and specificity.

For attributes assessed using a Tier 2 statistical test, qualification reports were provided for SEC, CEC, and SPR methods; validation report was provided for RPC. The qualification of purity methods SEC and CEC included an assessment for accuracy, precision, linearity and

specificity, LOQ and LOD. Specificity and precision of SPR (binding) method were evaluated; precision and linearity were evaluated for MFI method. All methods used in the analytical similarity assessment were reviewed and were found acceptable for their intended purpose and inclusion in the analytical similarity assessment of CHS-1701 and US-licensed Neulasta.

The sponsor provided detailed information regarding the age of CHS-1701 and US-licensed Neulasta lots used in the analytical similarity study.

Table 1: CHS-1701 Drug Product Lots Used to Demonstrate Analytical Similarity

CMO Lot number (CHS Lot Number)	CMO Parent DS Lot Number (CHS Lot Number)	Use	Date of DS Manufacture	Date of DP Manufacture	Approximate age at testing, months
2372-102 (1701-DP-103)	169A14-02 (1701-DS-103)	Clinical Trials CHS-1701-03 and CHS-1701-04, Analytical Similarity, Stability	30 Nov 2014	04 Dec 2014	4
2372-103 (1701-DP-104)	169A15-07 (1701-DS-104)	Clinical Trial CHS- 1701-05, Analytical Similarity, Stability	08 Feb 2015	20 Mar 2015	0
2372-104 (1701-DP-105)	169A15-08 (1701-DS-105)	Analytical Similarity, Stability	21 Feb 2015	25 Mar 2015	0
2372-105 (1701-DP-106)	169A15-09 (1701-DS-106)	Analytical Similarity, Stability	07 Mar 2015	31 Mar 2015	0
2372-110 (1701-DP-111)	169A15-14 (1701-DS-107)	Analytical Similarity, DP PPQ, Stability	11 Jul 2015	05 Aug 2015	2
2372-111 (1701-DP-112)	169A15-15 (1701-DS-108)	Analytical Similarity, DP PPQ, Stability	26 Jul 2015	14 Aug 2015	2
2372-112 (1701-DP-113)	169A15-16 (1701-DS-109)	Analytical Similarity, DP PPQ, Stability	08 Aug 2015	01 Sep 2015	1
2372-113 (1701-DP-114)	169A15-17 (1701-DS-110)	Analytical Similarity	22 Aug 2015	28 Sep 2015	0
2372-114 (1701-DP-115)	169A15-19 (1701-DS-111)	Analytical Similarity	14 Sep 2015	05 Oct 2015	0
2372-116 (1701-DP-117)	169A15-21 (1701-DS-112)	Analytical Similarity	27 Oct 2015	04 Nov 2015	2
2372-117 (1701-DP-118)	169A15-22 (1701-DS-113)	Analytical Similarity	10 Nov 2015	20 Nov 2015	1
2372-118 (1701-DP-119)	169A15-23 (1701-DS-114)	Analytical Similarity	24 Nov 2015	12 Jan 2016	0
2372-119 (1701-DP-120)	169A15-24 (1701-DS-115)	Analytical Similarity	08 Dec 2015	14 Jan 2016	0

Reviewer comment:

During the review process it was found that drug product lots 2372-116 through 2372-119 are not fully independent lots. Drug substance manufacturing scheme allows

(b) (4)



(b) (4)
 represents the actual manufacturing scheme for CHS-1701 drug product manufacture, thus these independent lots are representative of the manufacturing (commercial) process. Overall, 13 lots of the proposed biosimilar were included in tier 1 (statistical equivalence testing) and according to the sponsor all CHS-1701 lots were manufactured using different lots of mPEG aldehyde.

Reviewer assessment:

Inclusion of lots 2372-116 through 2372-119 in the analytical similarity assessment may be considered appropriate because the primary variability of the tier 1 attributes (potency and protein content) will likely come from the (b) (4) of manufacturing process (b) (4). The (b) (4) process will introduce some level of product variability; however, the majority of variability observed in the drug product will likely be attributed to (b) (4) steps (including those attributes that are monitored by tier 1 methods). In conclusion, selection of the CHS-1701 lots used in the analytical similarity assessment is acceptable.

Reference product lots are presented in Table 3. Expiry dates for the reference product lots (and thus manufacturing dates) cover a range of approximately two years. Due to inventory and distribution logistics for the reference product, each lot is expected to be several months into expiry dating at time of sourcing and only an approximate age is provided. For these reasons, analysis of US-licensed Neulasta early in its shelf life was not possible.

Table 3: Reference Product, US-licensed Neulasta Drug Product Lots Used In Analytical Similarity Assessment

Lot Number	Use	Date of Expiry	Approximate Age at Time of Testing, months
1040882	Analytical Similarity	May 2016	23
1042866	Analytical Similarity	June 2016	22
1047431	Analytical Similarity	February 2017	14
1047434	Analytical Similarity	March 2017	13
1048085	Clinical trials CHS-1701-03, CHS-1701-04 and Analytical Similarity	July 2016	21
1048834	Clinical trials CHS-1701-03 and CHS-1701-04, Analytical Similarity	February 2017	14
1050019	Analytical Similarity	June 2017	10
1051304	Analytical Similarity	May 2017	11
1051676	Analytical Similarity	February 2017	14
1054829	Clinical trial CHS-1701-04, Analytical Similarity	July 2017	15
1053071	Analytical Similarity	August 2017	8
1053082	Analytical Similarity	July 2017	9
1057095	Analytical Similarity	September 2017	13
1053081	Analytical Similarity	September 2017	13
1053956	Analytical Similarity	September 2017	13
1055572	Clinical trial CHS-1701-04, Analytical Similarity	October 2017	12
1057096	Clinical trial CHS-1701-04, Analytical Similarity	November 2017	11
1057133	Analytical Similarity	October 2017	12

1056717	Analytical Similarity	November 2017	14
1057097	Analytical Similarity	February 2018	11
1057373	Clinical trial CHS-1701-04, Analytical Similarity	January 2018	12
1059900	Clinical trial CHS-1701-05, Analytical Similarity	April 2018	9

Reviewer assessment:

The number and selection of CHS-1701 lots are acceptable as they are representative of the commercial process and are manufactured from different drug substance lots. The selection of US-licensed Neulasta lots is also acceptable as it covers a relatively long timeframe (15 months) that is sufficient to capture potential manufacturing variations of the reference product. Selection of the US-licensed Neulasta lots used in the analytical similarity assessment is acceptable.

Criticality Assessment

The sponsor assigned the quality attributes and methods to individual tiers (Tier 1, 2, or 3) based on an assessment of criticality risk ranking in conjunction with the quantitative versus qualitative nature of the data. Attributes that could potentially impact biological activity, PK and/or PD, safety, or immunogenicity (i.e. high clinical impact) were assigned high relevance. In addition to consideration of clinical impact, a meaningful assessment as to whether the proposed product is highly similar to the reference product depends on the capabilities of available state-of-the-art analytical assays to assess individual attributes with suitable sensitivity and accuracy. Therefore, other criteria that were considered in assigning attributes and methods to a tier included assay sensitivity and variability, and where applicable, the relative abundance of the measured variant. This assessment defines criticality with respect to similarity only.

- Tier 1 includes assays that evaluate the clinically relevant mechanism(s) of action with a high level of precision and accuracy. For Tier 1 attributes, statistical equivalence testing was performed to demonstrate similarity, except for primary structure, where an identity match was confirmed.
- Tier 2 contains assays with lower risk ranking, specifically those measuring attributes that impact clinical function only indirectly, those with lower levels of precision or those measuring species present in low abundance. Similarity for these attributes will be assessed based on quality ranges. For certain attributes, such as HMW species, unPEGylated species and PEG polydispersity by SEC-MALS, total oxidized and deamidated species by RPC, diPEGylated species by CEC and SVPs one-sided ranges were used. For others, such as molar mass, mass of PEG conjugate, receptor binding two-sided ranges were defined.
- Tier 3 contains attributes that are evaluated based on qualitative results or attributes of low criticality. Similarity will be assessed by comparisons of images or graphical representations of the raw data. No statistical analysis will be performed for tier 3 attributes due to the qualitative nature of the data.

Attribute/method assignment to a tier 1, 2, or 3 is provided in the table below.

Table 5: Attributes Risk and Tier Ranking for Similarity Assessment

Biological Function	Attribute	Method	Rationale for Tier Assignment			Tier
			Clinical Relevance	Analytical Capability	Relative Abundance of species measured	
Efficacy and Immunogenicity	Primary structure (including amino acid sequence and disulfide structure)	Peptide map by Glu-C digest with LC-MS/MS	high	high	main	NA ^a
Efficacy	Biological activity (percent potency)	Proliferative bioassay	high	high	main	1
Efficacy	Protein Content	UV	high	high	main	1
Efficacy	Receptor binding (K _D)	SPR	high	low	main	2
Efficacy	Molar mass (kDa)	SEC-MALS	medium	medium	main	2
Efficacy	Mass (Mw) of PEG conjugate (kDa)	SEC-MALS	medium	medium	main	2
Efficacy	PEG polydispersity (Pd)	SEC-MALS	low	medium	main	2
Efficacy	PEG polydispersity (Pd)	LC-MS	low	medium	main	3
Efficacy and immunogenicity	HMW species (including dimer/diPEG, oligomers) (percent area)	SEC-MALS	low-high	medium	minor	2
Efficacy and Immunogenicity	HMW species (including dimers/diPEG, and oligomers)	SDS-PAGE	low-high	low	minor	3
Efficacy and immunogenicity	unPEGylated filgrastim	SEC	low	medium	minor	3
Efficacy and Immunogenicity	Clips	SEC	medium	medium	below LOQ	3
Efficacy and Immunogenicity	Clips	SDS-PAGE	medium	low	below LOQ	3
Efficacy	diPEGylated species (percent area)	CEC	low-medium	medium	minor	2
Efficacy and immunogenicity	Total oxidized species (percent area)	RPC	low-high	medium	minor	2
Efficacy and immunogenicity	Total deamidated species (percent area)	RPC	low	medium	minor	2
Efficacy and Immunogenicity	Partially reduced species	RPC	medium	low	below LOQ	3
Efficacy and immunogenicity	Norleucine misincorporation	RPC	medium	medium	below LOQ	3
Immunogenicity	SVPs ≥ 2 μm (total counts/mL)	MFI	high	medium	minor	2
Efficacy	Intact mass and PEG linker analysis	LC-MS	medium	medium	main	3 ^b
Efficacy and immunogenicity	unPEGylated N-terminus	Edman degradation	low	low	main	3
Efficacy and immunogenicity	free PEG	SDS-PAGE with iodine Stain	low	low	below LOD	3
Efficacy and immunogenicity	Secondary/tertiary structure	CD, 2D NMR, DSC, fluorescence, HDX	medium	low	main	3
Efficacy	Extinction coefficient	SEC-UV-RI	low	medium	main	3
Immunogenicity	HCPs	ELISA by Cygnus kit	medium	low	below LOQ	3
Immunogenicity	Total protein pattern, including all impurities and HCPs	2D gels with silver stain	medium	low	minor	3
Efficacy and immunogenicity	Size profile: Sedimentation Behavior	AUC	low	low	main	3
Efficacy and immunogenicity	Charge profile	IEF gel	low	low	NA	3
Immunogenicity	Clarity	Turbidimetry	low	low	NA	3
Immunogenicity	Color	Visual inspection	low	low	NA	3

NA = not applicable; LOD = limit of detection; LOQ = limit of quantitation

^aThe result of this test not quantitative and therefore does not lend itself to statistical evaluation. Must be identical.

^bStatistical evaluation in Tier 2 not feasible.

Reviewer comment:

The tier assignment proposed by the sponsor appears appropriate. Classification of product quality attributes was done according to clinical relevance and analytical capability of the method used to assess an attribute. Tier 1 attributes (potency and protein content) were the subject of statistical analysis by the sponsor and the FDA review staff (statistical equivalence testing).

Reviewer assessment:

The selection of analytical methods used by the sponsor to evaluate the quality attributes of CHS-1701 and US-licensed Neulasta is acceptable. A comprehensive analytical similarity assessment was proposed to compare the structure and function of CHS-1701 and US-licensed Neulasta. The applicant has employed a large number of highly sensitive methods to characterize structural and functional similarities and differences between CHS-1701 and the reference product to support the demonstration that CHS-1701 is highly similar to US-licensed Neulasta.

Statistical evaluation of the tiered approach to assess the similarity

The general method of statistical equivalence testing using an equivalence acceptance criterion (EAC) for Tier 1 attributes and quality ranges for Tier 2 attributes is consistent with Agency advice received in the BPD Type 2 meetings. Specifically:

- For Tier 1 attributes, similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for CHS-1701 and US-licensed Neulasta is within the EAC of $(-1.5 \sigma, +1.5 \sigma)$ based on the standard deviation (σ) calculated from all US-licensed Neulasta lots
- For Tier 2 attributes, similarity is demonstrated if at least 12 out of 13 lots of CHS-1701 are within the one-sided $+1.9 \sigma$ limit or two-sided 2.3σ limits, as appropriate, where the standard deviation is estimated from concurrent testing of US-licensed Neulasta lots
- No statistical analysis was performed for Tier 3 attributes due to the qualitative nature of the data. Instead, the results were evaluated by qualitative comparison.

Reviewer comment:

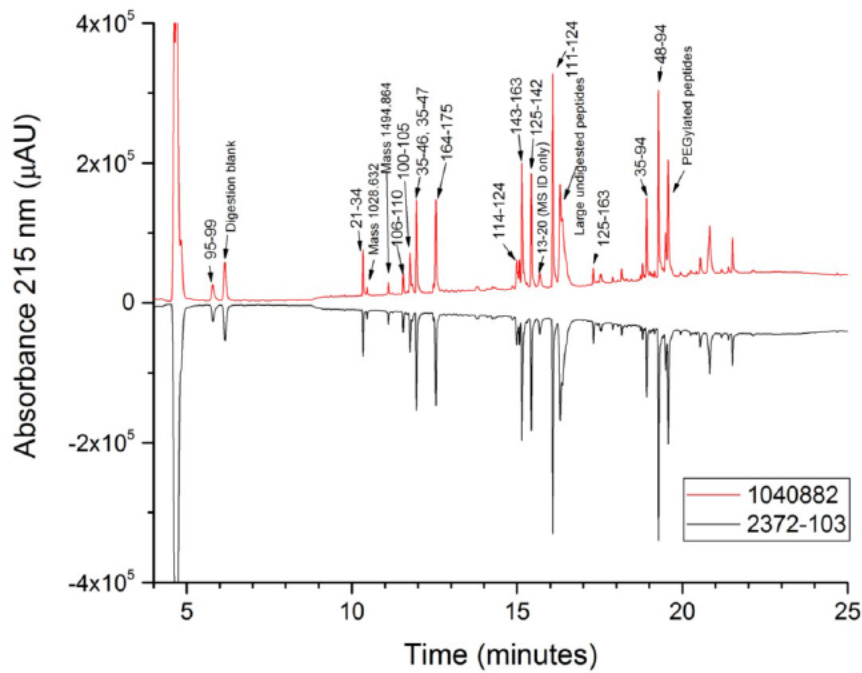
The statistical approach to evaluate the similarity between the proposed biosimilar and the reference product, as proposed by the sponsor, is acceptable. The majority of the methods used in this similarity study are included in the Tier 3; however, the most critical attributes are evaluated using either tier 1 or tier 2 methods. Tier 2 acceptance criteria and classification of attributes using one-sided or two-sided limits were reviewed and were found acceptable. The Tier 2 criteria included are considered appropriate.

Similarity to US-licensed Neulasta – Peptide Mapping by LC-MS/MS

Attribute: amino acid sequence	Criticality: high	Tier: NA

Peptide mapping was used to compare the sequence and disulfide structure of CHS-1701 and US-licensed Neulasta. The main goal of the first part of this analytical exercise is to verify whether all lots of both products have the correct primary structure. Samples were digested with endoproteinase Glu-C, typically the digestion reaction is performed overnight. Digests were analyzed both non-reduced and reduced (by the addition of dithiothreitol). The details regarding the method qualification were provided in a separate qualification report. The sponsor concluded that the acceptance criterion – to match sequence – is met for all lots. All 13 lots of CHS-1701 and all 22 lots of the reference product were used in this assessment.

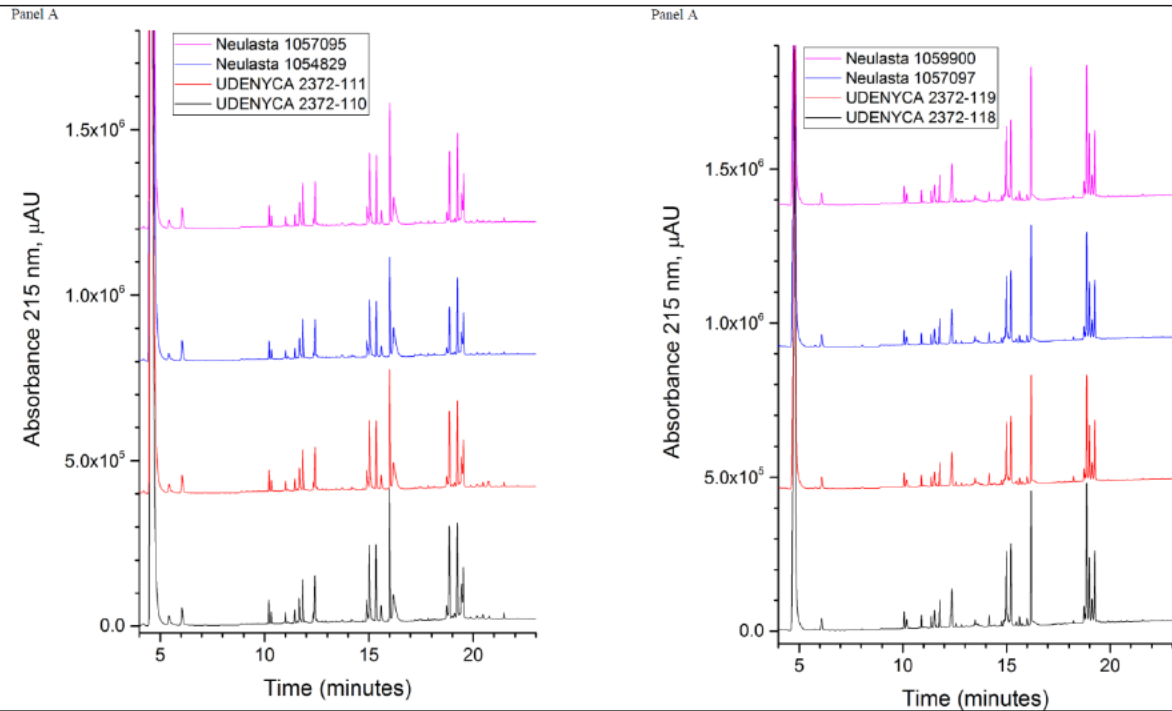
Figure 1: GluC Peptide Map of Representative CHS-1701 DP and US-licensed Neulasta Lots, UV Absorbance



Legend: Red (top) line: US-licensed Neulasta lot 1040882; Black (bottom) line: CHS-1701 lot 2372-103 (1701-DP-104)

Coherus provided peptide map chromatograms for all available lots (an example of an overlay of 4 lots is presented below in figure 3 and 4). The submission doesn't include individual chromatograms; however, the overlays of 4 chromatograms are provided with sufficient separation.

Figure 3 and 4: Reduced GluC Peptide Maps, Group 1 and 3 (2x4 Panels)



Reviewer comment:

The figure 3 and 4 above represents results of 8 enzymatic digests grouped into 2 panels, 4 chromatograms each. Most of the proposed biosimilar and the reference product chromatograms provided by the sponsor appear to follow a pattern similar to the one shown in panel A on the left, which is significantly different from the one provided on the right. There are number of peaks that appear to be missing, have different intensity or retention time in the left panel. The chromatograms on the left are representative for the majority of CHS-1701 the US-licensed Neulasta lots tested using peptide mapping; however, 4 lots of each product appear to have different chromatographic profiles.

An IR to the sponsor was sent on November 18, 2016 with request to explain the observed differences in number of peaks, peak areas, and retention times between the CHS-1701 and US-licensed Neulasta lots and justify why this result does not impact the conclusion of highly similar.

The sponsor responded that “the method has some inherent day-to-day variability in the chromatograms, due to differences in digestion efficiency and non-canonical cleavages (from enzyme lot-to-lot variations) and to normal variation in chromatographic performance. To control for any differences in the digestion or run conditions, the CHS-1701 reference standard (lot 169A14-02 PEG RS) is typically included as a system check standard with each group of similarity samples analyzed.” The response provided by the sponsor is acceptable.

Table 19: Reduced Glu-C Peptides

Lot	Peptide	95-99	21-34	106-110	100-105	35-47	35-46	164-175	114-124	143-163	125-142	111-124	125-163	106-124	35-94	48-94
	RT	5.9	10.4	11.6	11.8	12	12.1	12.6	15.1	15.1	15.5	16.2	17.4	18.2	19	19.4
	MC	0	1	0	0	1	0	0	1	0	0	2	0	3	2	0
	Charge	1	2	1	1	2	2	2	2	2	3	2	2	3	2	4
Theoretical	mass ^d	501.24	1511.81	588.31	614.33	1533.73	1404.69	1437.82	1382.62	2272.21	1770.88	1667.75	4025.08	2238.05	6457.35	4941.63
	m/z	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.41	886.45	834.88	1342.70	1120.03	1615.35	1648.22
2372-102 ^a	m/z ^e	502.23	756.89	589.30	615.31	767.86	703.33	719.90	692.30	758.31	886.34	834.87	1342.57	1120.03	1615.36	1648.07
2372-103 ^a	m/z ^e	502.18	756.84	589.24	615.25	767.80	703.28	719.92	692.25	758.32	886.35	834.89	1342.58	1119.96	1615.27	1648.14
2372-104 ^a	m/z ^e	502.18	756.93	589.24	615.25	767.78	703.38	719.94	692.34	758.32	886.35	834.90	1342.58	1120.05	1615.22	1648.09
2372-105 ^a	m/z ^e	502.18	756.82	589.24	615.26	767.79	703.27	719.84	692.23	758.32	886.35	834.79	1342.60	1119.93	1615.23	1648.11
2372-110 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.40	886.44	834.88	1342.70	1120.03	1615.35	1648.21
2372-111 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.42	886.45	834.88	1342.70	1120.03	1615.35	1648.22
2372-112 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.42	886.45	834.88	1342.70	1120.03	1615.35	1648.22
2372-113 ^b	m/z ^e	502.25	756.99	589.32	615.34	767.87	703.35	719.92	692.32	758.48	886.54	834.88	1342.70	1120.04	1615.35	1648.37
2372-114 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.48	886.54	834.88	1342.70	1120.04	1615.35	1648.37
2372-116 ^c	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.41	886.45	834.88	1342.62	1120.04	1615.35	1648.22
2372-117 ^c	m/z ^e	502.25	756.91	589.32	615.33	767.87	703.35	719.92	692.32	758.41	886.45	834.88	1342.62	1120.03	1615.35	1648.22
2372-118 ^c	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.41	886.45	834.88	1342.62	1120.04	1615.35	1648.22
2372-119 ^c	m/z ^e	502.25	756.91	589.32	615.33	767.87	703.35	719.92	692.32	758.41	886.45	834.88	1342.62	1120.03	1615.35	1648.22
1040882 ^a	m/z ^e	502.22	756.90	589.30	615.32	767.87	703.34	719.98	692.32	758.33	886.36	834.89	1342.60	1120.04	1615.37	1648.24
1042866 ^a	m/z ^e	502.19	756.83	589.25	615.26	767.86	703.27	719.84	692.24	758.33	886.36	834.79	1342.60	1119.94	1615.24	1648.11
1047431 ^a	m/z ^e	502.19	756.83	589.25	615.38	767.79	703.40	719.86	692.36	758.33	886.36	834.82	1342.60	1119.94	1615.24	1648.11
1047434 ^a	m/z ^e	502.19	756.83	589.25	615.26	767.79	703.27	719.84	692.24	758.33	886.36	834.79	1342.60	1119.94	1615.24	1648.11
1048085 ^a	m/z ^e	502.19	756.83	589.30	615.31	767.83	703.32	719.84	692.24	758.33	886.36	834.83	1342.60	1119.98	1615.24	1648.11
1048834 ^a	m/z ^e	502.19	756.83	589.25	615.26	767.87	703.27	719.84	692.24	758.33	886.36	834.87	1342.60	1119.94	1615.24	1648.11
1050019 ^a	m/z ^e	502.22	756.84	589.28	615.29	767.80	703.29	719.86	692.24	758.33	886.36	834.79	1342.60	1119.97	1615.22	1648.09
1051304 ^a	m/z ^e	502.22	756.87	589.28	615.30	767.84	703.32	719.95	692.28	758.33	886.36	834.93	1342.60	1120.01	1615.34	1648.21
1051676 ^a	m/z ^e	502.19	756.83	589.25	615.26	767.79	703.27	719.84	692.24	758.33	886.36	834.87	1342.60	1119.94	1691.12	1648.11
1053071 ^a	m/z ^e	502.19	756.82	589.25	615.26	767.79	703.27	719.84	692.24	758.33	886.36	834.79	1342.60	1119.94	1615.23	1648.11
1053082 ^a	m/z ^e	502.19	756.82	589.25	615.26	767.79	703.27	719.84	692.24	758.33	886.36	834.79	1342.60	1119.94	1615.24	1648.11
1053081 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.43	886.47	834.88	1342.70	1120.03	1615.35	1648.27
1053956 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.45	886.49	834.88	1342.70	1120.03	1615.35	1648.29
1054829 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.42	886.45	834.88	1342.70	1120.03	1615.35	1648.22
1055572 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.45	886.49	834.88	1342.70	1120.04	1615.35	1648.31
1057095 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.44	886.47	834.89	1342.70	1120.04	1615.35	1648.22
1057096 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.40	886.44	834.88	1342.70	1120.04	1615.35	1648.35
1057133 ^b	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.40	886.45	834.89	1342.70	1120.04	1615.35	1648.22
1056717 ^c	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.41	886.45	834.89	1342.62	1120.03	1615.35	1648.22
1057097 ^c	m/z ^e	502.25	756.91	589.32	615.34	767.87	703.35	719.92	692.32	758.41	886.45	834.88	1342.64	1120.04	1615.35	1648.22
1057373 ^c	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.41	886.45	834.89	1342.64	1120.04	1615.35	1648.22
1059900 ^c	m/z ^e	502.25	756.91	589.32	615.34	767.88	703.35	719.92	692.32	758.41	886.45	834.88	1342.62	1120.03	1615.35	1648.22

RT, retention time, minutes; MC, number of missed cleavages

^a Analyzed in group 1 analyses.

^b Analyzed in group 2 analyses.

^c Analyzed in group 3 analyses.

^d Theoretical Mass taken from Biopharmalynx "Calculated Peptide Mass" column in Peak Match Data table

^e Observed Mass taken from the "Control mass" column in Peak Match Data table

Reviewer comment:

It would be preferable to see the m/z differences between the theoretical and measured values instead or in addition to the actual results. For the most part the differences between the theoretical and observed values are very small for both products and these results support the similarity of CHS-1701 to US-licensed Neulasta. There is however, one m/z result for the US-licensed Neulasta lot 1051676 for the peptide 35-94 that is completely different from the rest of results and will require an explanation from the sponsor.

An IR to the sponsor was sent on November 18, 2016 with request to explain why the m/z result for lot 1051676 is different when compared with other lots.

The sponsor responded that "the m/z result for US-licensed Neulasta lot 1051676, peptide 35-97 was mistakenly reported as 1691.12, which is in fact the m/z result for peptide 47-94. The correct value for peptide 35-94 is 1615.24." Responses provided by the sponsor are acceptable.

The sponsor has not set pre-determined acceptance criteria for the similarity exercise, stating that the results of this method are not quantitative and therefore not amenable to statistical evaluation. For example, Coherus could have established quantitative acceptance criteria with regards to peak numbers, peak areas, or retention times. This would be expected if peptide mapping was intended as a purity test; however, there are several other purity tests (such as RPC, SEC, CEC) included in the analytical similarity assessment. The sponsor requires the result of peptide mapping to be identical (p.26 of the 3.2.R.1 Analytical Similarity Assessment); this is acceptable for the purposes of the analytical similarity assessment.

The sponsor provided the results of analytical similarity by peptide mapping for all available Coherus lots and all 22 US-licensed Neulasta lots. There are no significant differences when comparing the m/z values for all 15 fragments for the proposed biosimilar and the reference product. The peptide mapping analyses support highly similar primary structure for the proposed biosimilar CHS-1701 and US-licensed Neulasta. Additionally, LC-MS/MS analyses of digested pre-PEGylated G-CSF indicate that the primary structure of CHS-1701 is identical to the sequence of G-CSF reported in the literature.

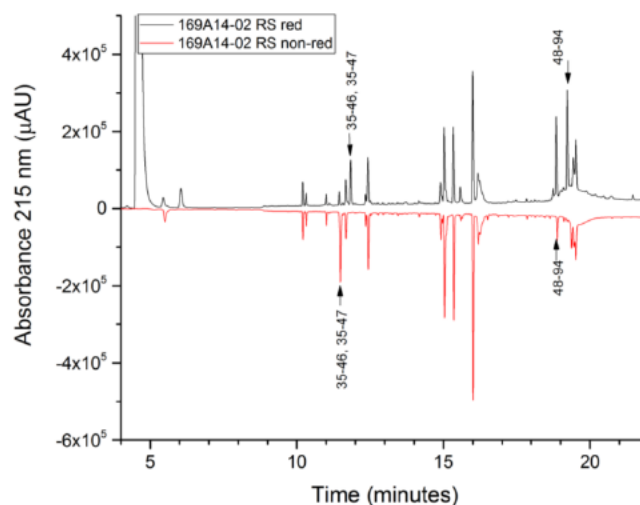
Reviewer assessment:

The results of the peptide mapping method used to compare the sequences of the proposed biosimilar and the reference product support a demonstration of high similarity in terms of the primary structure (amino acid sequence). Additionally, data support the conclusion that CHS-1701 and US-licensed Neulasta share an identical primary sequence.

Attribute: disulfide structure**Criticality: high****Tier: NA**

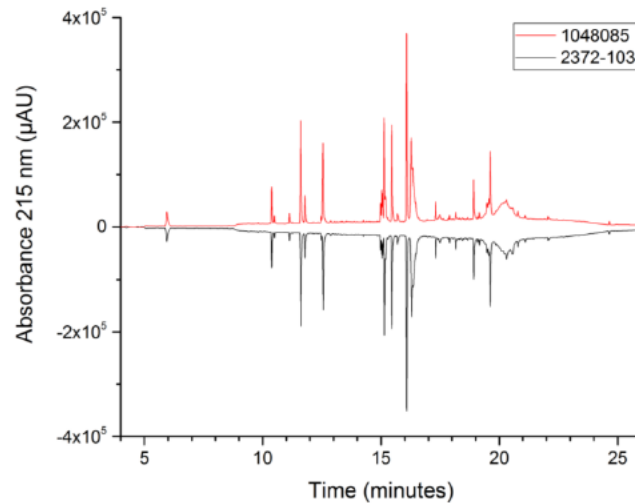
Peptide mapping is also used to determine the disulfide bonds, which is critical for folding of the protein and its function. This is achieved by comparison of reduced and non-reduced Glu-C peptide maps. The digestion reaction is performed overnight using DDT. Figure 5 shows a comparison of the reduced and non-reduced map for a representative CHS-1701 lot, with disulfide containing peptides labeled. All 13 CHS-1701 lots and 22 US-licensed Neulasta lots were tested.

Figure 5: Reduced and Non-reduced Glu-C Map, with Disulfide Containing Peptides Labeled



Legend: Black (top) line: CHS-1701 DS lot 169A14-02 (1701-DS-103), reduced; Red (bottom) line: CHS-1701 DS lot 169A14-02 (1701-DS-103), non-reduced.

Figure 6: Representative CHS-1701 and US-licensed Neulasta Lots, Non-Reduced Glu-C Map



Legend: Red (top) line: US-licensed Neulasta lot 1048085; Black (bottom) line: CHS-1701 lot 2372-103 (1701-DP-104)

Reviewer comment:

There are 3 peptides containing the disulfide bridges: peptides 35-46, 35-47 and 48-94. The first 2 contain the disulfide bridge Cys37-Cys43 and the last one contains the S-S bridge Cys65-Cys75. There is also a peptide 35-94, which contains both disulfide bridges. Note there should be a difference of 2H in mass between the peptides 35-46, 35-47 and 48-94 containing the reduced and non-reduced disulfide bridges. The sponsor performed the peptide mapping and disulfide determination on the pre-PEGylated molecule and it is consistent with DP results.

Table 20: Non-reduced Glu-C Disulfide Containing Peptides

Peptides characterized		Peptide	35-46	35-47	48-94		
				Disulfide Bond	37-43	37-43	65-75
				RT ^a	11.7	11.7	19.0
				Theoretical mass ^b	1402.67	1531.72	4939.61
		Theoretical m/z)	702.34	766.87	1647.55		
UDENYCA	2372-102 ^c	Observed m/z	702.34	766.86	1647.61		
	2372-103 ^c		702.34	766.87	1647.61		
	2372-104 ^c		702.34	766.86	1647.61		
	2372-105 ^c		702.34	766.87	1647.62		
	2372-110 ^d		702.35	766.87	1647.55		
	2372-111 ^d		702.35	766.87	1647.55		
	2372-112 ^d		702.35	766.87	1647.55		
	2372-113 ^d		702.35	766.87	1647.55		
	2372-114 ^d		702.35	766.87	1647.55		
	2372-116 ^e		702.34	766.87	1647.55		
	2372-117 ^e		702.35	766.87	1647.55		
2372-118 ^e	702.34	766.87	1647.55				
2372-119 ^e	702.34	766.87	1647.54				
Neulasta (US)	1040882 ^c	Observed m/z	702.34	766.86	1647.61		
	1042866 ^c		702.34	766.87	1647.61		
	1047431 ^c		702.34	766.86	1647.61		
	1047434 ^c		702.34	766.86	1647.61		
	1048085 ^c		702.34	766.86	1647.61		
	1048834 ^c		702.34	766.87	1647.61		
	1050019 ^c		702.34	766.86	1647.62		
	1051304 ^c		702.34	766.86	1647.61		
	1051676 ^c		702.34	766.87	1647.62		
	1053071 ^c		702.34	766.86	1647.61		
	1053082 ^c		702.34	766.87	1647.62		
	1053081 ^d		702.34	766.87	1647.55		
	1053956 ^d		702.35	766.87	1647.55		
	1054829 ^d		702.35	766.87	1647.55		
	1055572 ^d		702.34	766.87	1647.55		
	1057095 ^d		702.35	766.87	1647.55		
	1057096 ^d		702.35	766.87	1647.55		
	1057133 ^d		702.35	766.87	1647.55		
	1056717 ^e		702.35	766.87	1647.55		
	1057097 ^e		702.35	766.87	1647.55		
1057373 ^c	702.35	766.87	1647.55				
1059900 ^e	702.34	766.87	1647.55				

Reviewer comment:

A non-reductive peptide map coupled with mass spectrometry was conducted to verify the presence of disulfide bonds between Cys37-Cys43 and Cys65-Cys75. After Glu-C digestion under non-reducing conditions, peptides 35-46, 35-47, and 48-94 masses were measured on average at 1402.67, 1531.72 Da, and 4939.61 Da, respectively (the respective m/z results were 702.34, 766.87 and 1647.55). These data correspond well with theoretical masses for peptides with intact disulfide bonds.

A comparison of data obtained under reducing and non-reducing conditions using peptide mapping method and the proposed biosimilar and the reference product supports a demonstration of highly similar in terms of the disulfide bridges locations.

Attribute: Protein concentration Criticality: high Tier: 1

Concentrations of CHS-1701 and US-licensed Neulasta were determined by UV spectroscopy at wavelength of 280 nm for all 13 lots of the proposed biosimilar and 22 lots of the reference product. The extinction coefficient was not provided in this part of the analytical similarity assessment. However, there is a separate section in the analytical similarity assessment document discussing the extinction coefficient determination and differences in results for both products. The extinction coefficient used in this study was 0.86 mg⁻¹ cm⁻¹. Since the protein content was assigned as tier 1 attribute, the most stringent statistical evaluation was applied. Tier 1 attributes were evaluated for equivalence using an EAC of ± 1.5 σ. The

target value of protein content is 10 mg/mL. For Tier 1 attributes, similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for CHS-1701 and US-licensed Neulasta is within the EAC of (-1.5 σ , +1.5 σ) based on the standard deviation (σ) calculated from all US-licensed Neulasta lots.

Table 23: Protein Concentration by A280 of CHS-1701 and US-licensed Neulasta

Material	Lot	Concentration (mg/mL)
CHS-1701 Commercial scale	2372-102 (1701-DP-103)	9.7
	2372-103 (1701-DP-104)	9.7
	2372-104 (1701-DP-105)	9.8
	2372-105 (1701-DP-106)	9.6
	2372-110 (1701-DP-111)	10.0
	2372-111 (1701-DP-112)	10.0
	2372-112 (1701-DP-113)	10.1
	2372-113 (1701-DP-114)	10.0
	2372-114 (1701-DP-115)	10.0
	2372-116 (1701-DP-117)	9.9
	2372-117 (1701-DP-118)	9.9
	2372-118 (1701-DP-119)	9.8
	2372-119 (1701-DP-120)	10.0
US-licensed Neulasta	1040882	10.0
	1042866	10.0
	1047431	10.0
	1047434	9.9
	1048085	9.8
	1048834	9.9
	1050019	9.9
	1051304	10.1
	1051676	9.9
	1053071	9.9
	1053081	9.9
	1053082	9.9
	1053956	9.9
	1054829	9.9
	1055572	9.8
	1057095	10.0
	1057096	9.9
	1057133	9.8
	1057373	9.9
	1056717	9.8
1057097	9.9	
1059900	9.9 ^a	
CHS-1701 Number	13	
CHS-1701 Mean	9.88	
CHS-1701 Standard Deviation	0.15	
US-licensed Neulasta	22	
US-licensed Neulasta Mean	9.91	
US-licensed Neulasta Standard Deviation	0.08	

^aSample analyzed in triplicate. Average is reported. Individual values are: 9.9, 9.9, and 9.9.

Table 24: Summary Statistics for Concentration Using Unequal Variances

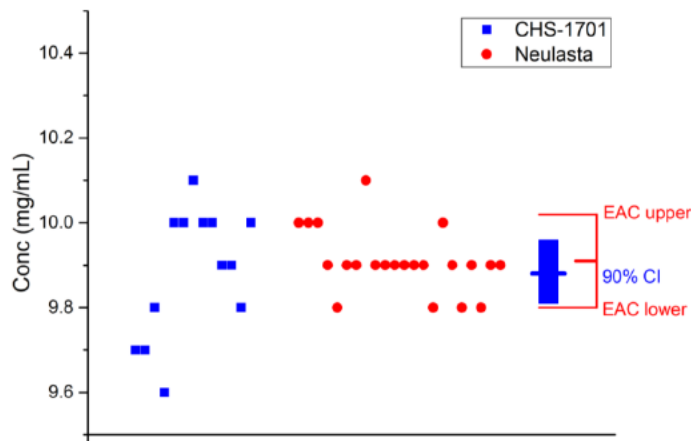
	Unequal Variances
Variance (unequal)	0.002
Standard Error (SE) of Difference	0.046
Degrees of Freedom (df) ^a	16
t statistic (based on df)	1.746
Difference between means	-0.02
90% CI of Mean Difference (lower)	-0.10
90% CI of Mean Difference (upper)	0.05
EAC ($\pm 1.5\sigma$)	± 0.11
	PASS

Reviewer comment:

The method was properly categorized as tier 1 method. Sufficient number of lots is used to perform meaningful review of data. Tier assignment and similarity data for tier 1 attributes were additionally evaluated by CMC stat reviewer. Statistical evaluation of tier 1 attributes was performed by CMC statistical reviewer and the conclusion was that protein concentration PASSED the equivalence testing.

Results for US-licensed Neulasta and CHS-1701 DP lots are compared graphically in Figure 11 below. These measurements were performed in the Coherus Analytical Laboratory using a SoloVPE instrument where sample preparation by way of dilution is not needed and the measurement is obtained directly from the test sample. While the results are very close to the lot release values, they may not be identical.

Figure 11: Graphical comparison of CHS-1701 to US-licensed Neulasta concentrations



One can notice in the figure above, that the protein content values ranged from 9.6 to 9.8 mg/mL for early lots (first 4) and lots manufactured later were closer to the target value of 10 mg/mL. In these subsequent commercial drug substance lots manufactured at the same facility, an equipment optimization was implemented to use more appropriately scaled equipment for the ^{(b) (4)} step (refer to Section 3.2.S.2.6, *Manufacturing Process Development*). This change resulted in drug substance, and consequently drug product (DP) concentrations closer to the target value for all subsequent batches. DP batches manufactured pre and post equipment optimization were shown to be comparable and deemed representative of the current commercial process with respect to protein concentration.

Reviewer assessment:

Early DP lots had lower than average protein content; however, because two of these lots were clinical lots, the sponsor was asked to include these lots in the analytical similarity assessment (refer to a Type 2 meeting held on September 29, 2015).

The sponsor provided data and statistical evaluation to support a demonstration of highly similar with respect to protein content for CHS-1701 and US-licensed Neulasta. The results presented above demonstrate that the proposed biosimilar and the reference product support a demonstration of highly similar (equivalency) in terms of protein content. The adequacy of the statistical evaluation is deferred to the CMC statistical reviewer: it was concluded that protein concentration PASSED the equivalence testing.

Attribute: Biological activity

Criticality: high

Tier: 1

The sponsor measures the potency of CHS-1701 using the cell-based proliferation assay, which measures the biological activity of pegfilgrastim based on its binding to, and induction of, the proliferation of NFS-60 cells. The primary mechanism of action of G-CSF is stimulation of progenitor cell proliferation, decreased maturation of postmitotic precursor cells, and mobilization of neutrophil storage pools from bone marrow. For Tier 1 attributes, similarity is demonstrated if the two-sided 90% confidence interval of the difference between means for CHS-1701 and US-licensed Neulasta is within the EAC of $(-1.5 \sigma, +1.5 \sigma)$ based on the standard deviation (σ) calculated from 21 lots.

Similarly to protein content, lot selection for this attribute included all 13 CHS-1701 lots in the assessment; however, 21 of 22 US-licensed Neulasta lots were included. One US-licensed Neulasta lot (1054829) was not tested due to material limitations. This lot was used in the clinical study CHS-1701-04 (immunogenicity) and the sponsor stated that material from this batch has been obtained from the reserved clinical supply returned post study close out. Potency testing for this lot is currently planned and the results can be submitted to the BLA upon the Agency’s request. Moreover, SPR results for this US-licensed Neulasta lot (lot 1054829) are within the same range as other US-licensed Neulasta lots, hence similar potency results would be expected.

Reviewer comment:

The exclusion of one US-licensed Neulasta lot in the tier 1 analytical similarity assessment of potency was justified by material limitations. This lot was used in the clinical study and limited supply was available. The sponsor should have planned to have sufficient amount to perform potency analysis and perhaps exclude some tier 3 testing instead. However, the testing of this lot (returned samples) has been planned and the results can be submitted to the Agency. The request to provide potency data for US-licensed Neulasta lot not included in potency assessment will be added to the CR letter.

Table 21: Potency by Bioassay

Material	Lot	Relative potency %
CHS-1701	2372-102 (1701-DP-103)	92
	2372-103 (1701-DP-104)	97
	2372-104 (1701-DP-105)	105
	2372-105 (1701-DP-106)	101
	2372-110 (1701-DP-111)	98
	2372-111 (1701-DP-112)	95
	2372-112 (1701-DP-113)	96

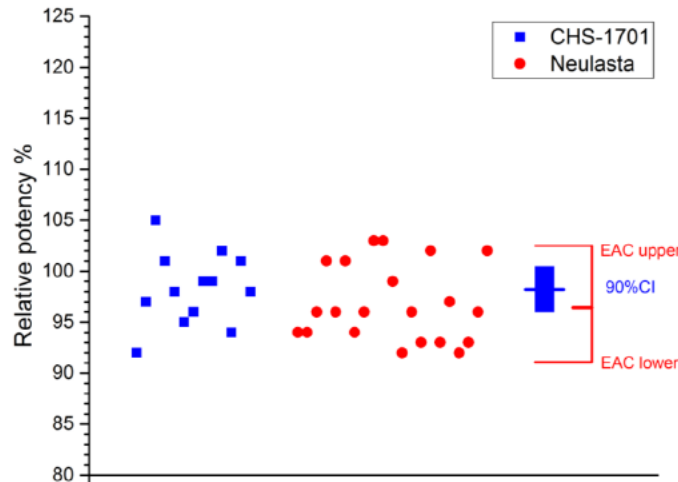
	2372-113 (1701-DP-114)	99
	2372-114 (1701-DP-115)	99
	2372-116 (1701-DP-117)	102
	2372-117 (1701-DP-118)	94
	2372-118 (1701-DP-119)	101
	2372-119 (1701-DP-120)	98
US-licensed Neulasta	1040882	94
	1042866	94
	1047431	96
	1047434	101
	1048085	96
	1048834	101
	1050019	94
	1051304	96
	1051676	103
	1053071	103
	1053081	99
	1053082	92
	1053956	96
	1055572	93
	1057095	102
	1057096	93
	1057133	97
	1056717	92
	1057097	93
	1057373	96
	1059900	102
CHS-1701 Number		13
CHS-1701 Mean		98.2
CHS-1701 Standard Deviation		3.5
US-licensed Neulasta		21
US-licensed Neulasta Mean		96.8
US-licensed Neulasta Standard Deviation		3.8

Table 22: Summary Statistics for Bioassay Using Equal and Unequal Variances

	Equal Variances	Unequal Variances
Pooled Standard Deviation (SD)	3.7	NA
Variance (unequal)	NA	1.7
Standard Error (SE) of Difference	1.3	1.3
Degrees of Freedom (df) ^a	30	27
t statistic (based on df)	1.697	1.703
Difference between Means	1.4	1.4
90% CI of Mean Difference (lower)	-0.8	-0.8

90% CI of Mean Difference (upper)	3.7	3.7
EAC ($\pm 1.5\sigma$)	± 5.7	± 5.7
	PASS	PASS

Figure 10: Biological Potency of CHS-1701 vs US-licensed Neulasta



Reviewer comment:

The method was properly assigned as tier 1 method. The sample size is sufficient for statistical similarity evaluation and to capture method variability and lot-to-lot variability. Additionally, there is no apparent correlation between the age of the US-licensed Neulasta lots and the potency results which leads to conclusion that the risk of lot age to impact the results is minimal. This is further supported by the stability data (refer to Section 3.2.P.8, Stability) as no significant changes in potency over time were observed.

Reviewer assessment:

The results presented above support a demonstration of highly similar (equivalency) in terms of biological activity for the proposed biosimilar and the reference product. The adequacy of the statistical evaluation of potency was performed by the CMC statistical reviewer and the conclusion was that potency PASSED the equivalence testing.

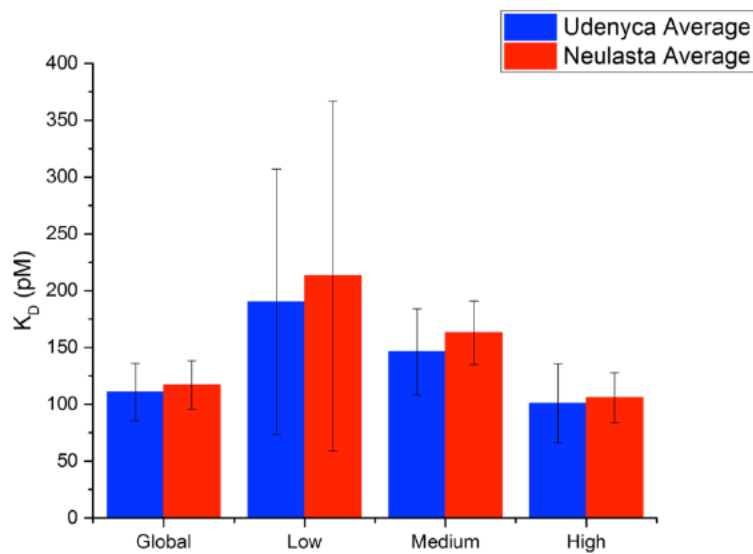
Attribute: Receptor binding

Criticality: high

Tier: 2

The receptor binding similarity of CHS-1701 to US-licensed Neulasta was assessed using the surface plasmon resonance (SPR) method. This method measures binding of PEG-G-CSF to the G-CSF receptor using surface plasmon resonance and can determine the affinity and kinetic parameters during binding. The SPR method has rather high variability, especially when PEGylated molecules bind to naturally occurring receptors. In addition, the precision of the SPR method is about 30%. This method is considered an orthogonal method to the potency assay discussed above.

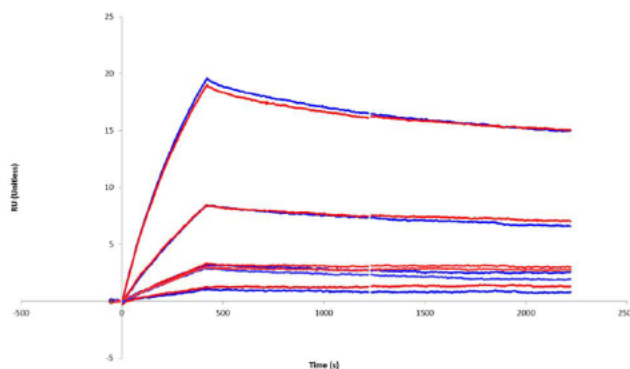
The sponsor performed the study using three immobilization levels: low (500 RU), medium (1000 RU), and high (1500 RU). These kinds of studies are usually done during method development in order to find the optimal immobilization; however, the sponsor opted to fit across multiple concentrations and multiple immobilization levels to cover a larger parameter space and improve the precision of KD determination.

Figure 12: Comparison of SPR Data Fitting by Global versus Single Fits**Reviewer comment:**

The approach to include results obtained from 3 different immobilization levels to get an average K_D value does not appear acceptable, and the sponsor did not provide a justification. It also appears that similar results were obtained using different immobilizations. The lowest immobilization yielded the highest K_D results but with highest variability. The highest immobilization provided results with the lowest K_D (and the worst fit).

An IR to the sponsor was sent stating that “averaging the test results by combining data generated at the different immobilization levels to improve the method variability does not appear appropriate as it may not be reflective of binding properties of CHS-1701 or US-licensed Neulasta to the G-CSF receptor. Provide surface plasmon resonance raw data and evaluate receptor binding dissociation constant (K_D) and on- and off-rates at each immobilization level.”

The sponsor provided data for individual immobilization levels (table 25 below). Indeed, especially for the lowest level, high variability was observed (K_D , k_a and k_d). On average, binding dissociation constant, on-rate (k_a) and off-rate (k_d) were slightly higher for US-licensed Neulasta lots across all densities but the differences were rather small and within the pre-established acceptance criteria.

Figure 13: Representative Sensograms of CHS-1701 DP and US-licensed Neulasta SPR Analysis

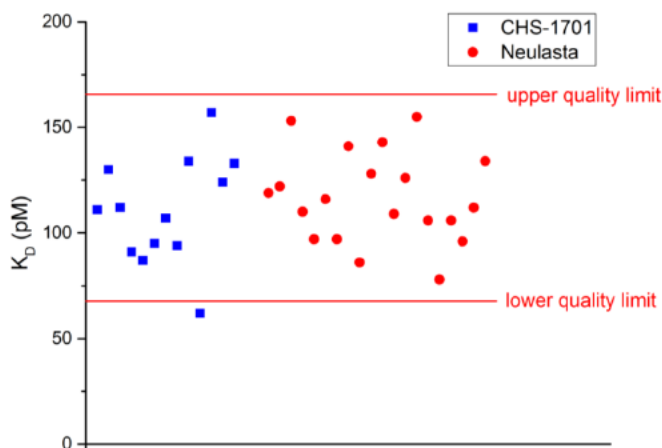
CHS-1701 Lot 2372-102 (Blue); US-licensed Neulasta Lot 1048085 (Red); Sample concentrations injected at 1, 4 (duplicate), 12, and 36 ng/mL. Spike caused by injection artifact at ~1250 seconds has been removed.

Table 25: K_D Values Based on Global and Single-Density Fits

Lot	K_D (pM)			
	Global Fit, All Immobilizations	Low Immobilization	Med Immobilization	High Immobilization
2372-102	111	358	144	(85)
2372-103	130	217	165	129
2372-104	112	90	149	121
2372-105	91	87	120	80
2372-110	87	(17)	118	84
2372-111	95	(0)	132	87
2372-112	107	(20)	179	84
2372-113	94	64	107	51
2372-114	134	380	155	124
2372-116	62	72	69	44
2372-117	157	232	211	139
2372-118	124	146	160	117
2372-119	133	259	189	157
1040882	119	141	162	101
1047434	122	161	163	102
1048085	153	(15)	222	135
1048834	110	97	138	97
1050019	97	114	143	74
1051304	116	204	154	100
1051676	97	(34)	210	131
1054829	141	557	167	116
1053071	86	(3)	136	71
1053082	128	545	175	116
1057095	143	(759)	172	121
1053081	109	146	151	92
1053956	126	128	182	105
1055572	155	(48)	208	160
1057096	106	70	153	96
1057133	78	(166)	118	(27)
1056717	96	140	131	90
1057097	134	302	186	121
1057373	112	147	152	103
1059900	106	225	131	83
CHS-1701 ave	111	190	146	101
CHS-1701 std dev	25.2	117	38	35
US-licensed Neulasta ave	117	213	163	106

US-licensed Neulasta std dev	21.3	154	28	22

Figure 14: Averaged receptor binding by SPR of CHS-1701 and US-licensed Neulasta Lots (K_D values)



Receptor binding dissociation constants (K_D) for all CHS-1701 lots except one fall within the US-licensed Neulasta average $\pm 2.3 \sigma$ meeting the acceptance criteria (Table 25 and Figure 14 above). Ranges for the dissociation constant (K_D) are within method variability for both data sets as are the on-rates (k_a) and off-rates (k_d) (k_a and k_d results are not included in the review but were provided in the BLA submission upon FDA request).

Reviewer comment:

The sponsor initially only provided a summary of the receptor binding results (K_D) by SPR method, excluding the details of k_a and k_d determinations and no raw data (sensorgrams). In the IR dated September 30, 2016, FDA requested missing data. All lots except one fall within US-licensed Neulasta average $\pm 2.3 \sigma$ range when receptor binding dissociation constants were compared (K_D). Similarly, the CHS-1701 k_a (on-rate) and k_d (off-rate) values are with the margins derived from US-licensed Neulasta lots. No significant differences between CHS-1701 and US-licensed Neulasta lots were observed for binding to the G-CSF receptor.

Reviewer assessment:

The SPR results presented above support a demonstration of highly similar receptor binding of the proposed biosimilar CHS-1701 and the reference product, US-licensed Neulasta.

Size exclusion chromatography

Attribute: Molar mass	Criticality: medium	Tier: 2

Size exclusion chromatography (SEC) was used to characterize the relative size distributions of CHS-1701 and US-licensed Neulasta. Multi-angle light scattering (MALS) in combination with UV absorbance and refractive index (RI) detection were used to determine the molecular weight of the eluting peaks. Additionally, this method was used to determine the molecule extinction coefficient, PEG mass, PEG polydispersity, oligomers, dimers, clips, and diPEGylated species. The sponsor categorized this method as

of medium potential impact on the product quality attributes and included it as tier 2 assay in the analytical similarity assessment. All 13 CHS-1701 lots and all 22 US-licensed Neulasta lots were used in this assessment.

Molar Mass (MW) of Main Peak

SEC-MALS analysis (Table 29 below) gave Mw values for the CHS-1701 main peak ranging from 38.7 to 39.7 kDa. These values fell within $\pm 2.3 \sigma$ of the US-licensed Neulasta average, 38.5 to 40.0 kDa, which met the acceptance criteria. Results are illustrated graphically in Figure 28. A representative chromatogram of the SEC-MALS results is also provided below in Figure 25.

Figure 25: SEC-MALS Light Scattering Chromatograms and Molar Mass, Group 1

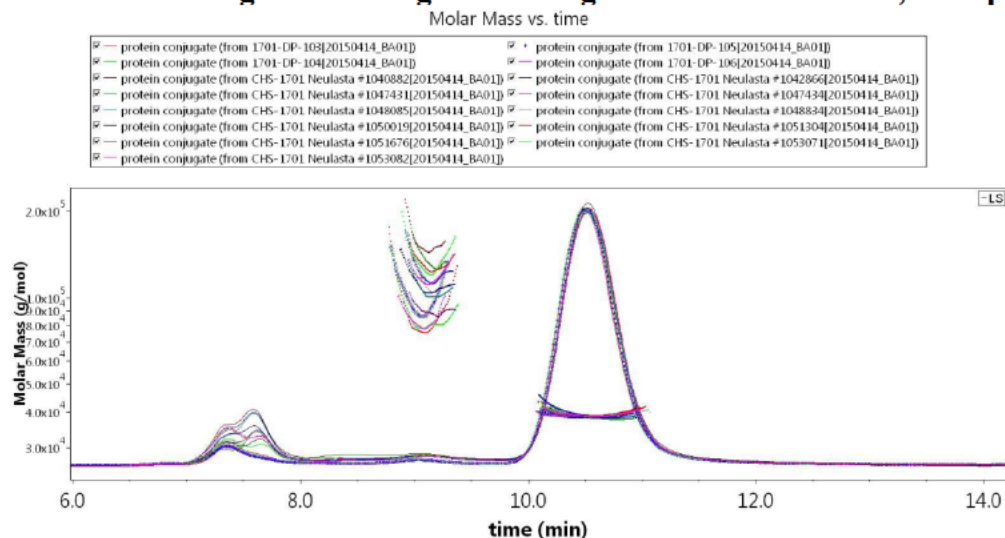


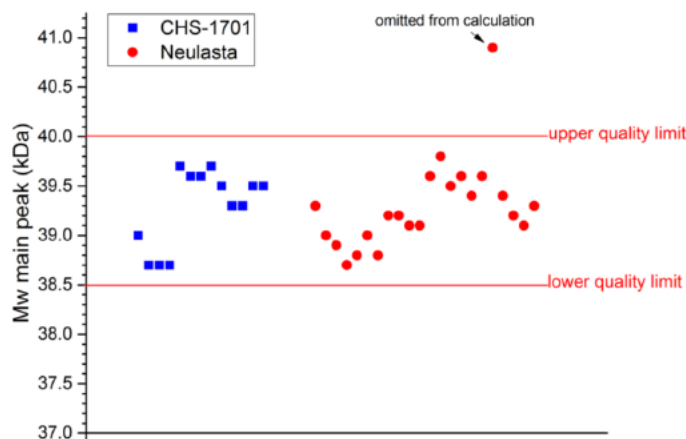
Table 29: SEC-MALS Results

Material	Lot	HM							Main			
		Mw (kDa)	Pd (Mw/Mn)	Fw	Mw (prot) (kDa)	Mw (PEG) (kDa)	Mw (kDa)	Pd (Mw/Mn)	Fw	Mw (prot) (kDa)	Mw (PEG) (kDa)	PEG Pd
US-licensed Neulasta	1040882 ^a	156.6	1.0098	0.471	74.2	82.4	39.3	1.0003	0.479	18.8	20.5	1.0008
	1042866 ^a	112.6	1.0078	0.358	40.4	72.2	39.0	1.0001	0.478	18.6	20.4	1.0006
	1047431 ^a	138.4	1.0083	0.376	52.2	86.2	38.9	1.0013	0.478	18.6	20.3	1.0005
	1047434 ^a	90.6	1.0017	0.300	27.2	63.4	38.7	1.0001	0.475	18.4	20.3	1.0007
	1048085 ^a	107.3	1.0059	0.337	36.3	71.0	38.8	1.0001	0.476	18.5	20.4	1.0007
	1048834 ^a	123.9	1.0112	0.373	46.3	77.5	39.0	1.0001	0.478	18.6	20.4	1.0007
	1050019 ^a	116.8	1.0137	0.337	39.6	77.2	38.8	1.0002	0.476	18.5	20.3	1.0010
	1051304 ^a	131.9	1.0038	0.331	43.6	88.3	39.2	1.0004	0.477	18.7	20.5	1.0011
	1051676 ^a	124.0	1.0105	0.326	40.6	83.4	39.2	1.0012	0.477	18.7	20.5	1.0007
	1053071 ^a	137.1	1.0132	0.383	52.7	84.5	39.1	1.0003	0.479	18.7	20.4	1.0010
	1053082 ^a	119.5	1.0040	0.367	43.8	75.7	39.1	1.0002	0.478	18.7	20.4	1.0008
	1053081 ^b	120.3	1.0167	0.369	44.7	75.6	39.6	1.0001	0.477	18.9	20.7	1.0001
	1053956 ^b	161.6	1.0172	0.359	58.3	103.2	39.8	1.0002	0.477	19.0	20.8	1.0001
	1054829 ^b	116.3	1.0157	0.379	44.4	71.9	39.5	1.0000	0.476	18.8	20.7	1.0001
1055572 ^b	130.6	1.0093	0.344	45.1	85.5	39.6	1.0001	0.476	18.9	20.8	1.0001	
1057095 ^b	111.3	1.0064	0.315	35.1	76.2	39.4	1.0001	0.476	18.7	20.6	1.0001	
1057096 ^b	133.1	1.0065	0.346	46.2	87.0	39.6	1.0000	0.476	18.8	20.7	1.0001	
1057133 ^b	127.5	1.0073	0.304	38.7	88.8	40.9	1.0040	0.474	19.4	21.5	1.0044	
1056717 ^c	168.8	1.0405	0.370	62.9	105.9	39.4	1.0015	0.479	18.9	20.5	1.0003	

CHS-1701	1057097 ^c	128.5	1.0102	0.393	50.7	77.8	39.2	1.0008	0.478	18.8	20.4	1.0004
	1057373 ^c	127.0	1.0111	0.378	48.1	78.9	39.1	1.0001	0.477	18.7	20.5	1.0006
	1059900 ^c	116.8	1.0051	0.368	43.1	73.7	39.3	1.0014	0.479	18.8	20.5	1.0003
	2372-102 ^a	88.1	1.0296	0.365	32.5	55.6	39.0	1.0002	0.475	18.5	20.5	1.0006
	2372-103 ^a	87.9	1.0228	0.305	27.0	60.9	38.7	1.0005	0.473	18.3	20.4	1.0003
	2372-104 ^a	100.1	1.0191	0.320	32.2	67.9	38.7	1.0001	0.475	18.4	20.4	1.0004
2372-105 ^a	84.8	1.0057	0.293	24.9	59.9	38.7	1.0000	0.475	18.4	20.3	1.0003	

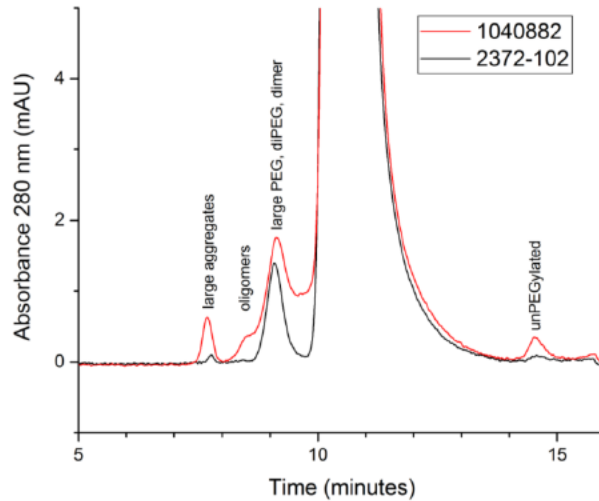
Material	Lot	HM					Main					
		Mw (kDa)	Pd (Mw/Mn)	Fw	Mw (prot) (kDa)	Mw (PEG) (kDa)	Mw (kDa)	Pd (Mw/Mn)	Fw	Mw (prot) (kDa)	Mw (PEG) (kDa)	PEG Pd
	2372-110 ^b	97.8	1.0016	0.468	45.9	51.9	39.7	1.0000	0.476	18.9	20.8	1.0001
	2372-111 ^b	83.5	1.0019	0.347	29.0	54.5	39.6	1.0001	0.473	18.7	20.9	1.0000
	2372-112 ^b	97.1	1.0017	0.355	34.5	62.6	39.6	1.0001	0.473	18.7	20.9	1.0001
	2372-113 ^b	84.4	1.0016	0.374	31.6	52.8	39.7	1.0000	0.472	18.8	20.9	1.0001
	2372-114 ^b	98.7	1.0012	0.344	34.0	64.7	39.5	1.0002	0.474	18.7	20.8	1.0000
	2372-116 ^c	110.5	1.0038	0.325	36.0	74.4	39.3	1.0011	0.474	18.7	20.7	1.0002
	2372-117 ^c	116.8	1.0008	0.357	41.8	75.1	39.3	1.0001	0.474	18.6	20.7	1.0004
	2372-118 ^c	110.5	1.0013	0.330	36.5	74.0	39.5	1.0003	0.475	18.7	20.7	1.0004
	2372-119 ^c	120.7	1.0066	0.356	43.1	77.6	39.5	1.0003	0.475	18.7	20.7	1.0004
Neulasta (US) Mean		127.3	1.0107	0.358	46.1	81.2	39.3	1.0006	0.477	18.8	20.6	1.0007
Neulasta (US) SD		17.9	0.0079	0.036	10.0	9.9	0.5	0.0009	0.001	0.2	0.3	0.0009
Neulasta (US) Mean +1.9 SD		-	-	-	-	-	-	-	-	-	-	1.0024
Neulasta (US) Mean +2.3 SD		-	-	-	-	-	40.4	-	-	-	21.2	-
Neulasta (US) Mean -2.3 SD		-	-	-	-	-	38.2	-	-	-	19.9	-
CHS-1701 Mean		98.5	1.0075	0.349	34.5	64.0	39.3	1.0002	0.474	18.6	20.7	1.0003
CHS-1701 Minimum		83.5	1.0008	0.293	24.9	51.9	38.7	1.0000	0.472	18.3	20.3	1.0000
UDENCYA Maximum		120.7	1.0296	0.468	45.9	77.6	39.7	1.0011	0.476	18.9	20.9	1.0006
Neulasta (US) Mean ^d		127.3	1.0109	0.361	46.5	80.8	39.2	1.0004	0.477	18.7	20.5	1.0005
Neulasta (US) SD ^d		18.4	0.0046	0.038	10.3	9.1	0.3	0.0004	0.001	0.2	0.2	0.0004
Neulasta (US) Mean +1.9 SD		-	-	-	-	-	-	-	-	-	-	1.0012
Neulasta (US) Mean +2.3 SD		-	-	-	-	-	40.0	-	-	-	20.9	-
Neulasta (US) Mean -2.3 SD		-	-	-	-	-	38.5	-	-	-	20.1	-

Figure 28: MW Main Peak by SEC-MALS, CHS-1701 vs. US-licensed Neulasta



Legend: Red lines represent the two-sided 2.3 σ limits calculated from US-licensed Neulasta results. The lot that generated the outlier value, 1057133, was not used in any clinical trial but evaluated for the purpose of similarity assessment only.

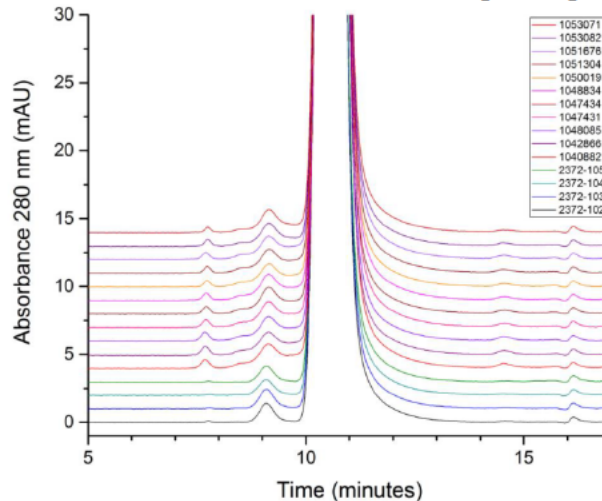
Figure 18: SEC-UV of Representative CHS-1701 and US-licensed Neulasta Lots, with Peaks Labeled



Legend: Red line: US-licensed Neulasta (US) lot 1040882; Black line: CHS-1701 lot 2372-102 (1701-DP-103)

A representative SEC-UV chromatogram is provided in the Figure 18 below and 15 lots of CHS-1701 and US-licensed Neulasta compared in the Figure 20:

Figure 20: SEC-UV, CHS-1701 and US-licensed Neulasta Group 1, Expanded Scale



Legend: US-licensed Neulasta (US) lots: 1053071, 1053082, 1051676, 1051304, 1050019, 1048834, 1047434, 1047431, 1048085, 1042866, 1040882; CHS-1701 lots: 2372-105 (1701-DP-106), 2372-104 (1701-DP-105), 2372-103 (1701-DP-104), 2372-102 (1701-DP-103)

Reviewer comment:

Overall, as seen in the Figure 20 above, CHS-1701 lots exhibited higher purity when compared with the reference product lots, some impurities were not detected in the proposed biosimilar product (unPEGylated species, oligomers and aggregates) and levels of others were lower in CHS-1701 lots (high molecular weight variants).

Table 28: SEC-UV with Relative Peak Areas for CHS-1701 and US-licensed Neulasta

Material	Lot	Main Peak	HMW		Dimer/ diPEG	Post peak	HMW total
			Aggregates	Oligomers			
	2372-102 (1701-DP-103)	99.3	NQ	NQ	0.7	NQ	0.7

CHS-1701	2372-103 (1701-DP-104)	99.3	NQ	NQ	0.7	NQ	0.7
	2372-104 (1701-DP-105)	99.4	NQ	NQ	0.6	NQ	0.6
	2372-105 (1701-DP-106)	99.4	NQ	NQ	0.6	NQ	0.6
	2372-110 (1701-DP-111)	99.1	NQ	NQ	0.8	NQ	0.8
	2372-111 (1701-DP-112)	99.2	NQ	NQ	0.7	NQ	0.7
	2372-112 (1701-DP-113)	99.4	NQ	NQ	0.6	NQ	0.6
	2372-113 (1701-DP-114)	98.9	NQ	NQ	1.0	NQ	1.0
	2372-114 (1701-DP-115)	99.5	NQ	NQ	0.5	NQ	0.5
	2372-116 (1701-DP-117)	99.1	0.1	NQ	0.8	NQ	0.9
	2372-117 (1701-DP-118)	99.0	NQ	NQ	0.9	NQ	0.9
	2372-118 (1701-DP-119)	99.1	NQ	NQ	0.9	NQ	0.9
	2372-119 (1701-DP-120)	99.1	NQ	NQ	0.9	NQ	0.9
US-licensed Neulasta	1040882	98.3	0.2	0.2	1.2	0.1	1.6
	1042866	98.4	0.2	0.1	1.1	0.1	1.4
	1048085	98.4	0.2	0.1	1.2	0.1	1.5
	1047431	98.3	0.1	0.1	1.4	0.1	1.6
	1047434	98.4	0.1	0.1	1.3	0.1	1.5
	1048834	98.3	0.1	0.1	1.3	0.1	1.5
	1050019	98.6	0.1	0.1	1.1	0.1	1.3
	1051304	98.6	0.1	0.1	1.1	0.1	1.3
	1051676	98.5	0.1	0.1	1.1	0.1	1.3
	1053082	98.6	0.1	0.1	1.1	0.1	1.3
	1053071	98.7	0.1	0.1	1.1	0.1	1.3
	1053081	98.6	0.1	0.1	1.1	0.1	1.3
	1053956	98.6	0.1	0.1	1.1	0.1	1.3
	1054829	98.7	0.1	0.1	1.1	0.1	1.3
	1055572	98.5	0.1	0.1	1.1	0.1	1.3
	1057095	98.6	0.1	0.1	1.1	0.1	1.3
	1057096	98.6	0.1	0.1	1.1	0.1	1.3
	1057133	98.7	0.1	0.1	1.1	0.1	1.3
1056717	98.6	0.1	0.1	1.1	0.1	1.3	
1057097	98.6	0.1	0.1	1.1	0.1	1.3	
1057373	98.6	0.1	0.1	1.1	0.1	1.3	
1059900	98.6	0.1	0.1	1.1	NQ	1.3	
Neulasta (US) Mean		98.54	0.11	0.10	1.14	0.10	1.36
Neulasta (US) Standard Deviation		0.13	0.04	0.02	0.09	0.02	0.11
Neulasta (US) ± 1.9 Standard Deviation		98.29	0.18	0.15	1.30	0.14	1.56
CHS-1701 Mean		99.22	0.01	NQ	0.75	NQ	0.75
CHS-1701 Minimum		98.9	NQ	NQ	0.5	NQ	0.5
CHS-1701 Maximum		99.5	0.1	NQ	1.0	NQ	1.0

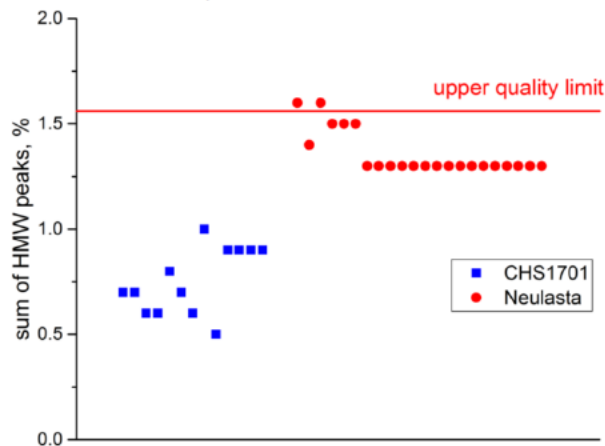
Reviewer comment:

Overall purity of CHS-1701 lots is higher than US-licensed Neulasta, based on size variants; purity (main peak) of the proposed biosimilar averaged 99.2% and the reference product was 98.5% (the main peak of the proposed biosimilar is above the quality limit of 98.3%). The similarity acceptance criterion was met.

HMW Species (% Area)

SEC analysis with UV detection (Table 28 above) showed total relative area of higher molecular weight species for the CHS-1701 lots ranging from 0.5 to 1.0%. These values were all lower than the US-licensed Neulasta average + 1.9 σ , 1.56%, which met the one-sided acceptance criteria. Results are illustrated graphically in Figure 30.

Figure 30: Total HMW Relative Area, CHS-1701 vs. US-licensed Neulasta



Red lines represent the two-sided 2.3 σ limits calculated from US-licensed Neulasta (US) results.

UnPEGylated Species

SEC analysis with UV detection (Table 28 above) showed no quantifiable unPEGylated species for any of the CHS-1701 lots. These values were all lower than the US-licensed Neulasta average + 1.9 σ , 0.14 %, which met the one-sided acceptance criteria.

Reviewer comment:

US-licensed Neulasta lots exhibited higher levels of high molecular weight (HMW) species than the proposed biosimilar. These impurities include aggregates, oligomers, dimer, diPEGylated, and double-size PEGylated species. Additionally, some of these impurities (unPEGylated species) were not observed in the proposed biosimilar. This difference in purity between CHS-1701 and US-licensed Neulasta is acceptable because it favors purity of CHS-1701 lots.

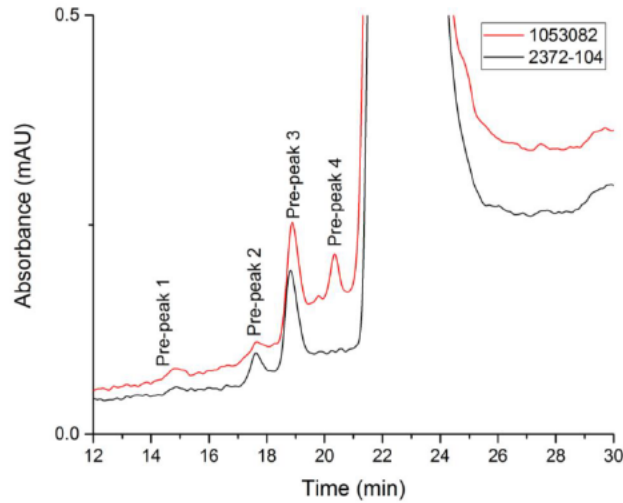
Reviewer assessment:

Size exclusion chromatography data support a demonstration of highly similar purity for CHS-1701 and US-licensed Neulasta.

Cation exchange chromatography

Charged variants that are present in CHS-1701 and US-licensed Neulasta were evaluated by cation exchange chromatography coupled with UV detector (absorbance at 280 nm). A representative chromatogram of one CHS-1701 and one US-licensed Neulasta lot, including a number of minor peaks before the main peak is provided below in Figure 31:

Figure 31: CEC Peak Identities, Representative CHS-1701 and US-licensed Neulasta lots



Legend: Red line: US-licensed Neulasta lot 1053082; Black line: CHS-1701 lot 2372-104 (1701-DP-105)

All 13 CHS-1701 lots and 22 US-licensed Neulasta lots were tested. Overall main peak purity by CEC is slightly higher for CHS-1701 than for US-licensed Neulasta, although values are similar (see Table 30 below). As shown in Figure 31 and Figure 33 above, profiles differ slightly in that pre-peak 4 is absent in CHS-1701 lots, while pre-peak 2 and sometimes pre-peak 1, are slightly larger in Coherus lots. Pre-peak identities are as follows (this information is also discussed in Section 3.2.S.3.2, *Impurities*):

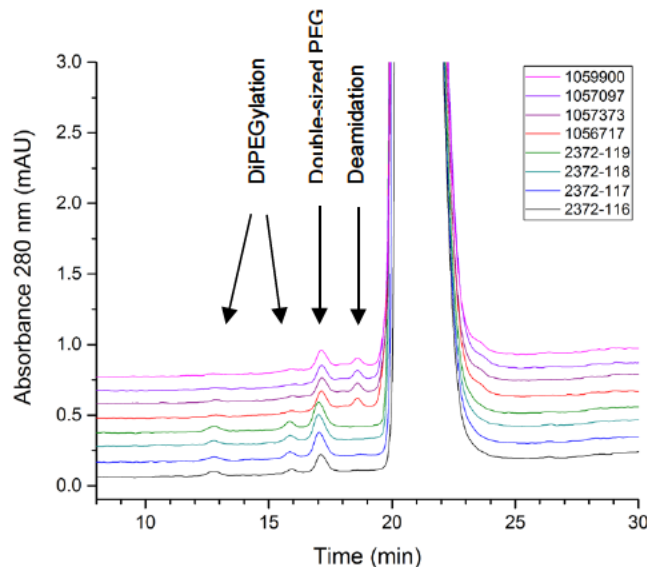
Pre-peak 1: N-terminal PEG plus K35 PEG

Pre-peak 2: N-terminal PEG plus K24 PEG

Pre-peak 3: Double-sized PEG at N-terminus, no lysine PEGylation

Pre-peak 4: Apparent deamidated species

Figure 33. Impurities by CEC in CHS-1701 and US-licensed Neulasta



Legend: US-licensed Neulasta lots: 1059900, 1057097, 1057373, 1056717; CHS-1701 lots: 2372-119, 2372-118, 2372-117, 2372-116

Table 30: CEC Relative Peak Areas for CHS-1701 and US-licensed Neulasta

Material	Lot	Pre-Peak-1 (diPEG M1 K35 PEG)	Pre-Peak 2 (diPEG M1 K24 PEG)	Pre-Peak 3 (Double- sized PEG)	Pre-Peak 4 (Apparent deamidated species)	Main Peak
CHS-1701	2372-102	0.1	0.1	0.4	NQ	99.4
	2372-103	0.1	0.1	0.4	NQ	99.4
	2372-104	NQ	0.1	0.3	NQ	99.6
	2372-105	0.1	0.1	0.3	NQ	99.5
	2372-110	0.1	0.1	0.4	NQ	99.4
	2372-111	0.1	0.1	0.3	NQ	99.5
	2372-112	0.1	0.1	0.3	NQ	99.6
	2372-113	0.1	0.1	0.6	NQ	99.1
	2372-114	NQ	0.1	0.2	NQ	99.8
	2372-116	0.1	0.1	0.4	NQ	99.4
	2372-117	0.1	0.1	0.5	NQ	99.2
	2372-118	0.1	0.1	0.6	NQ	99.2
	2372-119	0.1	0.1	0.6	NQ	99.2

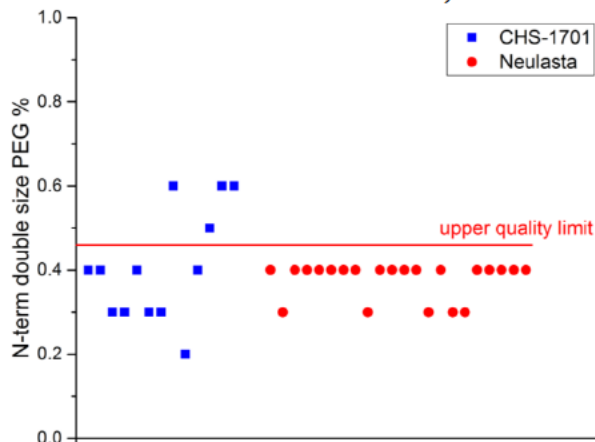
Material	Lot	Pre-Peak-1 (diPEG M1 K35 PEG)	Pre-Peak 2 (diPEG M1 K24 PEG)	Pre-Peak 3 (Double- sized PEG)	Pre-Peak 4 (Apparent deamidated species)	Main Peak
US- licensed Neulasta	1040882	NQ	NQ	0.4	0.3	99.3
	1042866	NQ	NQ	0.3	0.3	99.4
	1047431	NQ	NQ	0.4	0.3	99.3
	1047434	NQ	NQ	0.4	0.3	99.3
	1048085	NQ	NQ	0.4	0.3	99.3
	1048834	NQ	NQ	0.4	0.2	99.3
	1050019	NQ	NQ	0.4	0.2	99.4
	1051304	NQ	NQ	0.4	0.3	99.3
	1051676	NQ	NQ	0.3	0.3	99.4
	1053071	NQ	NQ	0.4	0.2	99.4
	1053081	NQ	NQ	0.4	0.2	99.5
	1053082	NQ	NQ	0.4	0.2	99.5
	1053956	NQ	NQ	0.4	0.1	99.5
	1054829	NQ	NQ	0.3	0.2	99.5
	1055572	NQ	NQ	0.4	0.1	99.5
	1057095	NQ	NQ	0.3	0.2	99.5
	1057096	NQ	NQ	0.3	0.1	99.5
	1057133	NQ	NQ	0.4	0.2	99.5
	1056717	NQ	NQ	0.4	0.2	99.4
	1057097	NQ	NQ	0.4	0.2	99.4
1057373	NQ	NQ	0.4	0.2	99.4	

1059900	NQ	NQ	0.4	0.2	99.4
Neulasta (US) Mean	-	-	0.38	0.22	99.41
Neulasta (US) Standard Deviation	-	-	0.04	0.07	0.08
Neulasta (US) +1.9 Standard Deviation	-	-	0.46	0.34	99.56
CHS-1701 Mean	-	-	0.41	-	99.41
CHS-1701 Minimum	-	-	0.2	-	99.1
CHS-1701 Maximum	-	-	0.6	-	99.8
CHS-1701 Standard Deviation	-	-	0.13	-	0.20

DiPEGylated Species

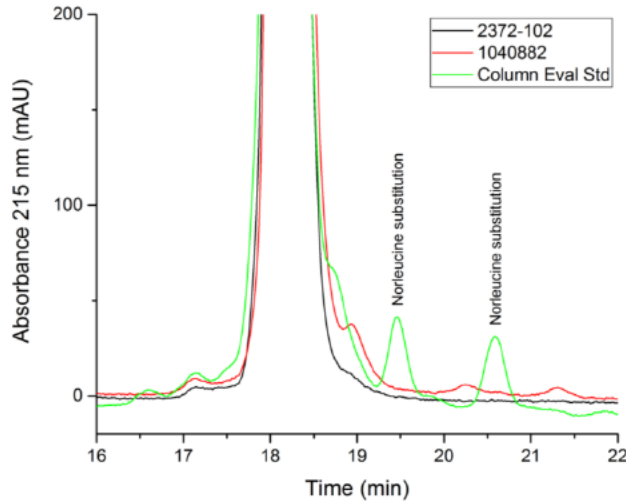
In sponsor’s evaluation, pre-peak 3 (containing a double length PEG at the N-terminus) is the only consistently quantifiable “diPEGylated” peak, and consequently the only peak that is amenable to statistical analysis. Most CHS-1701 lots showed levels less than or equal to the limit of the quality range, as defined as the Neulasta average +1.9 σ (0.46%). However, four of thirteen lots fell slightly outside this range with levels of 0.5% and 0.6%. Levels of pre-peak 3 in US-licensed Neulasta and CHS-1701 lots are compared graphically in Figure 38 below.

Figure 38: Relative Area N-terminal Double-Sized PEG, CHS-1701 vs US-licensed Neulasta



Red line represents the one-sided 1.9 σ limit calculated from US-licensed Neulasta (US) results.

The review of the data revealed that the levels of pre-peak 1 and pre-peak 2 (species with a second PEGylation at K35 and K24 respectively) are very low ($\leq 0.1\%$) in all lots tested (see Figure 33 and Table 30 above), although they appear slightly higher in CHS-1701. The small differences in pre-peak 1 and pre-peak 2 are further exaggerated because levels in US-licensed Neulasta lots are just below the threshold for quantitation and are thereby reported as $<0.1\%$, whereas most CHS-1701 lots have levels that are just above threshold and are thereby rounded up to 0.1%. Therefore, if estimated percent areas of all peaks are included, then the relative diPEGylated area of the majority of CHS-1701 lots is outside the range of the US-licensed Neulasta lots (Figure 39 below). While the statistical similarity criteria for percent area of diPEGylated species was not met, the observed differences are very small, on the order of tenths of a percent of the total peak area, and difficult to quantify accurately since the peaks are very near the LOQ. Summing several separate peaks near LOQ can further compound the reported difference.



Legend: Black line: CHS-1701 lot 2372-102 (1701-DP-103); Red line: US-licensed Neulasta lot 1040882; Green line: Column Evaluation Standard

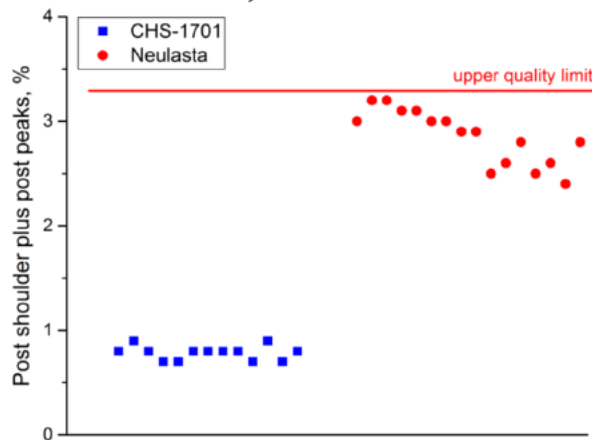
Reviewer comment:

Norleucine species were not observed in the proposed biosimilar or the reference product. The results are acceptable and support a determination of highly similar of both products.

Deamidated Species

Deamidated species elute after the main peak in RPC. Additional other species (e.g. partially reduced) also elute late, albeit in low abundance. Therefore, the sum of all post peaks is used to evaluate deamidation. The mean total sum of post-peaks for all US-licensed Neulasta comparator lots is 2.8% of integrated area. The one-sided acceptance criteria for US-licensed Neulasta mean value + 1.9 σ is 3.34%. Post-peaks in CHS-1701 lots ranged from 0.7% to 0.9%, which meet the acceptance criteria. Relative postpeak areas are illustrated graphically in Figure 41.

Figure 41: RPC Post-Peaks Relative Area, CHS-1701 DP vs. US-licensed Neulasta



Red line represents the one-sided 1.9 σ limit calculated from US-licensed Neulasta results.

Reviewer comment:

Levels of post-peaks (including deamidation) are significantly lower in CHS-1701 lots. This difference in purity between CHS-1701 and US-licensed Neulasta is acceptable because it favors purity of CHS-1701 lots. The difference is likely due to the older age of US-licensed Neulasta lots. These results are

acceptable and support a determination that CHS-1701 is highly similar to US-Neulasta. Clearly, based on the reference product data, deamidation is one of the degradation pathways for this product and should be closely monitored on stability.

Table 31 below demonstrates the levels of variants in CHS-1701 and US-licensed Neulasta using the RPC method.

Table 31: RPC Relative Peak Areas

Material	Lot	Pre-1	Pre-2	Main	Post-1	Post-2	Post- 3	Pre sum	Post sum
CHS-1701	2372-102	0.3	0.3	98.6	0.8	ND	ND	0.6	0.8
	2372-103	0.3	0.3	98.6	0.9	ND	ND	0.6	0.9
	2372-104	0.3	0.3	98.6	0.8	ND	ND	0.6	0.8
	2372-105	0.3	0.3	98.8	0.7	ND	ND	0.6	0.7
	2372-110	0.2	0.1	99.0	0.7	ND	ND	0.3	0.7
	2372-111	0.2	0.1	98.8	0.8	ND	ND	0.3	0.8
	2372-112	0.2	0.1	98.9	0.8	ND	ND	0.3	0.8
	2372-113	0.2	0.1	98.8	0.8	ND	ND	0.3	0.8
	2372-114	0.2	0.2	98.9	0.8	ND	ND	0.4	0.8
	2372-116	0.6	0.2	98.5	0.7	ND	ND	0.8	0.7
	2372-117	0.6	0.3	98.3	0.9	ND	ND	0.9	0.9
2372-118	0.6	0.3	98.5	0.7	ND	ND	0.9	0.7	
2372-119	0.5	0.3	98.4	0.8	ND	ND	0.8	0.8	
US-licensed Neulasta	1040882	0.5	0.3	96.2	2.2	0.5	0.3	0.8	3.0
	1042866	0.5	0.2	96.0	2.2	0.7	0.3	0.7	3.2
	1047431	0.5	0.3	96.0	2.2	0.7	0.3	0.8	3.2
	1047434	0.5	0.2	96.2	2.2	0.6	0.3	0.7	3.1
	1048085	0.7	0.3	95.9	2.1	0.7	0.3	1.0	3.1
	1048834	0.6	0.3	96.2	2.1	0.6	0.3	0.9	3.0
	1050019	0.5	0.2	96.2	1.9	0.8	0.3	0.7	3.0
	1051304	0.6	0.3	96.2	1.9	0.7	0.3	0.9	2.9
	1051676	0.5	0.3	96.4	2.0	0.6	0.3	0.8	2.9
	1053071	0.5	0.3	96.7	1.8	0.5	0.2	0.8	2.5
	1053081	0.5	0.2	96.9	1.8	0.5	0.3	0.7	2.6
	1053082	0.6	0.3	96.3	1.9	0.6	0.3	0.9	2.8
	1053956	0.4	0.2	96.9	1.8	0.5	0.2	0.6	2.5
	1054829	0.4	0.2	97.0	1.8	0.5	0.3	0.6	2.6
	1055572	0.4	0.1	97.0	1.7	0.5	0.2	0.5	2.4
	1057095	0.4	0.2	96.6	2.0	0.5	0.3	0.6	2.8
	1057096	0.4	0.2	97.1	1.7	0.5	0.2	0.6	2.4
	1057133	0.4	0.2	96.8	1.8	0.6	0.3	0.6	2.7
	1056717	0.8	0.4	96.4	1.8	0.5	0.3	1.2	2.6
	1057097	0.8	0.4	96.2	1.8	0.4	0.3	1.2	2.5
1057373	0.8	0.3	96.5	1.7	0.5	0.3	1.1	2.5	
1059900	0.8	0.3	96.6	1.6	0.5	0.2	1.1	2.3	
Neulasta (US) Mean		0.55	0.26	96.47	1.91	0.57	0.28	0.81	2.75
Neulasta (US) Standard Deviation		0.14	0.07	0.36	0.19	0.10	0.04	0.21	0.28
Neulasta (US) ± 1.9 Standard Deviation		0.82	0.40	95.78	2.27	0.76	0.36	1.20	3.29

CHS-1701 Mean	0.35	0.22	98.67	0.78	ND	ND	0.57	0.78
CHS-1701 Standard Deviation	0.17	0.09	0.21	0.07	ND	ND	0.23	0.07
CHS-1701 Minimum	0.2	0.1	98.3	0.7	ND	ND	0.3	0.7
CHS-1701 Maximum	0.6	0.3	99	0.9	ND	ND	0.9	0.9

Reviewer assessment:

In conclusion, it was determined based on RPC results (Table 31 above) the number and levels of impurities were lower in CHS-1701 when compared with the reference product which could potentially be attributed to the older age of US-licensed Neulasta lots. These results are acceptable and support a determination that CHS-1701 is highly similar to US-Neulasta.

Microflow imaging

Sub-visible particles in ranges $\geq 2\mu\text{m}$, $\geq 10\mu\text{m}$, and $\geq 25\mu\text{m}$ were assessed using microflow imaging (MFI) method in both products. 13 CHS-1701 and 18 of 22 lots of US-licensed Neulasta were evaluated. The images were filtered using an aspect ratio filter of ≥ 0.85 in order to exclude (b) (4) or air droplets from the assessment and only evaluate the particles of protein origin. A larger number of (b) (4) particles were present in the CHS-1701 lots compared to the reference product lots in the $\geq 25\mu\text{m}$ size range. However, after applying the aspect ratio filter of ≥ 0.85 , values for all ranges were below the US-licensed Neulasta average + 1.9σ of the mean value.

Table 32. The summary of MFI results for CHS-1701 and US-licensed Neulasta

Material	Lot	Total particle concentration ^a			Concentration, aspect ratio <0.85		
		$\geq 2\mu\text{m}$	$\geq 10\mu\text{m}$	$\geq 25\mu\text{m}$	$\geq 2\mu\text{m}$	$\geq 10\mu\text{m}$	$\geq 25\mu\text{m}$
Neulasta (US) Mean		44,486	789	22	9,330	50	2
Neulasta (US) Standard Deviation		22,856.2	361.3	12.5	5,213.0	30.5	4.5
Neulasta (US) + 1.96 Standard Deviation		87,913.1	1,475.9	46.2	19,234.7	107.6	10.8
CHS-1701 Mean		9,409	383	82	1,818	21	1
CHS-1701 Minimum		3,425	100	0	639	3	0
CHS-1701 Maximum		19,219	1,107	347	4,419	47	6

Reviewer comment:

The assessment of sub-visible particles in CHS-1701 and US-licensed Neulasta demonstrated that CHS-1701 had lower levels of sub-visible particles than US-licensed Neulasta when protein-like particles in $\geq 2\mu\text{m}$, $\geq 10\mu\text{m}$ and $\geq 25\mu\text{m}$ ranges were assessed. (b) (4) presence was detected in both products, but the differences in particulate count were negligible. These findings do not preclude a demonstration of similarity for this attribute due to the fact that (b) (4) particles observed in both products come from (b) (4) for both products. Overall particle count results after applying the ratio filter demonstrate lower levels of particles in CHS-1701 when compared with US-licensed Neulasta. This is acceptable.

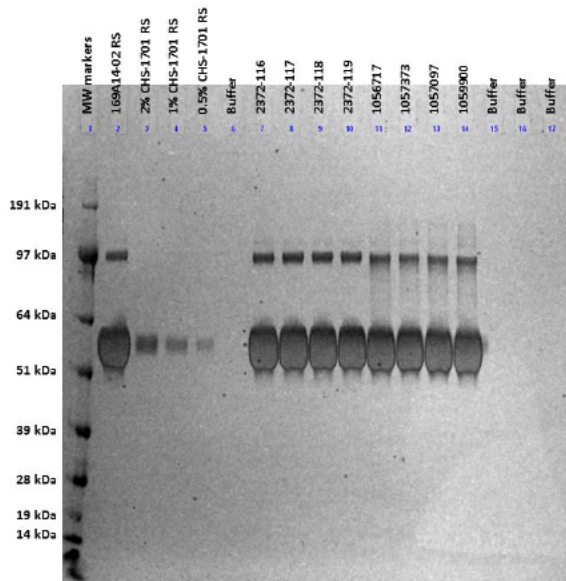
Reviewer assessment:

The results of sub-visible particles evaluation support a demonstration of highly similar of CHS-1701 to US-licensed Neulasta with respect to this quality attribute.

SDS PAGE with silver stain (tier 3)

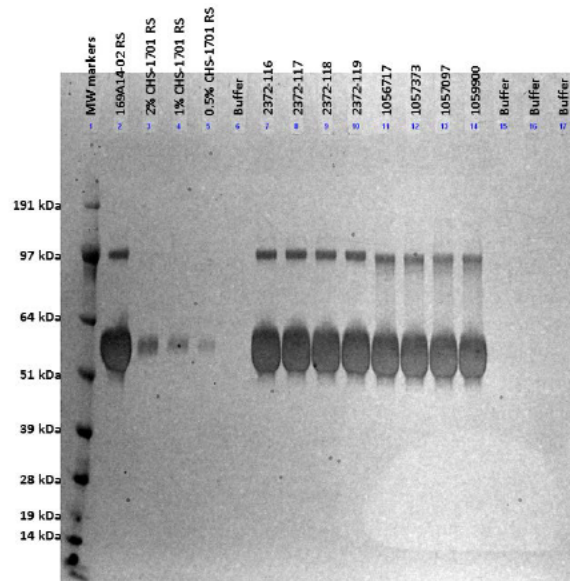
Reduced and non-reduced SDS-PAGE was used to analyze the proposed biosimilar and the reference product in terms of content of low and high molecular weight variants (LMWV and HMWV), clips and PEGylation variants. Representative SDS-PAGE gels comparing 4 lots of the CHS-1701 and 4 lots of US-licensed Neulasta are shown below.

SDS-PAGE Non-reduced Silver Stain



Lane 1: Molecular weight marker; Lane 2: CHS-1701 reference standard lot 169A14-02; Lane 3: 2% pegfilgrastim reference standard; Lane 4: 1% CHS-1701 reference standard; Lane 5: 0.5% pegfilgrastim reference standard; Lane 6: Buffer; Lane 7: CHS-1701 lot 2372-116 (1701-DP-117); Lane 8: CHS-1701 lot 2372-117 (1701-DP-118); Lane 9: CHS-1701 lot 2372-118 (1701-DP-119); Lane 10: CHS-1701 lot 2372-119 (1701-DP-120); Lane 11: Neulasta (US) lot 1056717; Lane 12: Neulasta (US) lot 1057373; Lane 13: Neulasta (US) lot 1057097; Lane 14: Neulasta (US) lot 1059900; Lane 15 – 17: Buffer

SDS-PAGE Reduced Silver Stain



Lane 1: Molecular weight marker; Lane 2: CHS-1701 reference standard lot 169A14-02; Lane 3: 2% pegfilgrastim reference standard; Lane 4: 1% CHS-1701 reference standard; Lane 5: 0.5% pegfilgrastim reference standard; Lane 6: Buffer; Lane 7: CHS-1701 lot 2372-116 (1701-DP-117); Lane 8: CHS-1701 lot 2372-117 (1701-DP-118); Lane 9: CHS-1701 lot 2372-118 (1701-DP-119); Lane 10: CHS-1701 lot 2372-119 (1701-DP-120); Lane 11: Neulasta (US) lot 1056717; Lane 12: Neulasta (US) lot 1057373; Lane 13: Neulasta (US) lot 1057097; Lane 14: Neulasta (US) lot 1059900; Lane 15 – 17: Buffer

No major differences were observed between the two products in either the reducing or non-reducing conditions (no disulfide bond cleavage). The main band of the product was observed ~ 55 kDa with an impurity band showing ~ 97kDa. Very faint bands were also observed above 97kD impurity; however, the bands were barely visible and appear to be more evident in the reference product. The sponsor did not provide any discussion of these results except for labelling the main impurity as a high molecular weight variant, presumably the diPEGylated material. This impurity appeared a little more defined and darker in CHS-1701 lots while it looked more washed out in US-licensed Neulasta lots. This observation is consistent with CEC results where more diPEGylated species were observed in the proposed biosimilar lots.

Reviewer comment:

As observed before using other chromatographic methods, the levels of impurities, especially HMWV are similar in both products though they appear a little more defined in CHS-1701 lots; however, it is difficult to accurately quantify this difference in SDS-PAGE gels.

Intact Mass by LC-MS (tier 3)

20 kDa Polyethylene glycol (PEG) is covalently attached at the N-terminal of the G-CSF molecule. PEG and its derivatives are synthetic polymers that form bioconjugates with peptides resulting in hydrophilic compounds that often exhibit increased circulatory half-life and reduced immunological response. Additionally, polyethylene chains can provide protection against degradation by proteolytic enzymes. However, proper characterization of PEG molecules and its conjugates is a relatively difficult task due to overlapping charge-state distributions and the inherent heterogeneity of these molecules resulting in very complicated mass spectra. Typically, instead of a single, very accurate result that can be obtained for unconjugated protein (such as G-CSF), a wide distribution of molecular weights is present because of the polymeric nature of the PEG. Limitations to analytical analyses imposed by the presence of PEG were previously observed and briefly discussed above, regarding the peptide map analysis. Intact mass measurements were performed using all 13 CHS-1701 lots and 16 of 22 US-licensed Neulasta lots. Representative deconvoluted mass spectra of the proposed biosimilar and the reference product are shown in Figure 8.

Figure 8. Representative mass spectra of CHS-1701 and US-licensed Neulasta

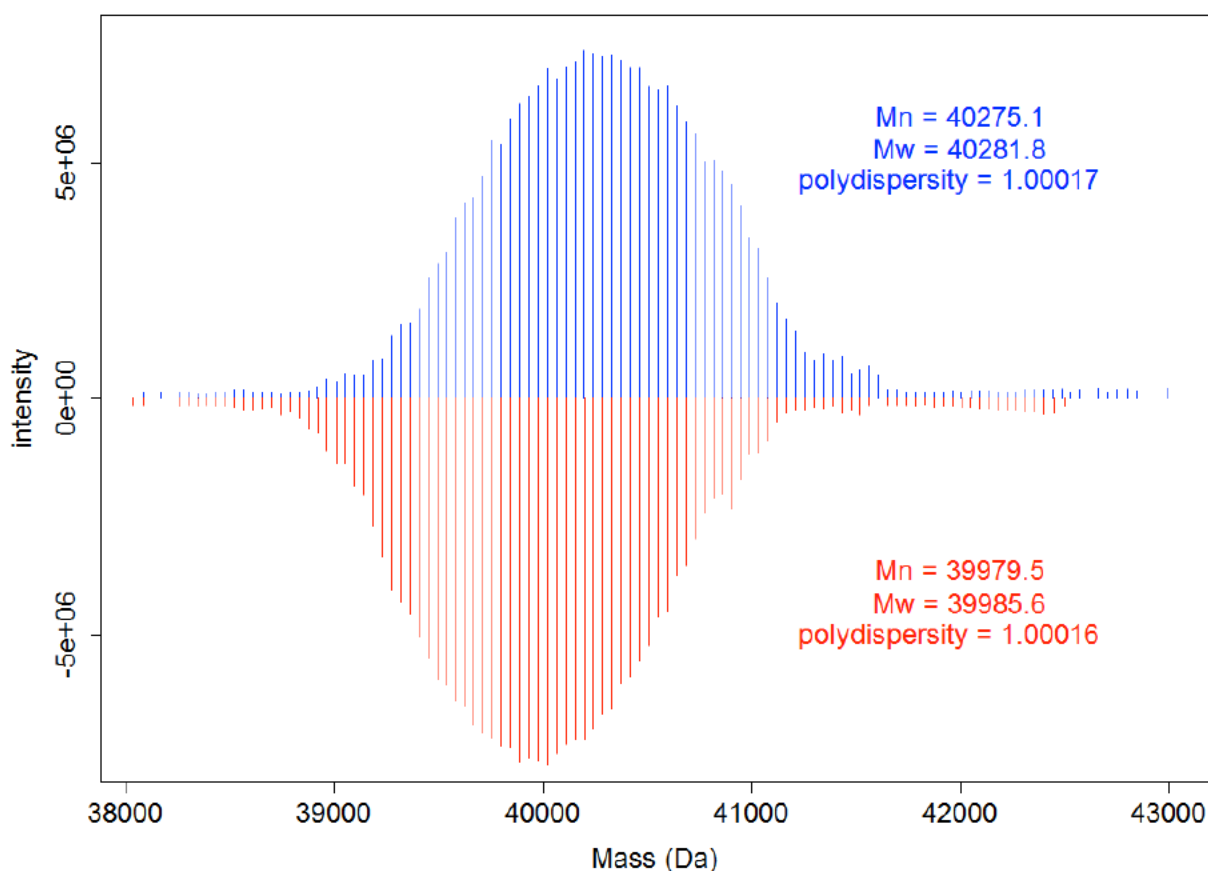


Figure excerpted from Coherus 351(k) BLA submission.

Legend: Blue (top) CHS-1701 reference standard; Red (bottom) US-licensed Neulasta lot 1059900

A range of masses separated by 44 Da (the mass of a single PEG unit) is observed for all lots analyzed. It is worth noting that the results of these analyses are very consistent and there is little variability for both products (see table 1 below).

Table 1. Average Masses and Polydispersity of US-licensed Neulasta and CHS-1701 DP Lots

Material	Lot	Mn	Mw	Pd
CHS-1701	2372-102 (1701-DP-103)	40290.4	40297.8	1.00018
	2372-103 (1701-DP-104)	40275.1	40281.8	1.00017
	2372-104 (1701-DP-105)	40286.9	40293.6	1.00017
	2372-105 (1701-DP-106)	40277.3	40284.1	1.00017
	2372-110 (1701-DP-111)	40286.4	40293.2	1.00017
	2372-111 (1701-DP-112)	40274.4	40281.2	1.00017
	2372-112 (1701-DP-113)	40276.4	40283.1	1.00017
	2372-113 (1701-DP-114)	40299.4	40306.3	1.00017
	2372-114 (1701-DP-115)	40269.4	40276.1	1.00017
	2372-116 (1701-DP-117)	40296.9	40303.5	1.00016
	2372-117 (1701-DP-118)	40295.3	40302.0	1.00017
	2372-118 (1701-DP-119)	40310.7	40317.5	1.00017
2372-119 (1701-DP-120)	40299.9	40306.8	1.00017	
US-licensed Neulasta	1048085	39975.0	39981.4	1.00016
	1050019	39931.6	39937.8	1.00015
	1051304	39926.2	39932.5	1.00016
Material	Lot	Mn	Mw	Pd
	1051676	39979.1	39985.4	1.00016
	1053071	39967.3	39973.8	1.00016
	1053081	39956.1	39962.6	1.00016
	1053082	39954.1	39960.2	1.00015
	1053956	39959.5	39965.9	1.00016
	1055572	39945.8	39952.1	1.00016
	1056717	39970.3	39976.8	1.00016
	1057095	39953.6	39959.8	1.00016
	1057096	39963.3	39969.6	1.00016
	1057097	39954.6	39961.0	1.00016
	1057133	39940.9	39947.1	1.00016
	1057373	39958.8	39965.0	1.00016
	1059900	39979.5	39985.6	1.00015
CHS-1701 Mean		40287.6	40294.4	1.00017
CHS-1701 Standard Deviation		12.50	12.53	0.000005
Neulasta (US) Mean		39957.2	39963.5	1.00016
Neulasta (US) Standard Deviation		15.61	15.64	0.000003

The average mass is centered on approximately 40.0 kDa for US-licensed Neulasta, while for CHS-1701 lots this value is approximately 40.3 kDa. This shift toward a larger average mass observed for CHS-1701 indicates that average PEG molar masses differ by about 2% and are higher for CHS-1701 (net masses after subtracting the expected mass of the protein moiety, 18.8 kDa). The difference in PEG size could

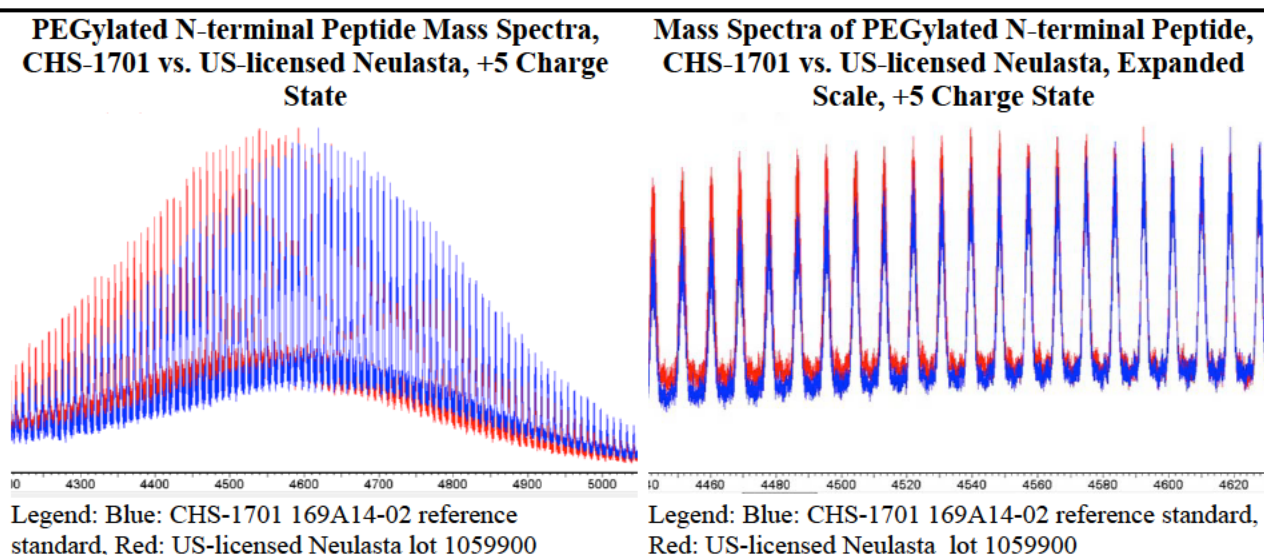
potentially be attributed to the variability of the PEG raw material (specification of (b) (4) kDa) and the size and age of the PEG aldehyde lot used for PEGylation.

Reviewer comment:

Even though the average masses differ slightly between the two products, the polydispersity values are almost identical indicating that the distribution of molecular weights in CHS-1701 and US-licensed Neulasta are comparable. It is not clear whether the different PEG size (less than 2%) could have any meaningful clinical impact. These differences do not preclude a demonstration of highly similar.

PEG linker analysis

PEG linker analysis was performed on a single lot of each product. An N-terminal tryptic peptide (17 amino acids long) containing the PEG group was analyzed by liquid chromatography coupled with mass spectrometry LC-MS. The idea behind this analysis was that if the masses of the short peptide + the linker + the PEG moiety are the same, then assuming the PEG and the peptide have the same masses, the linker has to have the same mass as well. Hence, the structure is the same in both products.³



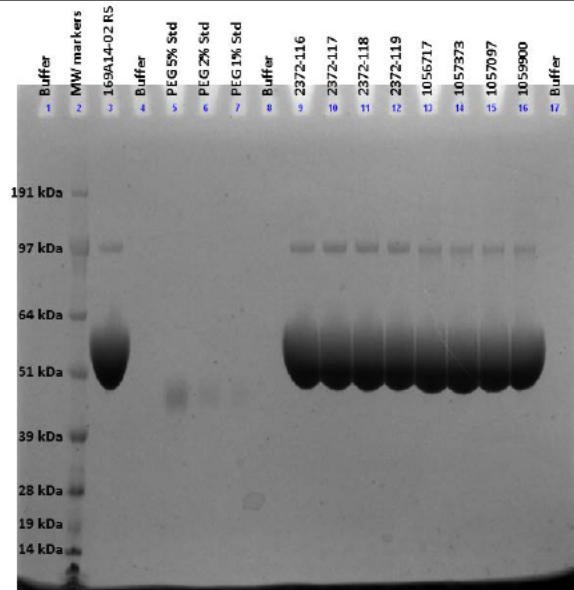
The exact overlay of both products and the peak separation by 44Da (which is attributed to the mass of ethylene glycol, the main subunit block of PEG) indicated that the masses of both digests are the same. Any modification of the linker would result in appearance of additional peaks located between the major signals of these fragments. The mass spectrometry data comparing the CHS-1701 and US-licensed Neulasta N-terminal tryptic peptides support the conclusion of same linker and are included in the analytical similarity assessment but not presented here.

Reviewer comment:

The above results indicate that PEG protein linkers in CHS-1701 and US-licensed Neulasta have the same atomic composition. This conclusion is further corroborated by the forced degradation studies discussed later in the memo.

UnPEGylated N-terminus by Edman sequencing

³ Molineux, G. *Curr. Pharm. Des.* 10 (2004), 1235-1244.



Nominal load 6 μg ; free PEG standards 0.3 μg , 0.12 μg , and 0.06 μg

Legend:

Lane 1: Buffer;
Lane 2: Molecular weight marker;
Lane 3: CHS-1701-chrs reference standard lot 169A14-02;
Lane 4: Buffer;
Lane 5: Free PEG 5% standard;
Lane 6: Free PEG 2% standard;
Lane 7: Free PEG 1% standard;
Lane 8: Buffer;
Lane 9: CHS-1701 lot 2372-116 (1701-DP-117);
Lane 10: CHS-1701 lot 2372-117 (1701-DP-118);
Lane 11: CHS-1701 lot 2372-118 (1701-DP-119);
Lane 12: CHS-1701 lot 2372-119 (1701-DP-120);
Lanes 13 – 16: Neulasta (US) lots 1056717, 1057373, 1057097, 1059900;
Lane 17: Buffer

Figure excerpted from Coherus 351(k) submission

Reviewer comment:

The SDS-PAGE with iodine stain results indicate that there appears to be no free PEG in either CHS-1701 or US-licensed Neulasta lots which supports the demonstration of highly similar free PEG content. There are some limitations to this assessment (e.g. the method is not very sensitive). The sponsor claims a detection level of approximately 1%; however, the method qualification report suggests that the limit of detection of free PEG is 2% rather than 1%. Additionally, this method is more of a qualitative assessment.

Reviewer assessment:

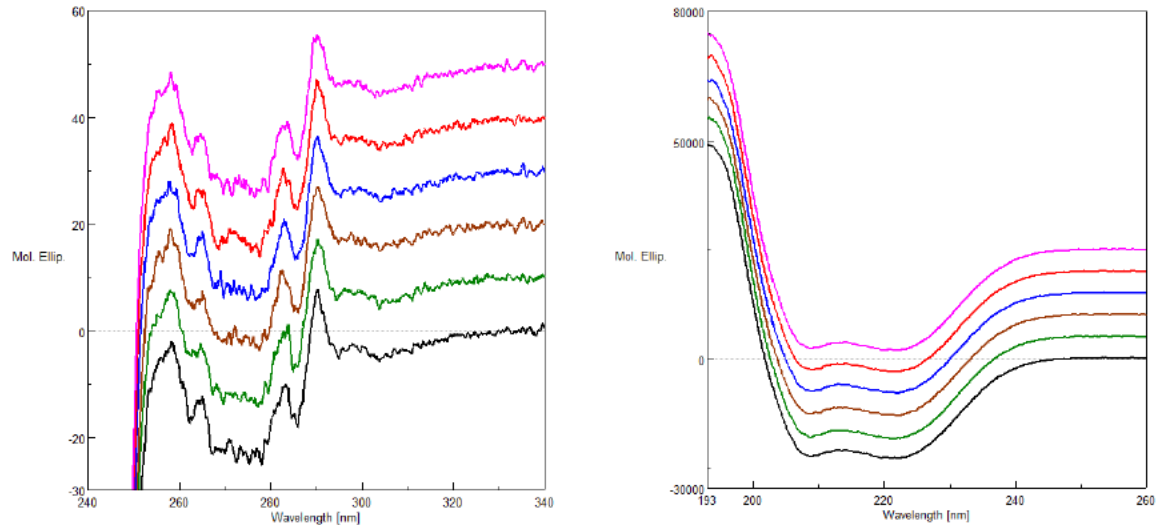
The free PEG can be considered as a process related impurity (the PEG aldehyde used for PEGylation of G-CSF protein) or a product related impurity (if it is cleaved from the product). Considering the type of linkage between the PEG and G-CSF, which is a stable amide-type linker, it is highly unlikely the free PEG could be a result of a cleavage under normal conditions. Additionally, removal of PEG from the product would result in appearance of G-CSF protein, which is easily detectable by chromatographic methods and not present in either CHS-1701 or US-licensed Neulasta. This correlation with other methods provides additional assurance of no free PEG determination as evaluated by the sponsor. Thus, any PEG detected in the proposed biosimilar or the reference product is likely a process-related impurity (e.g. PEG aldehyde). (b) (4)

Therefore, there is very little risk associated with this impurity because of the reasons discussed above.

Higher order structure

A variety of methods was used to evaluate secondary and tertiary structures of CHS-1701 and US-licensed Neulasta, including circular dichroism, 2D NMR, fluorimetry, differential scanning calorimetry, and hydrogen deuterium exchange.

The secondary structure was assessed using circular dichroism in the far UV region and tertiary structure was assessed by near UV CD spectra. Thirteen CHS-1701 lots and 20 of 22 US-licensed Neulasta lots were evaluated by comparing near and far UV CD spectra (representative spectra are presented in Figure 3).

Figure 3. Near and far UV CD spectra for representative CHS-1701 and US-licensed Neulasta lots**Near UV CD spectra****Legend:**

Black: US-licensed Neulasta lot 1057133;
Green: US-licensed Neulasta lot 1057096;
Brown: US-licensed Neulasta lot 1055572;
Blue: CHS-1701 lot 2372-114 (1701-DP-115);
Red: CHS-1701 lot 2372-113 (1701-DP-114);
Pink: CHS-1701 lot 2372-112 (1701-DP-113)

Far UV CD spectra**Legend:**

Black: US-licensed Neulasta lot 1057133;
Green: US-licensed Neulasta lot 1057096;
Brown: US-licensed Neulasta lot 1055572;
Blue: CHS-1701 lot 2372-114 (1701-DP-115);
Red: CHS-1701 lot 2372-113 (1701-DP-114);
Pink: CHS-1701 lot 2372-112 (1701-DP-113)

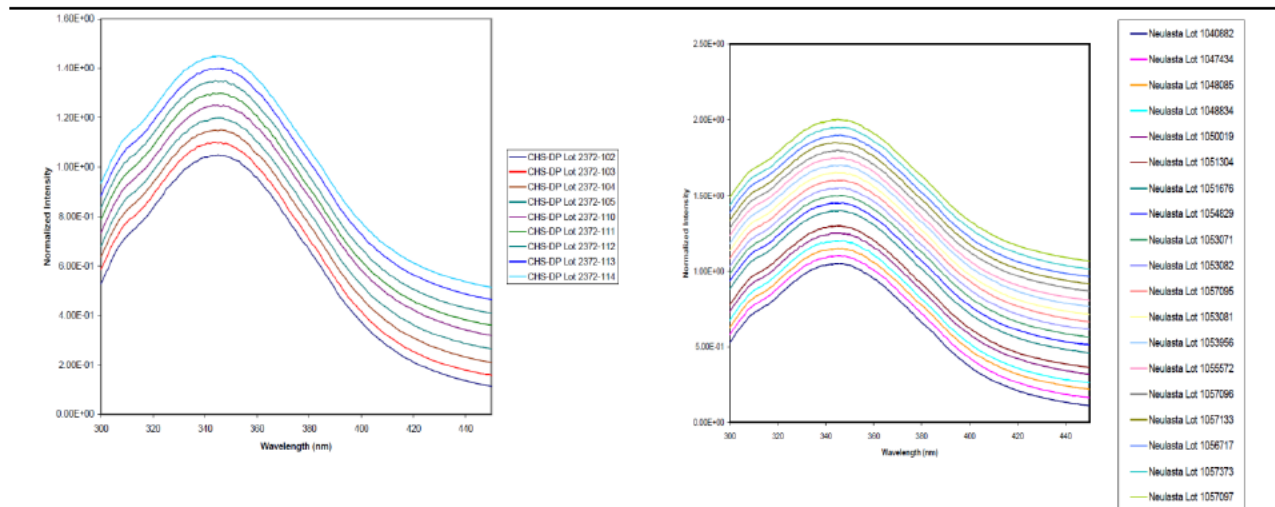
Figures excerpted from Coherus 351(k) BLA submission.

Reviewer comment:

The results of the assessments (analysis of near and far UV CD spectra) support a demonstration of highly similar secondary and tertiary structures.

Fluorescence spectra also provide information about tertiary protein structure and the presence of tyrosine residues. Proteins that have tryptophan amino acids in their structure exhibit fluorescence at ~345 nm which reflects their tertiary structure (conformational changes can be observed). Additionally, tyrosine residues exhibit fluorescence at ~303 nm, which can also be observed by this method. Fluorescent spectra are provided in the Figures 88 and 89 below.

Figure 88: Fluorescence Spectra of CHS-1701 Lots**Figure 89: Fluorescence Spectra of US-licensed Neulasta Lots**

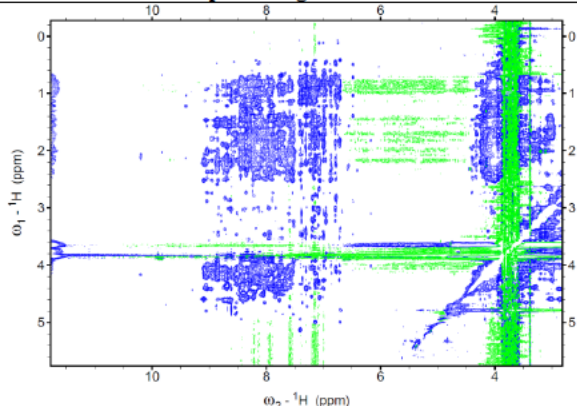


Reviewer comment:

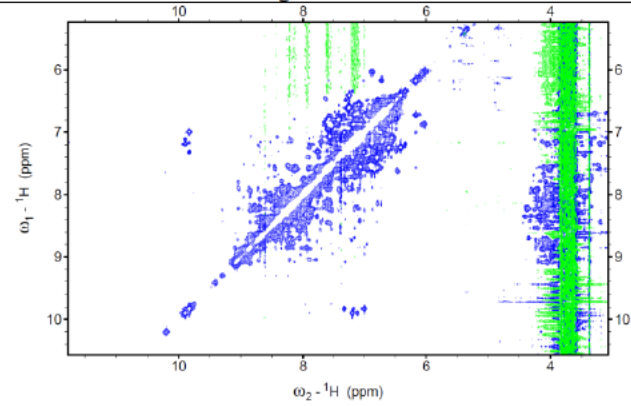
The analysis of the fluorescence results supports a demonstration of highly similar fluorescence of CHS-1701 to US-licensed Neulasta.

2D nuclear overhauser effect spectroscopy (NOESY) was used to evaluate secondary and tertiary structure of CHS-1701 and US-licensed Neulasta lots. This 2D NMR technique provides fingerprint-like analysis through space interactions between protons (¹H) that are close to each other within the protein structure. Signals observed using this method represent proton-proton interactions that depend on their environment in the three-dimensional protein structure. Due to the complexity of these spectra, they were divided into 2 groups: amide-amide and amide-aliphatic interactions. Representative spectra from analysis of one CHS-1701 and one US-licensed Neulasta lot are provided below.

2D NOESY Amide-Aliphatic Region CHS-1701 lot 2372-102

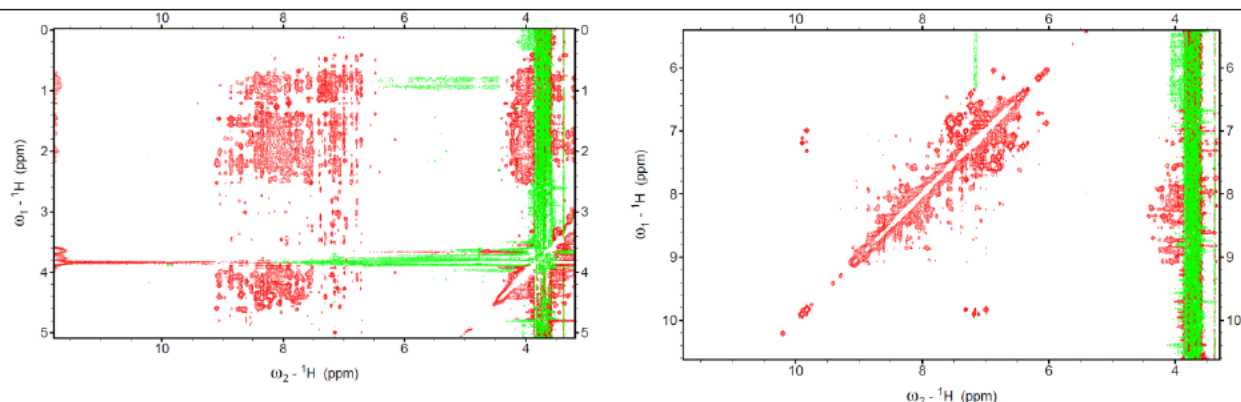


2D NOESY Amide-Amide Region CHS-1701 lot 2372-102



2D NOESY Amide-Aliphatic Region US-licensed Neulasta lot 1040882

2D NOESY Amide-Amide Region US-licensed Neulasta lot 1040882

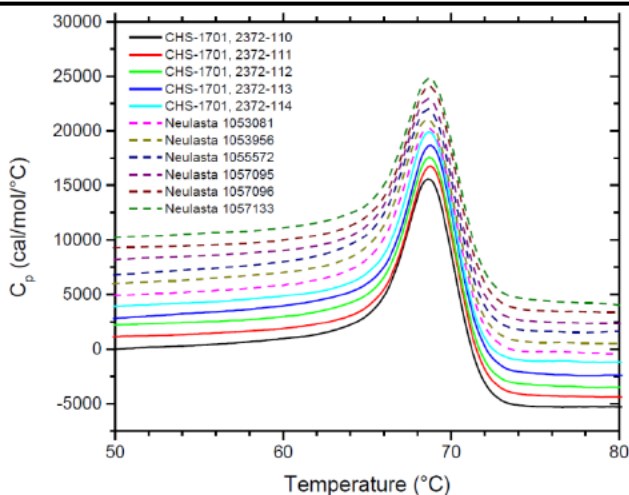


There is a big signal from the PEG moiety (green) providing some interference in the amide-aliphatic range; however, overall signal separation appears to be relatively good. The sponsor provided individual spectra for all tested lots as well as the overlay of all the data for both regions. The visual comparison of data leads to conclusion that the resonance patterns for both products are similar.

Reviewer comment:

The analysis of 13 CHS-1701 and 17 US-licensed Neulasta lots support a demonstration of highly similar of the proposed biosimilar to US-licensed Neulasta with respect to secondary and tertiary structure when analyzed by 2D NOESY NMR.

Differential scanning calorimetry (DSC) was also used to assess the secondary and tertiary structure of CHS-1701 and US-licensed Neulasta. This method provided a number of melting curves which reflect intramolecular and intermolecular protein interactions. DSC thermograms for 6 CHS-1701 and 6 US-licensed Neulasta lots are provided in the Figure below.



Legend:

CHS-1701 lots: 2372-110 (1701-DP-111), 2372-111 (1701-DP-112), 2372-112 (1701-DP-113), 2372-113 (1701-DP-114) and 2372-114 (1701-DP-115);
US-licensed Neulasta lots: 1053081, 1053956, 1055572, 1057095, 1057096, 1057133.

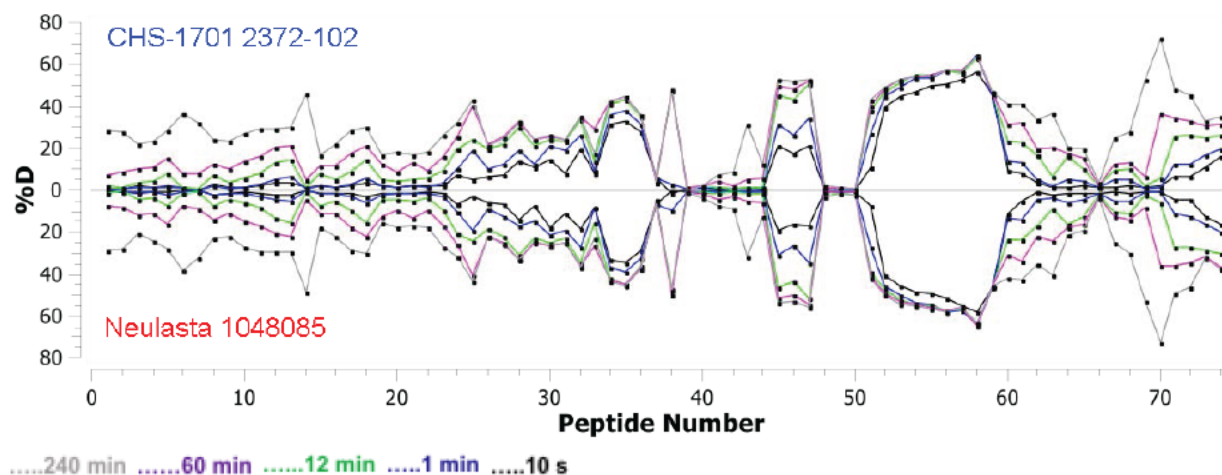
Similar melting curves were observed in both products with unfolding temperature averaging 68.8 °C for CHS-1701 and 68.7 °C for US-licensed Neulasta lots.

Reviewer comment:

The analysis of the differential scanning calorimetry results support a demonstration of highly similar melting curves and unfolding temperatures of CHS-1701 and US-licensed Neulasta.

Hydrogen deuterium exchange (HDX) method was used to assess the tertiary structure, conformation, and protein dynamics using 3 CHS-1701 and 3 US-licensed Neulasta lots. The overall pattern of solvent (D_2O) accessibility for one CHS-1701 and one US-licensed Neulasta lot is provided in the Figure 96 below and is consistent with literature data.⁴

Figure 96: Deuterium Uptake Lot 2372-102 vs 1048085



Results are presented as a measure of percent deuterium exchange compared to total number of protons for each individual peptide generated in a pepsin digest, numbered from the N-terminus to the C-terminus.

Reviewer comment:

The analysis of the hydrogen deuterium exchange results support a demonstration of highly similar tertiary structure, conformation, and protein dynamics of CHS-1701 and US-licensed Neulasta.

Extinction coefficient (280) was determined for both products (all available lots) using UV and RI (refractive index) detection when SEC-MALS data was generated. Protein extinction coefficient correlates with aromatic amino acid content which additionally confirms structural similarity of both products.⁵ UV detectors can detect only the moiety of G-CSF, whereas RI detectors can detect the moieties of both protein and PEG. Using RI and UV detectors in conjunction with a MALS instrument, it is possible to identify the stoichiometry of PEG–protein conjugates. For the purpose of analytical similarity assessment a PEG molar mass of 21.3 kDa was used in calculations (this is an average value from PEG raw material CoA). Comparison of results is presented in the Figure 98 below.

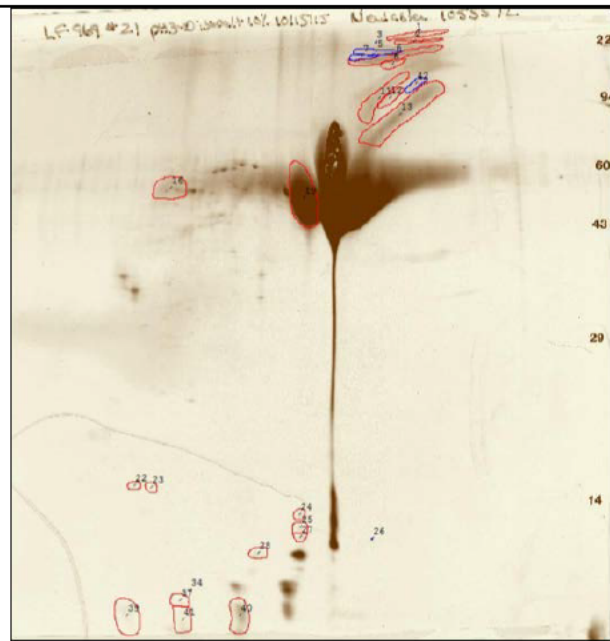
Figure 98: UV Extinction Coefficient from RI

⁴ Wei, H., Ahn, J., and YQ Yu., *Journal of the American Society for Mass Spectrometry* 23 (2012), 498-504.

⁵ Wen, J., Arakawa, T., Wypych, J., Langley, K.E., Schwartz, M.G., Philo, J.S., *Techniques in Protein Chemistry* 8 (1997), 113-119.



Polypeptide spots increased in CHS-1701 vs US-licensed Neulasta are outlined in blue, while spots decreased in CHS-1701 vs. US-licensed Neulasta are outlined in red. 100 µg of each sample was loaded.



Polypeptide spots increased in CHS-1701 vs US-licensed Neulasta are outlined in blue, while spots decreased in CHS-1701 vs. US-licensed Neulasta are outlined in red. 100 µg of each sample was loaded.

Minor differences are observed between both products; however, there appear to be several more intense spots in US-licensed Neulasta gel. The sponsor did not provide any discussion of the observed differences; it is also not clear whether the sponsor attempted to identify HCP that slightly more abundant in CHS-1701. Risk-based assessment of differences in process-related impurities identified between CHS-1701 and the reference product was provided. It concluded that:

- The spectrum and character of HCP in both products are highly similar
- The manufacturing process, (b) (4) is able to remove HCPs to very low levels
- Multiple techniques are used to evaluate levels of HCPs and for some of them the level is below the LOQ
- HCPs are tested at the (b) (4) further ensuring the removal of HCPs
- Quantity of HCPs is so low that there is no effect on product activity
- No product degradation that could be attributed to HCPs, such as glycosidase or protease, was observed on stability
- The levels of HCPs are not very high; it is not clear if any differences in HCPs in both products could trigger different immune responses.

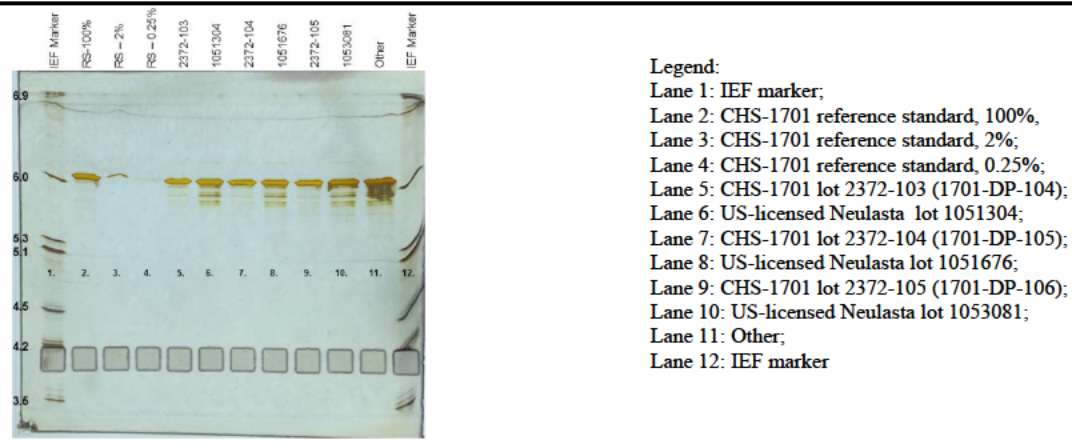
Reviewer comment

Data provided in this 351(k) BLA assessing the host cell proteins in CHS-1701 and US-licensed Neulasta is acceptable; there is no expectation that the process-related impurities present in CHS-1701 should “match” those observed in the reference product (US-licensed Neulasta). Risk assessment of HCPs was performed and the conclusion was that there is very little risk associated with any HCPs present in the drug product. However, minor differences between both products are observed. These differences do not preclude a demonstration of highly similar; however, residual uncertainty remains due to higher incidence of immunogenicity for CHS-1701 vs. US-licensed Neulasta.

Charge variants by isoelectric focusing

Isoelectric focusing (IEF) with silver stain was used to assess charge variants and isoelectric point in the proposed biosimilar and the reference product. An example of isoelectric focusing gel is provided in the Figure 101 below.

Figure 101: IEF with Silver Stain



As observed earlier using chromatographic methods, especially RPC and CEC, there are more impurities/charge variants in US-licensed Neulasta lots and this is confirmed by IEF results. Minor bands are more visible in US-licensed Neulasta lots, which is consistent with lots age and observed deamidation (on average US-licensed Neulasta lots are 1-2 years older than CHS-1701 lots). Isoelectric point (pI) appears to be ~6 in all tested lots when compared with the IEF marker.

Reviewer comment:

Isoelectric focusing provides results that are consistent with previous findings (there is more deamidation in US-licensed Neulasta) and support demonstration of highly similar charge variants between CHS-1701 and US-licensed Neulasta lots.

Size variants by analytical ultracentrifugation (AUC)

Size variants were previously assessed by SEC and analytical centrifugation (AUC) as an orthogonal method to evaluate this quality attribute. One potential advantage the AUC method has over SEC is that there are no column-protein interactions that may affect SEC results. On the other hand, AUC is less sensitive than size exclusion method and less abundant size variants could potentially be missed. Overall, the AUC results demonstrate that sedimentation patterns between CHS-1701 and US-licensed Neulasta are highly similar. However, there appear to be slight differences in the total aggregates measured by SEC and AUC. Higher levels of high molecular weight species were detected by size exclusion chromatography (~1.5% for US-licensed Neulasta lots), whereas there was about 0.3% measured by AUC. Sedimentation coefficient (S) was almost identical for the proposed biosimilar (1.127) and the reference product (1.131).

Reviewer comment:

Analytical ultracentrifugation results support a demonstration of highly similar size variants between CHS-1701 and US-licensed Neulasta lots.

Comparative stability studies

Stability profiles of CHS-1701 and US-licensed Neulasta lots were compared under intended storage conditions and accelerated storage using three analytical methods that were identified as stability indicating: RPC, SEC, and bioassay. Additionally, forced degradation studies were performed to determine the degradation pathways and degraded forms resulting from the stress conditions. Specifically, these studies included:

- Recommended storage conditions (5°C ± 3°C, up to 12 months)
- Accelerated storage (25°C ± 2°C, up to 6 months)
- Forced degradation conditions (photosensitivity, oxidation, heat, acid and base treatment)

Three CHS-1701 lots and 3 US-licensed Neulasta lots were used in these studies, the details are provided in the table 43 below.

Table 43. CHS-1701 and US-licensed Neulasta drug product lots used in the recommended and accelerated storage conditions

Biosimilar	Mfr Lot Number (Coherus lot number)	Date of Manufacture
CHS-1701	2372-103 (1701-DP-104)	20 Mar 2015
	2372-104 (1701-DP-105)	25 Mar 2015
	2372-105 (1701-DP-106)	31 Mar 2015
Reference Product	Lot Number	Date of Expiry
US-licensed Neulasta	1053071	August 2017
	1053081	September 2017
	1053956	September 2017

Reviewer comment:

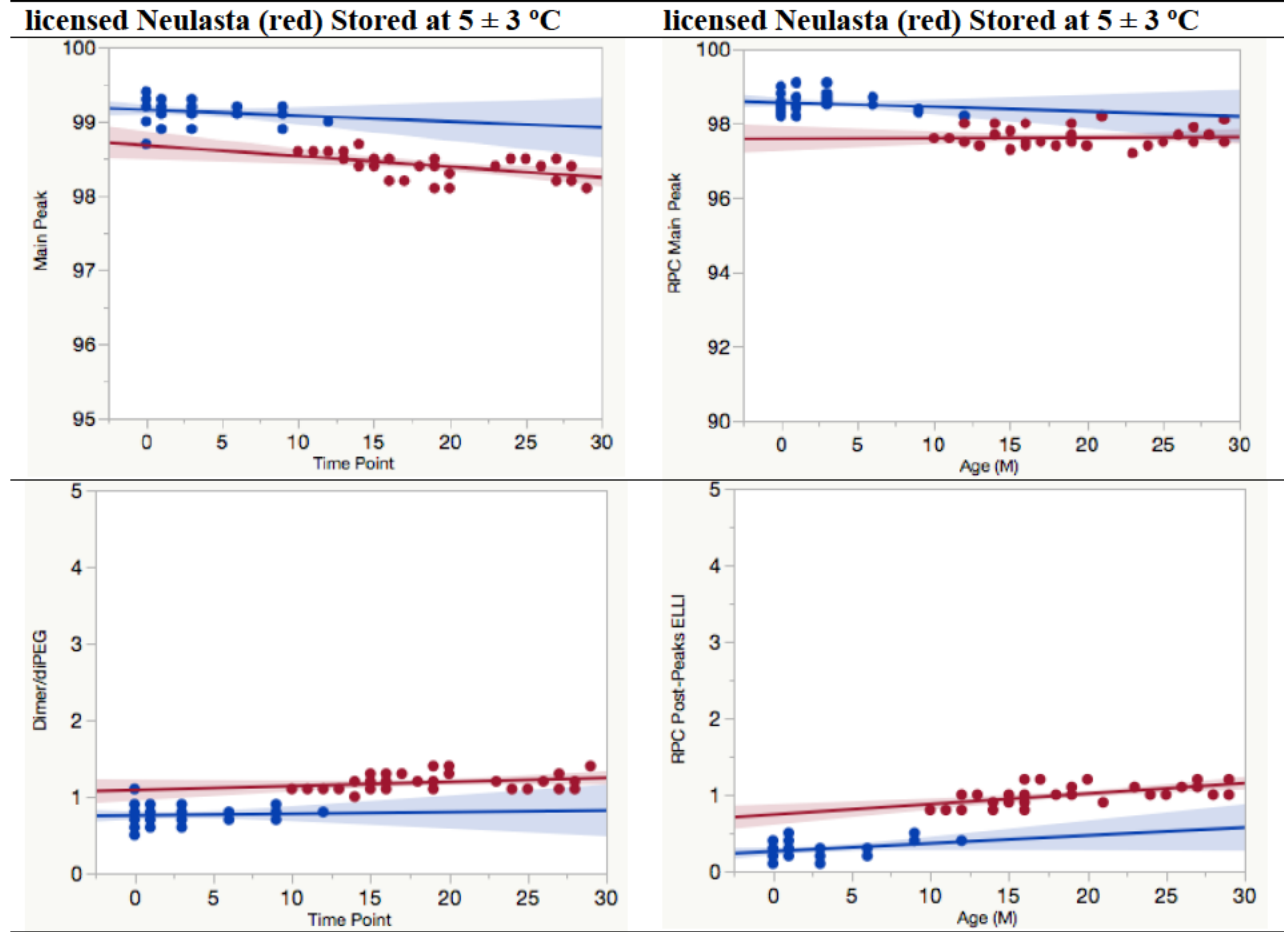
Only 3 analytical methods were identified as stability indicating and used in the evaluation: RPC, SEC and bioassay. Bioassay was not part of forced degradation studies in the characterization section of the BLA; however, the sponsor provided data demonstrating that increased levels of impurities, such as deamidated or oxidized species, affect product potency. Mechanical stress was not included in the forced degradation study.

Since potency was not included in the forced degradation studies, data are missing that are necessary to make a determination of highly similar. A comment regarding this issue will be included in the CR letter.

Comparative stability studies: recommended storage conditions (5°C ± 3°C)

Small differences were observed between the proposed biosimilar and the reference product by RPC and SEC, but they were attributed to the age of lots used in this study (US-licensed Neulasta lots are ~ 1 year old at the beginning of the study and their cumulative stability is not known). The levels of some impurities (oligomers, dimers by SEC, and post-peaks including deamidated species by RPC) were a little higher at the start of the study in the reference product; however, overall relative degradation rate appeared to be similar in both products.

SEC Trending of CHS-1701 (blue) and US- RPC Trending of CHS-1701 (blue) and US-



Reviewer comment:

Very little difference was observed between the CHS-1701 lots and US-licensed Neulasta lots under recommended storage conditions using stability indicating assays.

- Overall degradation rates appeared to be similar; however, higher levels of impurities in US-licensed Neulasta lots are likely due to the age of material used in the study,
- No difference or meaningful trend was observed for bioassay between CHS-1701 lots and US-licensed Neulasta lots.

The results of comparative stability assessment under recommended storage conditions indicate that CHS-1701 and US-licensed Neulasta have similar stability profiles.

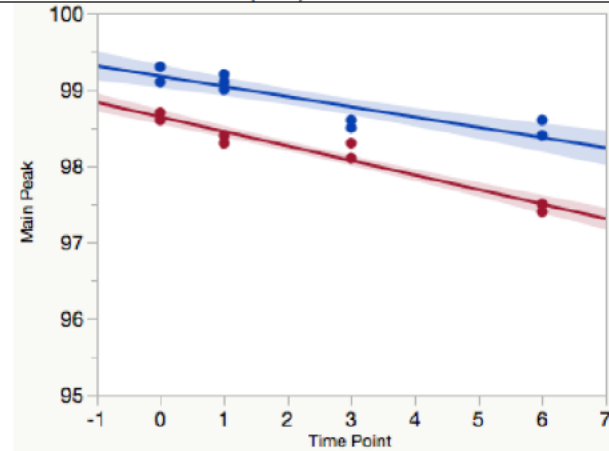
Comparative stability studies: accelerated storage conditions (25°C ± 2°C)

Product degradation was more pronounced at 25°C ± 2°C (accelerated stability conditions) than could be observed under recommended storage conditions. Both products, CHS-1701 and US-licensed Neulasta degraded faster as observed by RPC, SEC, and CEC methods (CEC was used to measure the level of deamidated species regardless). Bioassay did not reveal any trend or difference between either product, which is consistent with recommended storage condition results.

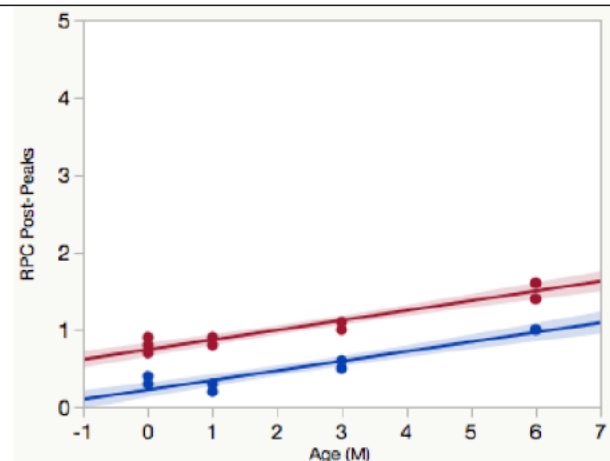
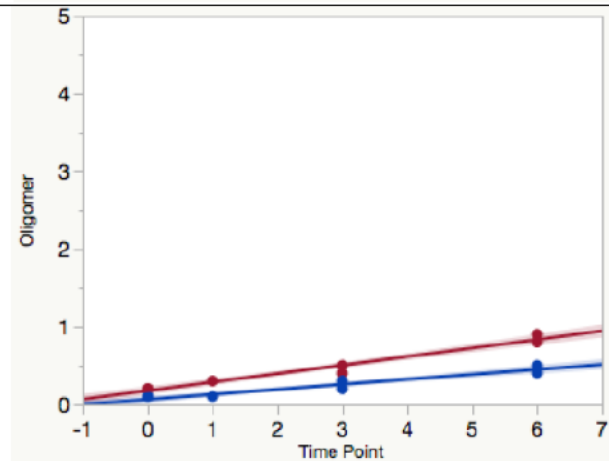
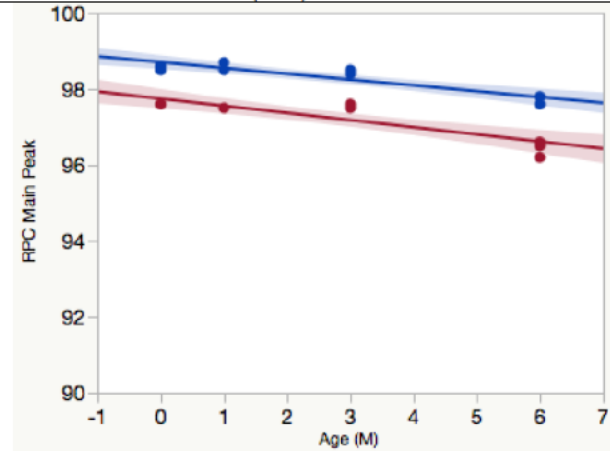
SEC method revealed increase in oligomer, dimer, and unPEGylated species, suggesting the rate of degradation appears similar for CHS-1701 and the reference product.

Similarly, RPC results also demonstrate similar increase in impurity levels, especially post-peaks including deamidated species at elevated temperature. This trend is additionally confirmed by CEC results where increased deamidation in both products can be observed (data not included).

SEC Trending of CHS-1701 (blue) and US-licensed Neulasta (red) Stored at 25 ± 3 °C



RPC Trending of CHS-1701 (blue) and US-licensed Neulasta (red) Stored at 25 ± 3 °C



Reviewer comment:

Some differences were observed between the CHS-1701 lots and US-licensed Neulasta lots under accelerated storage conditions using stability indicating assays and CEC assay (deamidated species).

- Overall degradation rates appeared to be similar for the proposed biosimilar and the reference product; however, higher levels of impurities in US-licensed Neulasta lots are observed at the baseline (likely due to the age of material used in the study),*
- Purity methods (RPC, SEC) used in this assessment are able to detect product degradation; overall degradation profiles are very similar for both products,*
- No difference or meaningful trend was observed for bioassay between CHS-1701 lots and US-licensed Neulasta lots.*

The results of comparative stability assessment under accelerated storage conditions indicate that CHS-1701 and US-licensed Neulasta have similar stability profiles.

Comparative stability studies: forced degradation

Three lots of CHS-1701 and 3 US-licensed Neulasta lots were selected for the forced degradation study. The stress conditions included oxidation, light exposure, heat treatment, acid and base exposure. The sponsor did not include mechanical stress or potency evaluation and did not provide any explanation why this particular type of stress was not part of the study. The information about the lots selected for the study and their age at the time of testing is provided in the table 44 below.

Table 44: CHS-1701 and US-licensed Neulasta Drug Product Materials Used for Forced Degradation Studies

Biosimilar	Mfr Lot Number (Coherus lot number)	Date of Manufacture	Age at Study Initiation, Months
CHS-1701	2372-103 (1701-DP-104)	24 Mar 2015	12
	2372-104 (1701-DP-105)	26 Mar 2015	11
	2372-105 (1701-DP-106)	02 Apr 2015	11
Reference Product	Lot Number	Date of Expiry	
US-licensed Neulasta	1053071	August 2017	19
	1057096	November 2017	16
	1059900	April 2018	11

Two of the US-licensed Neulasta lots are older than CHS-1701 lots; however, US-licensed Neulasta lot 1059900 is approximately the same age as all 3 CHS-1701 lots. The summary of stress conditions are provided in the table 45 below.

Table 45: Forced Degradation Conditions

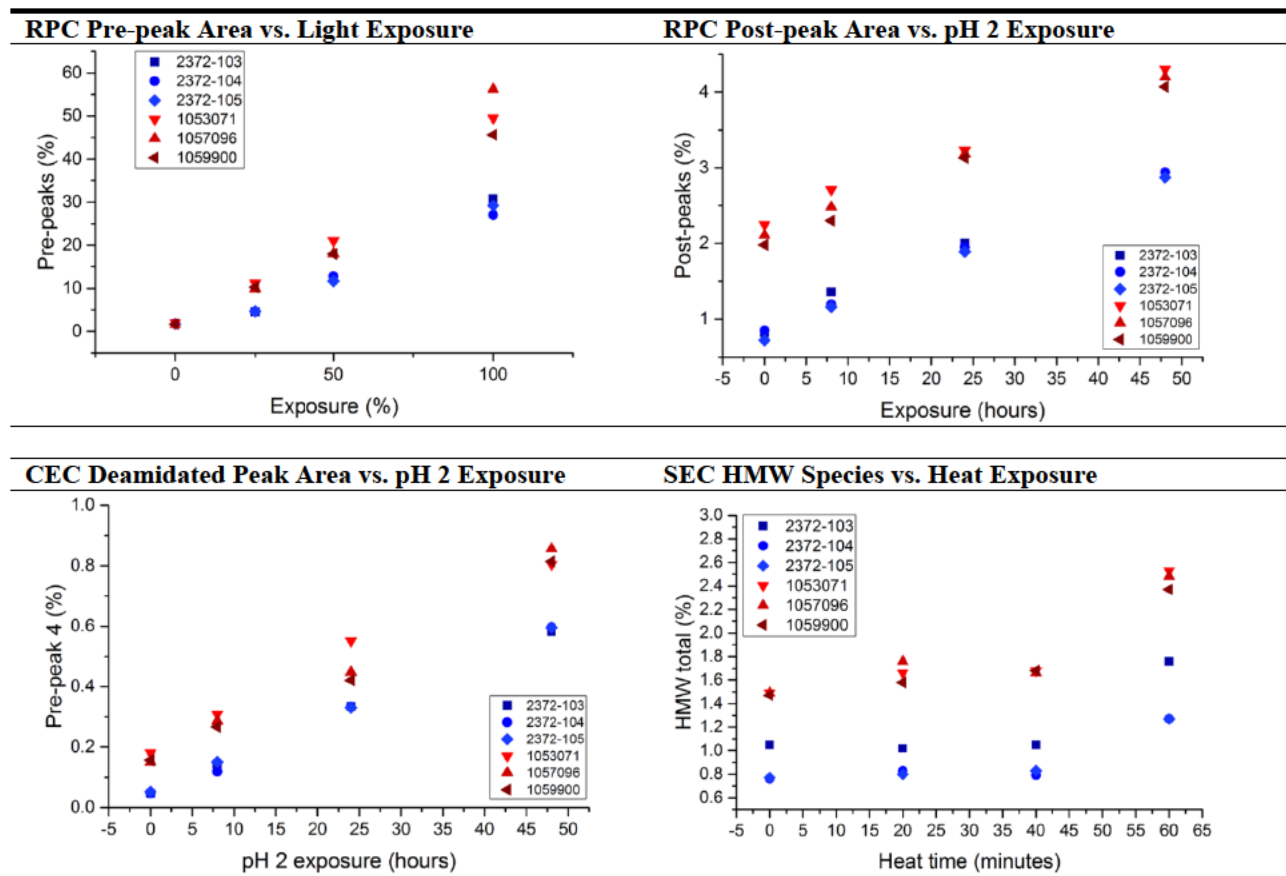
Stress	Concentration	Conditions	Time Point(s)			
Photosensitivity	10 mg/mL	Light Exposure (ICH Q1B option 2) ^a	0% Exposure	25% Exposure	50% Exposure	100% Exposure
Oxidation	10 mg/mL	0.05% H ₂ O ₂ at 37 °C	0 min	10 min	20 min	40 min
Heat	1 mg/mL	60 °C	0 min	20 min	40 min	60 min
Acid	N/A ^b	Titrate formulation buffer to pH 2 and dialyze samples; incubate 37 °C	0 hours	8 hours	24 hours	48 hours
Base	N/A ^b	Titrate formulation buffer to pH 8 and dialyze samples; incubate 37 °C	0 hours	8 hours	24 hours	48 hours

In addition to stability indicating methods such as RPC and SEC, the sponsor also used CEC and SDS-PAGE to evaluate product degradation pathways under different degrading conditions. However, the bioassay was not included.

Reviewer comment:

The sponsor explained that potency was not included in the forced degradation studies because HPLC methods were shown to be the most sensitive methods in detecting changes in degraded samples. This is not adequate justification for excluding the potency assay in the forced degradation study. In fact, additional data demonstrated that significant levels of impurities (10% of deamidated or oxidized species) can decrease potency by approximately 10%. A comment regarding this issue will be included in the CR letter.

Figures below summarize the main degradation pathways and compare both products under different stress conditions.



Blue colored shapes represent CHS-1701 lots and red/orange ones represent US-licensed Neulasta lots.

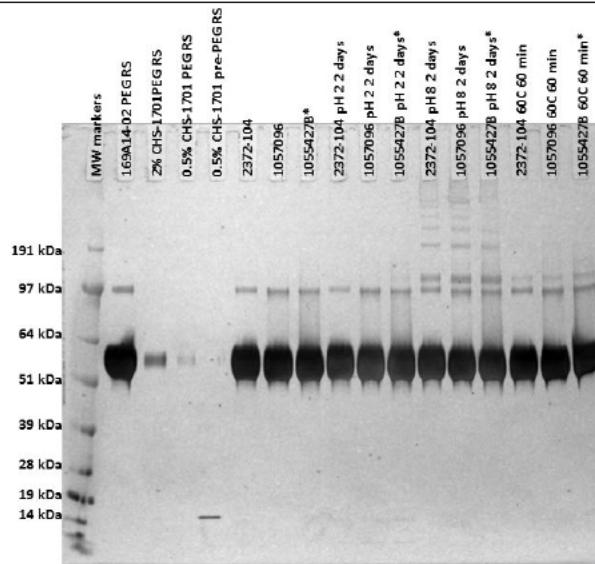
Reviewer comment:

In almost all cases the qualitative changes in product impurity profiles are similar between CHS-1701 and US-licensed Neulasta; however, US-licensed Neulasta lots exhibited greater rate of degradation. The only exception to this is oxidation using peroxide (assessed by RPC) where almost identical results were obtained. Of note, the impurity results (as seen above) provided in this assessment constitute the sum of individual impurities detected by any method; for example, RPC post peak area result as presented above

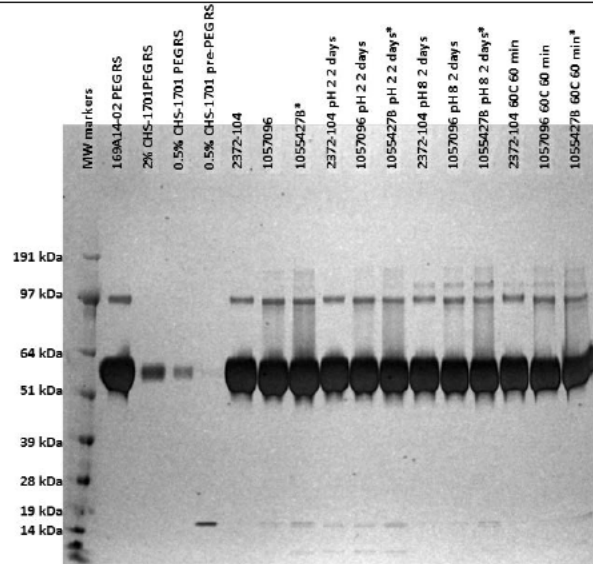
is a sum of 3 separate peaks. This approach is acceptable because tabular summaries and stacked chromatograms (raw data) from each study/lot were included in the BLA submission.

To further support the similarity of CHS-1701 to US-licensed Neulasta, conditions with the highest degradation rates were additionally analyzed using non-reduced and reduced SDS-PAGE method. Representative non-reduced and reduced gels including results of acid, base, and heat exposure are provided below.

SDS-PAGE non-reduced



SDS-PAGE reduced



Reviewer comment:

There is very little difference in the way both products degrade as observed by non-reduced and reduced SDS PAGE method under acidic and basic conditions and heat exposure. SDS-PAGE qualitative data, in addition to chromatographic results, further support analytical similarity between CHS-1701 and US-licensed Neulasta.

Reviewer assessment:

The results of the comparative stability studies under recommended and accelerated storage conditions, as well as the forced degradation studies, indicate that CHS-1701 and US-licensed Neulasta have similar stability profiles.

Overall analytical similarity conclusion:

The proposed biosimilar CHS-1701 has been evaluated and compared to US-licensed Neulasta using a variety of structural, physicochemical, and functional assays. The list of analyses and their corresponding tier assignments are considered appropriate. The data provided would not preclude a determination that CHS-1701 is highly similar to US-licensed Neulasta. However, a final conclusion if the data support such a demonstration cannot be made at this time. The following three limitations are noted:

1). There is residual uncertainty regarding similarity with respect to evaluation of immunogenicity between CHS-1701 and US-licensed Neulasta. For additional discussion on this uncertainty, see the separate reviews by F. Mills and H. Yan. While the differences observed in the analytical similarity assessment between CHS-1701 and US-licensed Neulasta would not necessarily be expected to influence immunogenicity, the absence of immunogenicity data results in an inability to evaluate their potential

impact on product performance. These would include small differences noted in the levels of diPEGylated species and the size of the PEG moiety covalently linked to G-CSF protein. Overall, the purity is similar between CHS-1701 and US-licensed Neulasta, with US-licensed Neulasta containing slightly higher product related variants due to the age of the material.

2). Data are missing or incomplete that are necessary to make a determination of highly similar: These data include:

- Characterization data were not included for CHS-1701 for subvisible particles in the range 2-10 microns*
- The Potency assay was not included side-by-side forced degradation studies between CHS-1701 and US-licensed Neulasta*

3. Method validation and supplemental information for multiple analytical techniques were incomplete or inadequate (see additional information in section 3.2.S.4.3, 3.2.P.5.3, and CR letter):

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Immunogenicity assays are reviewed separately. Refer to immunogenicity review by Dr. Haoheng Yan.



Joslyn
Brunelle

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Date: 5/22/2017 04:08:06PM
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Joel
Welch

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Jacek
Cieslak

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Date: 5/23/2017 01:45:21PM
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To: Administrative File, STN 761035/0
From: Marion Michaelis, CSO, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: Pending
Applicant: Coherus Bioscience, Inc.
Mfg Facility: **Drug Substance:** KBI Biopharma, Inc., Boulder, CO
FEI: 3011326133
Drug Product: (b) (4)
FEI: (b) (4)
Product: Established/Proper Name: CHS-1701, proposed biosimilar to US-licensed pegfilgrastim
Dosage: Pre-filled Syringe, Solution for Injection (subcutaneous), 6 mg / 0.6 mL
Indication: 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

Due Date: 6/8/2017

RECOMMENDATION:

Approval is recommended from a facility perspective.

SUMMARY

Coherus Bioscience, Inc (Coherus) submitted this new Biologics License Application (BLA) dated August 9, 2016 for CHS-1701. The commercial CHS-1701 drug product has been developed as a proposed biosimilar to the reference product, Neulasta® (pegfilgrastim). As part of this BLA there were three pre-license (PLI) inspections conducted which were the following:

- KBI Biopharma, Inc. (KBI) (FEI:3011326133) – Drug Substance (DS) Manufacturing Inspection Conducted 12/5-9/ 2016 - Outcome Classified as VAI (CMS #151032)
- (b) (4), FEI: (b) (4) – Drug Product (DP) Manufacturing Inspection Conducted (b) (4) – Outcome Classified as VAI (CMS# (b) (4))
- Coherus Bioscience, Inc (Coherus), FEI:3009682611 – Device Inspection – Combination Product Inspection Conducted 3/13-16/2017 – Outcome Classified as NAI

The scope of this review is primarily for equipment and facilities. Items documented as “reviewed on inspection” in this memo are discussed in the Establishment Inspection Report (EIR) associated with the individual PLI for this application.

From a facility perspective approval is recommended. A Complete Response (CR) Letter is being issued for other review disciplines. The PLI inspection conducted at KBI for DS manufacturing during the review of this application was a first time inspection at KBI and resulted in a nine item 483. When the BLA is resubmitted KBI should be evaluated for re-inspection.

REVIEW:

Drug Substance Manufacturing

3.2.S.2.1 DS Manufacturers

Coherus is proposing the following manufacturing and testing facilities for CHS-1701 drug substance:

SITE INFORMATION	FUNCTION	FEI NUMBER
KBI Biopharma, Inc., 2500 Central Avenue, Boulder, CO 80301	CBI- Drug Substance Manufacturing, Release and Stability Testing	3011326133
(b) (4)	CTL- Drug Substance Release and Stability Testing	(b) (4)

Inspection History:

KBI Biopharma, Inc. (FEI: 3011326133) – DS Manufacturing and Release and Stability Testing
 Inspection Conducted 12/5-9/2016 by CDER/OPF. This inspection was a PLI for this application for CHS-1701 DS manufacturing and first time inspection of this Boulder, CO facility. The inspection was conducted in accordance with CP 7346.832, Pre-Approval Inspections, ICH Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Coverage during the inspection included facilities, equipment and processes, procedures and conformance to the application. The inspection resulted in the issuance of a 9-item FDA Form 483. A summary of the nine observations was the following: instruction for defining where a batch begins was not clearly defined, annual GMP training lacked comprehensive GMP subject matter, storage of CHS-170 bulk drug substance, materials control, standard operating procedure instruction and quality oversight were found to lack instruction or were inadequate in several areas. The initial field recommendation was withhold. The withhold recommendation was downgraded to VAI after reviewing the firm response to the 483 observations which is documented under CMS #151032.

Reviewer Comments

This application will have a CR letter issued for discipline other than facilities. When the application is re-submitted the KBI facility should be evaluated for re-inspection.

(b) (4) (FEI: (b) (4)) – DS Release and Stability Testing

The most recent inspection was conducted (b) (4) and was a comprehensive surveillance inspection of this contract testing lab that was conducted as part of the (b) (4)-DO work plan and was classified as NAI and profile CTL was covered. Prior to this an inspection took place (b) (4). This inspection was

CONCLUSION:

Adequate information of the facilities, equipment were provided for CHS-1701 DS and DP manufacturing and therefore approval is recommended from a facility perspective.

Marion
Michaelis -S

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ou=FDA, ou=People,
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cn=Marion Michaelis -S
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Marion Michaelis
Consumer Safety Officer
CDER/OPQ/OPF/DIA/B1

Zhihao
Qiu -S

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Zhihao Peter Qiu, Ph.D.
Branch Chief
CDER/OPQ/OPF/DIA/B1

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.

QAL: Reyes Candau-Chacon, Ph.D.

BLA: 761039/0
Applicant: Coherus BioSciences, Inc.
US License Number: 2023
Submission Reviewed: 351(k) BLA
Product: CHS-1701 (UDENYCA™)
Indication: 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
Dosage Form: Single use, pre-filled syringe for subcutaneous injection (6 mg/0.6 mL) with a safety needle device
Manufacturing Site: [REDACTED] (b) (4)
FEI# [REDACTED] (b) (4)
FDA Receipt Date: August 9, 2016
Action Date: June 9, 2017

Conclusion and Approvability Recommendation

The drug product portion part of this BLA is not recommended for approval from a sterility assurance and product quality microbiology perspective.

The following deficiencies should be communicated to the sponsor:

1. [REDACTED] (b) (4)

Conclusion

- I. The BLA was reviewed from a product quality microbiology perspective and is not recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.
- III. No inspection follow-up items were identified.

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Jessica
Hankins

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Reyes
Candau-Chacon

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 5 May 2017
To: Administrative File, **STN 761039/0**
From: Monica Commerford, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV
Through: Reyes Candau-Chacon, Ph.D. Acting Quality Assessment Lead,
CDER/OPQ/OPF/DMA/BIV
Subject: New Biologics License Application
Applicant: Coherus BioSciences, Inc.
US License: 2023
Product: CHS-1701 (Proposed name: UDENYCA, a proposed biosimilar to US licensed Neulasta)
Dosage: Pre-filled syringe, subcutaneous liquid solution for injection (6 mg/0.6 mL)
Indication: Decrease incidence of infection manifested by febrile neutropenia in patients receiving myelosuppressive anti-cancer drugs
Facilities: KBI Biopharma, Inc.
2500 Central Ave.
Boulder, CO 80301
(FEI: 3011326133)
Receipt Date: 9 August 2016
Action date: 9 June 2017

Recommendation for Approvability: The drug substance section of BLA 761039 is not recommended for approval from a microbial control and product quality microbiology perspective.

The following deficiencies were identified and should be communicated to the sponsor:

1.

(b) (4)



(b) (4)

Review Summary

Coherus BioSciences, Inc. has submitted this Biological License Application (BLA) for CHS-1701 to be used in patients receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia to decrease infection manifested by febrile neutropenia. The drug substance (DS) is manufactured at KBI Biopharma, Inc., in Boulder, CO (FEI: 3011326133). The drug product (DP) is manufactured at (b) (4) (FEI: (b) (4)).

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Conclusion

- I. The Drug Substance section of the BLA is not recommended for approval from a product quality microbiology perspective; a list of deficiencies and comments/clarifications is included in the “Recommendation for Approvability” section of this memo.
- II. Information and data in this BLA not related to microbial control should be reviewed by an OBP reviewer.
- III. A pre-license inspection was conducted at KBI BioPharma, Inc. on December 5 – 9, 2016 by OPF/DMA (Monica Commerford), ORA (Diane Raccasi), OPF/DIA (Marion Michaelis), and OBP (Michele Dougherty, Ying Xin Fan, and Andrea Franco). A nine-item FDA Form 483, Inspectional Observations, was issued. See Panorama for the current compliance of the facility.



Monica
Commerford
(Markovski)

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Reyes
Candau-Chacon

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