

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761075Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date: June 5, 2018

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

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

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

Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

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

Drug Name (established name): FULPHILA (pegfilgrastim-jmdb)¹

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761075

Applicant: Mylan GmbH

¹ The proposed proprietary name, FULPHILA, and the nonproprietary (proper) name, pegfilgrastim-jmdb, are conditionally acceptable until such time as the application is approved.

1 INTRODUCTION

On December 4, 2017, Mylan GmbH resubmitted for the Agency's review an original Biologics License Application (BLA) 761075 for FULPHILA (pegfilgrastim-jmdb) injection, for subcutaneous use, a proposed biosimilar product to NEULASTA (pegfilgrastim) injection, for subcutaneous use. This submission is in response to an Agency Complete Response (CR) letter issued on October 6, 2017.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Hematology Products (DHP) on May 24, 2018 and May 11, 2018 respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 13, 2018.

2 MATERIAL REVIEWED

- Draft FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use PPI received on December 9, 2017 and received by DMPP on May 24, 2018.
- Draft FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use PPI received on December 9, 2017 and received by OPDP on May 16, 2018.
- Draft FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use IFU received on December 9, 2017 revised by the Review Division throughout the review cycle, and received by DMPP on May 24, 2018.
- Draft FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use IFU received on December 9, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on May 16, 2018.
- Draft FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use Prescribing Information (PI) received on December 9, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on May 24, 2018.
- Draft FULPHILA (pegfilgrastim-jmdb), injection, for subcutaneous use Prescribing Information (PI) received on December 9, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on May 16, 2018.
- Approved NEULASTA (pegfilgrastim) injection, for subcutaneous use comparator labeling dated December 17, 2017.

3 REVIEW METHODS

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

60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

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

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON R MILLS
06/05/2018

SAMUEL M SKARIAH on behalf of ROBERT L NGUYEN
06/05/2018

LASHAWN M GRIFFITHS
06/05/2018

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

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

Memorandum

Date: June 4, 2018

To: Katie Chon, PharmD, RPh, Regulatory Project Manager, Division of Hematology Products (DHP)
Virginia Kwitkowski, Associate Director for Labeling, DHP

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

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

Subject: OPDP Labeling Comments for Fulphila (pegfilgrastim-xxxx) injection, for subcutaneous use

BLA: 761075

In response to DHP's consult request dated May 11, 2018, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Fulphila (pegfilgrastim-xxxx) injection, for subcutaneous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Katie Chon) on May 16, 2018. OPDP's comments on the PI are provided below.

IFU and Carton and Container Labeling: OPDP has reviewed the attached proposed IFU and carton and container labeling received by electronic mail from DHP (Katie Chon) on May 16, 2018, and we do not have any comments.

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

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/s/

SAMUEL M SKARIAH on behalf of ROBERT L NGUYEN
06/04/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: May 17, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761075
Product Name and Strength: Fulphila*
(MYL-1401H)**
Injection
6 mg/0.6 mL
Applicant/Sponsor Name: Mylan GmbH
FDA Received Date: March 28, 2018
OSE RCM #: 2017-2463-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

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

2 CONCLUSION

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

* Fulphila has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name Fulphila is only conditionally accepted until final approval of MYL-1401H.

** "MYL-1401H" is used throughout this review in place of the nonproprietary name for this product. Pegfilgrastim-jmdb is conditionally approved only with the approval of MYL-1401H.

^a Garrison N. Label and Labeling Review for Fulphila (BLA 761075). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 13. RCM No.: 2017-2463.

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/s/

NICOLE B GARRISON
05/17/2018

HINA S MEHTA
05/17/2018

**MEMORANDUM
NONPROPRIETARY NAME SUFFIX**

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

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

Date of This Review:	April 30, 2018
Responsible OND Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761075
Product Name and Strength:	Fulphila (pegfilgrastim-jmdb) Injection, 6 mg/ 0.6 mL
Product Type:	Drug-Device Combination Product
Applicant/Sponsor Name:	Mylan GmbH
OSE RCM #:	2018-73
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum is to reassess the FDA-generated suffix, -jmdb, for BLA 761075, which was found conditionally acceptable on July 28, 2017^a, for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761075

1.1 REGULATORY HISTORY

Mylan was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter^b. FDA generated a four-letter suffix, -jmdb, on July 28, 2017. However the BLA 761075 received a Complete Response (CR) letter on October 10, 2017. Mylan submitted a response to the CR letter for Fulphila on December 4, 2017.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

pegfilgrastim-jmdb

We reassessed the previously generated four-letter suffix, -jmdb, using the principles described in the applicable guidance^c.

We determined that the FDA-generated suffix -jmdb, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. In email correspondence dated January 26, 2017, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Hematology Products (DHP) via e-mail on April 27, 2018.

4 CONCLUSION

We find the suffix -jmdb acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to pegfilgrastim-jmdb.

^a Garrison, N. Nonproprietary Name Suffix Memorandum for pegfilgrastim-jmdb (BLA 761075). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 28. RCM No. 2017-1123.

^b Merchant, L. General Advice Letter for BLA 761075. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 March 23.

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

4.1 RECOMMENDATION FOR MYLAN

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

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/s/

CASMIR I OGBONNA
04/30/2018

DANIELLE M HARRIS
05/02/2018

LABEL AND LABELING REVIEW

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

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

Date of This Review: April 13, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761075
Product Name and Strength: Fulphila*
(MYL-1401H)**
Injection
6 mg/0.6 mL
Product Type: Drug-device Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Mylan GmbH
Submission Date: December 4, 2017 and January 22, 2018
OSE RCM #: 2017-2463
DMEPA Primary Reviewer: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD
DMEPA Associate Director (Acting): Mishale Mistry, PharmD, MPH

*Fulphila has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name Fulphila is only conditionally accepted until final approval of MYL-1401H.

** The proper name for Fulphila has not yet been conditionally accepted. We therefore continue to refer to the proposed product as "MYL-1401H" throughout this review in place of the proper name for this product.

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Fulphila (“MYL-1401H”) injection (BLA 761075) for areas that could lead to medication errors. The Division of Hematology Products (DHP) requested this review to inform their evaluation of the 351(k) BLA class 2 re-submission for Fulphila (“MYL-1401H”) injection.

1.1 REGULATORY HISTORY

US-licensed Neulasta was approved in January 2002 to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs, associated with a clinically significant incidence of febrile neutropenia. In 2015, US-licensed Neulasta was approved to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

In July and August of 2016, Mylan submitted what the company refers to as its Human Factors “Use-Related Risk Analysis (URRA)” and draft IFU in response to DMEPA’s recommendation in the June 2016 BPD Type 2/ Type 4 meeting to submit a comprehensive use-related risk analysis of the proposed MYL-1401H prefilled syringe (PFS) to determine the necessity of a human factors (HF) validation study^a. We reviewed Mylan’s URRA and draft IFU in August of 2016^b. In our review dated August 26, 2016, we noted that the proposed product has two user modifications, which include a passive needle guard and a plunger with a larger head when compared to the US-licensed Neulasta PFS. The Applicant stated that these modifications should provide enhanced usability to the user as the passive needle guard reduces the occurrence of needle stick injury and the larger plunger head provides additional grip and stability to the push of the plunger. We found those differences acceptable. In addition, our review noted the URRA did not include an assessment of the measurement and administration of pediatric doses less than 6 mg (0.6 mL) as the current PFS presentation proposed by the Applicant can be used to dose only patients weighing 45 kg or more. The Applicant received agreement by the Agency on the plan for a deferral of pediatric assessments in their Initial Pediatric Study Plan on June 27, 2016.

Our review of the URRA did not identify any use-related risk for the proposed MYL-1401H product when compared to US-licensed Neulasta that would warrant Mylan conduct a human

^a Memorandum of Meeting Minutes for MYL-1401H (IND 123389). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Hematology and Oncology Products, Division of Hematology Products (US); 2016 JUN 01. 11 p.

^b Garrison, N. Use-Related Risk Analysis Memorandum for MYL-1401H (IND 123389). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Aug 26. 7 p. OSE RCM No.: 2016-1662.

factors study of the proposed MYL-1401H product. We found Mylan’s rationale for not performing an HF validation study to be acceptable at that time.

The application received a Complete Response (CR) letter on October 10, 2017 due to facility inspections and product quality issues. The CR letter explained that FDA reserved comment on the proposed labeling (including the PI and carton and container labeling) until the application is otherwise adequate. Mylan submitted a response to the CR letter for Fulphila (“MYL-1401H”) BLA 761075 on December 4, 2017. The information conveyed in the BLA resubmission does not impact our earlier assessments, conclusions, and recommendations.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Mylan re-submitted their 351(k) application for Fulphila (MYL-1401H) injection. We evaluated the proposed container label, carton labeling, Prescribing Information (PI) and, Instructions for Use (IFU) for Fulphila (MYL-1401H injection, BLA 761075. Fulphila has the same dosing, route of administration, strength, and storage requirements as US-licensed Neulasta (BLA 125031). The applicant is pursuing only one of the indications of US-licensed Neulasta (i.e., to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia), as the sponsor of US-licensed Neulasta has an unexpired orphan-drug status exclusivity for the treatment of Acute Radiation Syndrome (ARS). Fulphila is supplied as a single-dose, ungraduated prefilled syringe (PFS) with an UltraSafe

Passive™ needle guard. US-licensed Neulasta is supplied as a single-dose, ungraduated PFS with a manual needle guard and as a PFS for use with a delivery device, the OnPro kit.

Differences Identified in Labeling

The Fulphila IFU follows similar steps and injection technique as US-licensed Neulasta IFU. However, we note the Fulphila needle guard can be triggered by two actions, which are not present in the US-licensed Neulasta IFU. We reviewed these differences and concluded that they are acceptable in our previous review^c. We also provide recommendations in section 4.1 below intended to harmonize the Fulphila IFU with the US-licensed Neulasta IFU where appropriate. For example, US-licensed Neulasta IFU provides labeled images on preparing for injection and injecting the dose. Additional information listed under using the prefilled syringe also informs users not to inject a dose of US-licensed Neulasta to children weighing less than 45 kg from a Neulasta PFS. However, this information is omitted from the Fulphila IFU. Revision of the Fulphila IFU to include labeled images and important administration information may help to reduce the risk of administration errors and will harmonize this information with the US-licensed Neulasta IFU. We provide recommendations in Section 4.1 below to convey information regarding dosing limitations of the PFS in the IFU, which is consistent with the labeling of US-licensed Neulasta. We defer to the Clinical team and Patient Labeling team to provide additional recommendations for the Fulphila IFU.

In our review of the container labels and carton labeling, we note that the finished dosage form is not included. Additionally, we recommend relocating the barcode that does not contain the NDC to avoid confusion, and decreasing the prominence of “Rx Only” statement. We also recommend clarifying the significance of numbers located next to the barcode. We provide these recommendations to the Applicant in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

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

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

We provide recommendations in Sections 4.1 and 4.2 below and advise they be implemented prior to approval of BLA 761075.

4.1 RECOMMENDATIONS FOR THE DIVISION

^c Garrison, N. Use-Related Risk Analysis Memorandum for MYL-1401H (IND 123389). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Aug 26. 7 p. OSE RCM No.: 2016-1662.

A. Instructions for Use

1. Important Information

a. Include the following statements:

- i. You should not inject a dose of Fulphila to children weighing less than 45 kg from a Fulphila prefilled syringe. A dose less than 0.6 mL (6 mg) cannot be accurately measured using the Fulphila prefilled syringe.
- ii. Do not use a prefilled syringe after the expiration date on the label.

2. Storage

- a. To improve readability, consider using bullets to clearly outline the important information and to ensure proper storage of this product.

3.

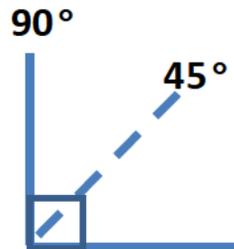
(b) (4)

Please label the syringe to include the “label and expiration date” and “gray needle cap.” We recommend this to provide congruency with the text and the image.

- b. Include the statement (b) (4): Throw the gray needle cap (b) (4).”

4. Step 3: Inject the dose

- a. In step (b) (4) include in the image a figure demonstrating both 45 and 90 degrees. For example:



4.2 RECOMMENDATIONS FOR MYLAN GMBH

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

A. Container label (syringe label)

1. For this product, ensure that the strength, expressed as total protein content per total volume, is the primary and prominent expression on Principal display panel (PDP). See USP General Chapters <7> Labeling. Revise the strength presentation to appear as 6 mg/0.6 mL. Consider removing “(b) (4)”, as it is not the proper presentation of strength for this dosage form.
2. If space permits, consider adding the dosage form “Injection” to appear below the proper name as follows:

Fulphila

(pegfilgrastim-xxxx)
Injection
6 mg/0.6 mL

3. Include the route of administration “For subcutaneous use” to appear above the package type term “single-dose prefilled syringe”

B. Carton labeling (outer)

1. See A.1 and A.2 and revise the outer carton labeling accordingly.
2. Decrease the prominence of the statement “Rx Only” [REDACTED] (b) (4) [REDACTED] as this information appears more prominent than the strength on the principal display panel^a.
3. Revise and relocate the statement, “[REDACTED] (b) (4)” to “Dosage- See prescribing information for dosage and instructions for use” to the side or back panel.

C. Carton labeling (inner tray)

1. See A.1 and A.2 and revise the inner tray of the carton labeling accordingly.
2. See B.3 and revise the inner tray of the carton labeling accordingly.
3. As currently presented, there are two barcodes on the inner tray of the carton labeling. Since the barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers. Therefore, we recommend you move the barcode that does not contain the NDC number away from the barcode containing the NDC number, and present it in a size that does not compete with, or distract from, the presentation of required information on the label^{d,e}.

^d Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013, lines [479-492]. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

^e Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014; 19(2): 1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fulphila that Mylan submitted on December 4, 2017 and January 22, 2018, and US-licensed Neulasta.

Table 2. Relevant Product Information for Fulphila and US-licensed Neulasta		
Product Name	Fulphila	US-licensed Neulasta
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	Pegylated-GCSF	Pegylated-GCSF
Indication	<ul style="list-style-type: none"> To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. 	<ul style="list-style-type: none"> To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection	Injection
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	<p><i>Cancer patients receiving myelosuppressive chemotherapy</i></p> <ul style="list-style-type: none"> Give 6mg subcutaneously once per chemotherapy cycle. Do not administer between 14 days before and 24 hours administration of cytotoxic chemotherapy. 	<p><i>Cancer patients receiving myelosuppressive chemotherapy</i></p> <ul style="list-style-type: none"> Give 6mg subcutaneously once per chemotherapy cycle. Do not administer between 14 days before and 24 hours administration of cytotoxic chemotherapy. <p><i>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome</i></p>

	<ul style="list-style-type: none"> Use weight-based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. <p>Dosing of Fulphila for pediatric patients</p> <table border="1" data-bbox="529 443 946 955"> <thead> <tr> <th>Body weight</th> <th>Fulphila Dose</th> <th>Volume to administer</th> </tr> </thead> <tbody> <tr> <td>Less than 10 kg*</td> <td>See below*</td> <td>See below*</td> </tr> <tr> <td>10 to 20 kg</td> <td>1.5 mg</td> <td>0.15 mL</td> </tr> <tr> <td>21 to 30 kg</td> <td>2.5 mg</td> <td>0.25 mL</td> </tr> <tr> <td>31 to 44 kg</td> <td>4 mg</td> <td>0.4 mL</td> </tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Fulphila</p>	Body weight	Fulphila Dose	Volume to administer	Less than 10 kg*	See below*	See below*	10 to 20 kg	1.5 mg	0.15 mL	21 to 30 kg	2.5 mg	0.25 mL	31 to 44 kg	4 mg	0.4 mL	<ul style="list-style-type: none"> Give 6 mg subcutaneously for adult victims with body weight \geq 45 kg for two doses given ^{(b) (4)} weeks apart; for pediatric patients weighing less than 45 kg, use weight based dosing. <p>Dosing of Neulasta for pediatric patients</p> <table border="1" data-bbox="976 562 1417 1035"> <thead> <tr> <th>Body weight</th> <th>Neulasta Dose</th> <th>Volume to administer</th> </tr> </thead> <tbody> <tr> <td>Less than 10 kg*</td> <td>See below*</td> <td>See below*</td> </tr> <tr> <td>10-20 kg</td> <td>1.5 mg</td> <td>0.15 mL</td> </tr> <tr> <td>21-30 kg</td> <td>2.5 mg</td> <td>0.25 mL</td> </tr> <tr> <td>31-44 kg</td> <td>4 mg</td> <td>0.4 mL</td> </tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta</p>	Body weight	Neulasta Dose	Volume to administer	Less than 10 kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL
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Less than 10 kg*	See below*	See below*																														
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Body weight	Neulasta Dose	Volume to administer																														
Less than 10 kg*	See below*	See below*																														
10-20 kg	1.5 mg	0.15 mL																														
21-30 kg	2.5 mg	0.25 mL																														
31-44 kg	4 mg	0.4 mL																														
How Supplied	<ul style="list-style-type: none"> Single-dose prefilled syringe for manual use containing 6 mg/0.6mL of pegfilgrastim-xxxx, supplied with a 29-gauge, ½-inch needle with an UltraSafe Passive Plus™ Needle Guard. 	<ul style="list-style-type: none"> Single dose prefilled syringe for manual use, containing 6 mg/0.6 mL of pegfilgrastim, supplied with a 27-gauge, ½-inch needle with an UltraSafe® Needle Guard. OnPro kit: 6 mg/0.6 mL solution in a single prefilled syringe copackaged with the On-body Injector for Neulasta. 																														
Storage	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 72 hours. Avoid freezing; if frozen, thaw in the refrigerator before	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.	administration. Discard syringe if frozen more than once.
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APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 29, 2018, we searched DMEPA's previous reviews using the terms using the terms, Fulphila and MYL-1401H. Our search identified two proprietary name reviews^{f,g}, one use-related risk analysis memorandum^h, and one nonproprietary name suffix memoⁱ. We confirmed that our previous recommendations were implemented or considered.

^f Whaley, E. Proprietary Name Review for Fulphila (IND 123389). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Apr 25. Panorama No. 2016-2908596.

^g Garrison, N. Proprietary Name Review for Fulphila (BLA 761075). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Mar 28. Panorama No. 2017-12352969.

^h Garrison, N. Use-Related Risk Analysis Memorandum for MYL-1401H (IND 123389). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Aug 26. RCM No.: 2016-1662.

ⁱ Garrison, N. Nonproprietary Name Suffix Memorandum for Fulphila (BLA 761075). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Jul 28. RCM No.: 2017-1123.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^j along with postmarket medication error data, we reviewed the following Fulphila labels and labeling submitted by Mylan GnbH on December 4, 2017 and January 22, 2018.

- Container label (syringe)
- Carton labeling (inner tray)
- Carton labeling (outer)
- Prescribing Information
- Instructions for Use

G.2 Label and Labeling Images

Container label (syringe)

(b) (4)



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

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/s/

NICOLE B GARRISON
04/13/2018

HINA S MEHTA
04/13/2018

MISHALE P MISTRY
04/23/2018

MEMORANDUM

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

DATE: October 10, 2017

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

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

Amy Rosenberg, M.D.
Director
Division of Biotechnology Review and Research III
Office of Biotechnology Products
Office of Pharmaceutical Quality

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

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

SUBJECT: Amendment of EIR review for the surveillance
inspection of [REDACTED] (b) (4)
[REDACTED]

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies [REDACTED] (b) (4) MYL-1401H-1001 (BLA 761075), and MYL-1401H-1002 (BLA 761075) conducted at [REDACTED] (b) (4).

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

The evaluation of inspectional findings was provided in the review dated June 23, 2017 and an amendment dated July 27, 2017 based on the [REDACTED] (b) (4) response to Form FDA 483. This review is being amended to include evaluation of additional data [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED] presented in
[REDACTED] (b) (4) amended method validation report [REDACTED] (b) (4)

After evaluating the new [REDACTED] (b) (4) stability results, I conclude that data from the audited studies MYL-1401H-1001 and MYL-1401H-1002 are reliable because the additional stability data adequately demonstrated the stability of positive controls. Thus I recommend the data from studies MYL-1401H-1001 and MYL-1401H-1002 and other studies of similar design be accepted for further Agency review.

[REDACTED] (b) (4)

Inspected Studies:

[REDACTED] (b) (4)

BLA 761075

Study Number: MYL-1401H-1001

Study Title: "Analysis of normal human serum samples using a cell based assay for the detection of neutralizing antibodies against MYL-1401H and

Neulasta[®] (US and/or EU) to support phase I clinical study MYL1401H-1001.”

Dates of Study

Conduct: [REDACTED] (b) (4)

Study Number: MYL-1401H-1002

Study Title: “Analysis of normal human serum samples using a cell based assay for the detection of neutralizing antibodies against MYL-1401H and Neulasta[®] US to support phase I clinical study MYL1401H-1002.”

Dates of Study

Conduct: [REDACTED] (b) (4)

OSIS Pharmacologist Gajendiran Mahadevan, Ph.D. audited the analytical portion of the above studies at [REDACTED] (b) (4)
[REDACTED] from [REDACTED] (b) (4)

I thoroughly audited the study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm’s management and staff. As a part of surveillance approach, several key study components that best represent the firm’s bioanalytical operations were selected and audited across multiple studies conducted at [REDACTED] (b) (4).

At the conclusion of the inspection, I observed objectionable findings and issued Form FDA 483 to [REDACTED] (b) (4) (**Attachment-1**). The firm responded to Form FDA 483 on [REDACTED] (b) (4) [REDACTED] (**Attachment-2**) and submitted amended method validation reports on [REDACTED] (b) (4) [REDACTED] [REDACTED]

[REDACTED] (**Attachment-3**). The Form FDA 483, the firm’s response to Form FDA 483, and my evaluation follow.

Observation 1

[REDACTED] (b) (4)

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(b) (4)

Conclusion:

After reviewing the inspectional findings, the response to 483, and the data in the amended method validation report [REDACTED] (b) (4) I conclude the data from the audited studies are reliable. Therefore, I recommend that the data from studies MYL-1401H-1001 and MYL-1401H-1002 (BLA 761075) be accepted for further Agency review.

(b) (4)

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Analytical Site:

VAI: [REDACTED] (b) (4)

FEI#: [REDACTED] (b) (4)

cc:

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

OPQ/OBP/DBRRIII/Rosenberg/Verthelyi/Bowen

Draft: GM 10/04/2017; 10/6/2017
Edits: PY 10/06/2017; AD 10/09/2017

ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881051c61>

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

FACTS: [REDACTED] (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
10/11/2017

LI-HONG P YEH
10/11/2017

ARINDAM DASGUPTA
10/11/2017

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

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

Memorandum

Date: September 25, 2017

To: Katie Chon, PharmD, RPh, Regulatory Project Manager, Division of Hematology Products (DHP)
Virginia Kwitkowski, Associate Director for Labeling, DHP

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

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

Subject: OPDP Labeling Comments for MYL-1401H

BLA: 761075

This memo is in response to Katie Chon's of DHP labeling consult request dated February 2, 2017. OPDP notes DHP indicated a Complete Response letter will be issued for this application. As such, final labeling negotiations will not be initiated during the current review cycle. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DHP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
09/25/2017



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research**

Office of Pharmaceutical Quality
Office of Biotechnology Products
10903 New Hampshire Avenue
Silver spring, MD 20993

Review Memorandum

STN	BLA 761075
Type	351 (k)
Subject	Immunogenicity Review
Submission Date	12/09/2016
Review/Revision Date	03/24/2017, 05/04/2017, 07/28/2017, 8/31/2017, 9/19/2017
Primary Reviewer	Zhenzhen Liu, Ph.D., DBRR III
Secondary Reviewer	Maria-Teresa Gutierrez-Lugo, Ph.D. , DBRR III
Tertiary Reviewer	Susan Kirshner, Ph.D., DBRR III
RPM	Katie Chon
Consults	Immunogenicity
Applicant	Mylan GmbH
Product	MYL-1401H Solution for Subcutaneous Injection, a proposed biosimilar to US-licensed Neulasta (pegfilgrastim)
Indication	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
Filing Action Date	02/21/2017
PDUFA Due Date	10/06/2017

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I. SUMMARY BASIS OF RECOMMENDATION

This review memo updates and replaces the review memo uploaded in Panorama on September 1, 2017. This version includes information on re-evaluation of NAb assay sensitivity using pre-dose normal human and breast cancer sera. (b) (4)

The additional data does not impact the original assessment and recommendation provided in the previous review memo.

A. RECOMMENDATION

From an immunogenicity perspective, I recommend approval of this 351(k) BLA for MYL-1401H as a biosimilar to US-licensed Neulasta, pending re-evaluation of freeze/thaw and bench-top stability of positive controls from method validation study (b) (4) associated with clinical studies MYL-1401H-1001 and MYL-1401H-1002.

B. JUSTIFICATION

The sponsor validated an electrochemiluminescence (ECL) method to screen for and confirm anti-drug antibody (ADA) in patient serum, and a cell-based assay to characterize neutralizing activity of ADA. The methods are suitable to evaluate ADA incidence, specificity, and neutralizing activity.

The sponsor monitored immunogenicity in a 6-dose (6 mg each) parallel arm study in patients with breast cancer (Study MYL-1401H-3001). The design of the study was appropriate to assess immunogenicity. In total, 0 out of 126 patients were identified as positive for ADA after treatment with MYL-1401H as compared to 1 out of 67 patients treated with EU-approved Neulasta. No patients in either treatment group developed ADA with G-CSF specific neutralizing activity. The difference in treatment-induced ADA incidence between groups is within 2%, indicating that there is no clinically significant difference between MYL-1401H and EU-approved Neulasta with respect to immunogenicity. The sponsor established a scientific bridge, including both analytical and PK/PD components, between MYL-1401H, EU-approved Neulasta, and US-licensed Neulasta (refer to Product Quality and Clinical Pharmacology Review Memos, respectively). The results from the breast cancer patient study using EU-approved Neulasta as a comparator supports the demonstration of no clinically meaningful difference in immunogenicity between MYL-1401H and the reference product US-licensed Neulasta.

In addition, the sponsor conducted two comparative clinical studies in healthy volunteers to further support that there are no clinically meaningful differences between MYL-1401H, EU-approved Neulasta, and US-licensed Neulasta with

respect to immunogenicity (Studies MYL-1401H-1001 and MYL-1401H-1002). Study MYL-1401H-1001 is a single-dose (2 mg) crossover study in 216 healthy subjects designed to determine the PK/PD similarity between MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta. It monitored immunogenicity after a single dose and showed treatment-induced ADA incidences of 22.2%, 29.4%, and 36.2% in MYL-1401H, EU-approved Neulasta, and US-licensed Neulasta treatment groups, respectively. Study MYL-1401H-1002 is a 2-dose (6 mg) parallel-arm study in 50 healthy subjects designed to determine the immunogenicity similarity of MYL-1401H and US-licensed Neulasta. It monitored immunogenicity throughout the study and showed treatment-induced ADA incidences of 27.3% and 29.2% in MYL-1401H and US-licensed Neulasta treatment groups, respectively. The results of these two studies show that there is no increase in ADA incidence for MYL-1401H as compared to US-licensed Neulasta. However, given the cross-over study design and small sample size, these two studies provided limited additional information supporting the demonstration of no clinically meaningful differences in immunogenicity between MYL-1401H and US-licensed Neulasta. The difference in immunogenicity rates between study MYL-1401H-3001 and studies MYL-1401H-1001 and MYL-1401H-1002 is most likely due to differences in the treatment populations. Subjects in Study MYL-1401H-3001 chemotherapy treated were patients with cancer who were very likely immune suppressed. Subjects in studies MYL-1401H-1001 and MYL-1401H-1002 were healthy volunteers who were not immune suppressed.

Overall, the immunogenicity assays are suitable for intended purpose and there are no clinically meaningful differences with respect to immunogenicity in patients treated with MYL-1401H and US-licensed Neulasta. Therefore, I recommend approval of this 351(k) BLA from an OBP immunogenicity perspective.

II. COMMENTS TO SPONSOR

None.

III. REVIEW

Mylan is seeking approval for MYL-1401H (pegylated recombinant human granulocyte stimulating factor (PEG GCSF)) as a proposed biosimilar to US-licensed Neulasta, manufactured by Amgen. The sponsor is seeking licensure only for the neutropenia indication, which is currently approved for US-licensed Neulasta. In support of this 351(k) BLA, Mylan monitored immunogenicity of MYL-1401H and US-licensed Neulasta or EU-approved Neulasta in healthy volunteers (MYL-1401H-1001 and MYL-1401H-1002) and patients with breast cancer (MYL-1401H-3001). The 351(k) BLA submission includes method validation reports (section 1 and 2 of the review) and clinical immunogenicity data analysis (section 3 of the review). During the review cycle, three

Information Requests (IRs) were communicated to the sponsor to provide additional data and information to allow for a full assessment of the immunogenicity similarity between MYL-1401H and US-licensed Neulasta. All IR responses were reviewed and found acceptable. The Table below provides the location of additional immunogenicity assay information provided in the submission.

eCTD Sequence	Date	IR responses regarding
0023	07/07/2017	<p><u>ADA binding assay</u></p> <ul style="list-style-type: none"> • Revision of confirmatory cut points using 1% false positive rate • Justification of titer cut point using 0.01% false positive rate • Verification of cut points using pre-dose clinical samples • Data on labeling efficacy and stability of master-mix <p><u>NAb assay</u></p> <ul style="list-style-type: none"> • Additional dose-response curves to justify MYL-1401H concentration used in the NAb assay • Justification of screening cut point using 5% false positive rate for breast cancer human serum • Justification of statistical method for determining confirmatory cut point • Additional data on the control over the use of NFS-60 cells
0027	07/31/2017	<ul style="list-style-type: none"> • Re-analysis of clinical data using confirmatory cut points at 1% false positive rate (part 1)
0028	08/04/2017	<ul style="list-style-type: none"> • Re-analysis of clinical data using confirmatory cut points at 1% false positive rate (part 2)
0031	08/18/2017	<ul style="list-style-type: none"> • Re-evaluation of assay sensitivity using pre-dose normal human serum
0037	09/08/2017	<ul style="list-style-type: none"> • Re-evaluation of assay sensitivity using pre-dose breast cancer human serum
Pending	09/08/2017 (expecting)	<ul style="list-style-type: none"> • Re-evaluation of freeze/thaw and bench-top stability of positive controls for NAb assay using freshly prepared comparators and pooled pre-dose normal human serum.

Table Prepared by OBP immunogenicity reviewer

1. VALIDATION OF ANTIDRUG ANTIBODY SCREENING ASSAY

1.1 Background

An electrochemiluminescence (ECL) assay using the Meso Scale Discovery (MSD) platform for the detection, confirmation, and titration of anti-PEG GCSF antibodies in human serum was developed and validated at (b) (4)

Two method validation reports for two populations, healthy volunteers and breast cancer patients were submitted. An initial total ADA assay validation report, 8308-904, was

provided in support of comparative immunogenicity testing in healthy subjects for clinical studies MYL-1401H-1001 and MYL-1401H-1002. A subsequent total ADA assay validation report, 8310-739, was provided in support of comparative immunogenicity testing in breast cancer patients for clinical study MYL-1401H-3001. The Table below provides the information for these two method validation reports.

Validation Report	Relevant clinical study	Completion date	Amended date
8308-904	MYL-1401H-1001 MYL-1401H-1002 (Healthy subjects)	27 April 2016	06 June 2016
8310-739	MYL-1401H-3001 (Breast cancer patients)	08 June 2016	N/A

Table prepared by OBP immunogenicity reviewer

Validation report 8310-739 is more relevant because the method was used to assess total ADA in the study that was best designed to evaluate whether there is clinically meaningful difference in immunogenicity between MYL-1401H and US-licensed Neulasta. In this section, information in 8310-739 was reviewed with reference to Report 8308-904 where appropriate.

- **Method Principle**

The method uses a bridging immunoassay format that uses the MSD detection technology. Samples undergo acid dissociation to release any anti-PEG GCSF antibodies complexed with free drug. Samples are neutralized and incubated with Master Mix, containing Biotinylated MYL-1401H and Sulfo-Tag labeled MYL-1401H, allowing ADA to bind to MYL-1401H biotin and MYL-1401H Sulfo-Tag, thus forming the bridging complexes. After incubation, the antibody complex bridge is added to a pre-blocked streptavidin coated MSD plate and incubated, followed by washing. The MYL-1401H Biotin in the complex binds to streptavidin coated wells, allowing any unbound material to be washed away. Read buffer containing tripolyamine is added and the Sulfo-Tag conjugated to MYL-1401H produces a chemiluminescent signal when an electrical voltage is applied. The signal is directly proportional to the level of ADA present in the sample.

All samples were subjected to an initial screening assay, and those falling at or above a plate specific cut point were identified as screen positive. Screen positive samples were subjected to a confirmatory assay in which samples were pre-incubated with excess MYL-1401H or GCSF (Neupogen) or PEG prior to analysis for domain characterization.

- **Testing Facility**



1.2 Controls and Reagents

- **Matrix**

Pooled normal human serum (NHS) consisting of individual NHS samples were used to prepare positive controls and negative controls.

- **Individual Human Serum**

In total, 48 individual drug-naïve breast cancer human serum (BCHS) samples and 48 individual drug-naïve NHS samples were used for population-specific cut point.

- **Negative Control (NC)**

Pooled NHS was used as the negative control.

- **Positive Controls (PCs)**

The following positive controls were used in this study:

Antibody	Lot number	Concentration	Storage	Retest Date	Suggested Aliquot volume
Rabbit Anti-Neulasta/PEG GCSF antibody	1166/13/08/09/PC/001	0.38 mg/mL	-60 to -80°C, Once thawed, 2 to 8°C	9-Aug-2017	1mL
Mouse anti-PEG (AGP3) reference antibody	1166/14/11/10/PC/002	1.0 mg/mL	-60 to -80°C, Once thawed, 2 to 8°C	10-Nov-2016	50µL
Mouse anti-PEG (AGP4) reference antibody	1166/14/11/10/PC/003	1.1 mg/mL	-60 to -80°C, Once thawed, 2 to 8°C	10-Nov-2016	50µL

Low (LPC, 30 ng/ml) and high (HPC, 2000 ng/ml) concentrations of anti-Neulasta/PEG GCSF antibody, Low (LPC, 150 ng/ml) and high (HPC, 2000 ng/ml) concentrations of anti-PEG reference antibody were prepared and used during assay validation.

- **Reagents**

Reagent Name	Lot number used	Supplier	(b) (4) Reference No.	Expiration Date	Storage Conditions
PEG GCSF (MYL-1401H) Biotin Conjugate	PEL-PER-BR-NA-003	(b) (4)	AU-14-Jan-2016-00117	25 Aug 2017	2-8°C
PEG GCSF(MYL-1401H) Sulfotag Conjugate	PEL-PER-DR-NA-003		AU-14-Jan-2016-001087	25 Aug 2017	2-8°C
Neulasta® EU	1048603D	Mylan Pharmaceuticals	2015-088-041B	31 Jan 2017	2-8°C
Neulasta® EU	1053573B	Mylan Pharmaceuticals	2015-088-041B	30 Jun 2017	2-8°C
PEG GCSF (MYL-1401H)	BF14008786	(b) (4)	2015-116-005	Mar 2016	2-8°C
Neupogen® (GCSF)	1055770		Mylan Pharmaceuticals	2015-116-007	Nov 2016
PEG (b) (4)	G14916	(b) (4)	NA	02 Oct 2017	(b) (4)
Anti-BMO2/Humira® polyclonal antibody	1212/13/05/03/PC/001		NA	10 Apr 2017	-60 to -80°C, 2-8°C after thawing
Humira® EU	0478XD08		NA	31 Mar 2016	2-8°C
Rabbit Anti-Neulasta®/PEG GCSF Antibody (Bulk ADA)	1166/13/08/09/PC/001		NA	09 Aug 2017	-60 to -80°C, 2-8°C after thawing
Primate Anti-Neulasta®/PEG GCSF Antibody (For Drug Tolerance)	1166/14/11/10/PC/004		NA	10 Nov 2016	-60 to -80°C, 2-8°C after thawing
Rabbit Anti-Neulasta® Antibody (Anti-NEU ADA, for antigenic equivalence)	1166/15/04/24/PC/006		NA	23 Apr 2017	-60 to -80°C, 2-8°C after thawing
Mouse Anti-PEG (AGP3) Antibody	1166/14/11/10/PC/002		NA	10 Nov 2016	-60 to -80°C, 2-8°C after thawing
Mouse Anti-PEG (AGP4) Antibody	1166/14/11/10/PC/003		NA	10 Nov 2016	-60 to -80°C, 2-8°C after thawing
Rabbit Anti-PEG GCSF Antibody (Anti-MYL ADA, for antigenic equivalence)	1166/15/04/24/PC/005		NA	23 Apr 2017	-60 to -80°C, 2-8°C after thawing

*The above reagents were used in study 8310-739.

1.3 Validation Parameters

The ECL assay was validated for system suitability acceptance criteria, screening cut point, confirmatory cut point, titer cut point, sensitivity, selectivity, precision, drug tolerance, prozone effect, and stability of antibody and reagent. The Table below provides summary of results from both validation reports.

Parameter	Report 8310-739 (BCHS)	Report 8308-904 (NHS)
MRD	1:6	1:6
Normalization Factor	1.19	1.17
Plate Specific Cut Point	Mean NC response × Normalization factor	
Confirmatory Cut Point (MYL-1401H)	24.4%	24.8%
Confirmatory Cut Point (GCSF)	30.3%	19.3%
Confirmatory Cut Point (PEG)	27.5%	17.0%
Titer Cut Point Factor	1.45	1.32
Relative Sensitivity	7.9 ng/mL for anti-PEG GCSF 6.1 ng/mL for anti-PEG	5.2 ng/mL for anti-PEG GCSF 4.3 ng/mL for anti-PEG
Drug Tolerance	<ul style="list-style-type: none"> Bulk PC at 31.25 ng/mL can be detected in the presence of 1 µg/mL of drug; Anti-PEG PC at 31.25 ng/mL can be detected in the presence of 1 µg/mL of drug. 	<ul style="list-style-type: none"> Bulk PC at 31.25 ng/mL can be detected in the presence of 1 µg/mL of drug; Anti-PEG PC at 31.25 ng/mL can be detected in the presence of 1 µg/mL of drug.
Prozone	No hook effect was observed up to a concentration of 20000 ng/mL	
Room Temperature Stability	24 hours	
Refrigerator Stability	72 hours	
Free /Thaw Stability	Up to 6 cycles at -60 to -80°C	

Table prepared by OBP immunogenicity reviewer

The individual validation parameters were reviewed in section 1.5 below.

1.4 System Suitability

- NC, LPC and HPC ranges were calculated using their response values from all validation runs (100 runs for BCHS validation study and 107 runs for NHS validation study). For the PC samples, instead of the response values, ratio to mean NC values were calculated and used for calculating the system suitability ranges. The data were

provided in Study Report 8310-739, Appendix II, Table 6 and Study Report 8308-904, Appendix II, Table 15. The control ranges were summarized in Tables below. The ranges were calculated using the following formula:

$$\begin{aligned} \text{NC range} &= \text{Mean (NC responses)} + t_{0.01, df} \times \text{SD (NC responses)} \\ \text{LPC range} &= \text{Mean (LPC/NC ratios)} \pm t_{0.005, df} \times \text{SD (LPC/NC ratios)} \\ \text{HPC range} &= \text{Mean (HPC/NC ratios)} \pm t_{0.005, df} \times \text{SD (HPC/NC ratios)} \end{aligned}$$

BCHS

Control	Lower Limit	Upper Limit
NC Response (RLU)	NA	81
Bulk ADA HPC/NC Ratio	45.9	178.5
Bulk ADA LPC/NC Ratio	1.3	4.1
Anti-PEG ADA HPC/NC Ratio	36.8	113.8
Anti-PEG ADA LPC/NC Ratio	4.4	26.6

NHS

Control	Lower Limit	Upper Limit
NC Response (RLU)	NA	77
Bulk ADA HPC/NC Ratio	60.1	226.5
Bulk ADA LPC/NC Ratio	1.7	4.5
Anti-PEG ADA HPC/NC Ratio	44.7	183.7
Anti-PEG ADA LPC/NC Ratio	1.17	8.4

- Plate acceptance criteria: CV% of replicates of all samples should be <25%.

Unless otherwise stated, all runs passed system suitability and plate acceptance criteria.

Reviewer Comment: The system suitability ranges are well established and they are suitable for ensuring this qualitative assay performed as expected. Because the plate acceptance criteria and system suitability were met, the assay is capable of producing meaningful data for validation analysis.

1.5 Validation Exercise

1.5.1 Master-mix Interchangeability

Prior to full validation, a study was performed to determine the ability of the biotinylated and Sulfo-Tagged reagent sets prepared from MYL-1401H, US-licensed Neulasta, or EU-approved Neulasta to detect ADA raised from each drug. Three types of anti-PEG GCSF antibodies [anti-Neulasta/PEG GCSF ADA (hereafter referred to as bulk ADA), anti-Neulasta ADA, and anti-MYL-1401H ADA¹] were spiked in pooled NHS at 20, 100, 250, 1000, 2000, 5000, and 20000 ng/ml concentrations. Each anti-PEG GCSF antibody dilution series was evaluated in the screening assay and dose-response curves were

¹ **Rabbit Anti-Neulasta/PEG GCSF Antibody (Bulk ADA):** This ADA was produced by purifying hyper-immune sera from rabbits immunized with Neulasta using an affinity column prepared with MYL-1401H.

Rabbit Anti-Neulasta Antibody (anti-NEU ADA): This ADA was produced by purifying hyper-immune sera from rabbits immunized with Neulasta using an affinity column prepared with Neulasta.

Rabbit Anti-MYL-1401H/PEG GCSF Antibody (anti-MYL ADA): This ADA was produced by purifying hyper-immune sera from rabbit immunized with MYL-I401H using an affinity column prepared with MYL-I401H.

generated. The data presented in Table 1 through Table 9 (not shown) demonstrate that each set of master-mixes can detect all three anti-PEG GCSF antibodies (ECL counts above the cut-point). The precision (%CV) of the mean ECL responses between all three master mixes was less than 16.5% for all 7 reference material concentrations across all runs, which fulfills the plate acceptance criteria.

Reviewer Comment: The results suggest that a single assay with master-mix prepared from MYL-1401H can be used to detect ADAs against MYL-1401H, US-licensed and EU-approved Neulasta.

1.5.2 Antigenic Equivalence (AE)

Prior to full validation, a study was performed to determine the ability of each unlabeled drug to inhibit the detection of the ADA using the labeled MYL-1401H master-mix reagents. The three ADAs (the same as those mentioned in above section) were spiked in pooled NHS at HPC level. These HPC samples were evaluated in the confirmatory assay using varying concentrations of unlabeled US-licensed Neulasta, EU-approved Neulasta, or MYL-1401H (5000, 1000, 600, 400, 250, and 150 ng/mL) to generate two inhibition curves for each drug in each run. Data generated from antigen equivalence assessments were provided in both study reports (Study Report 8310-739, Appendix II, Table 2-4 and Study Report 8308-904, Appendix II, Table 11-13). In summary, the HPC responses showed a comparable dose-dependent reduction with increasing concentrations of unlabeled US-licensed Neulasta, EU-approved Neulasta, and MYL-1401H. The precision of the mean percent inhibition values between three drugs was <20% at all drug concentrations across all runs with the exception of several runs, which were due to high %CV across the two inhibition curves.

Reviewer Comment: The results support the antigenic equivalence of the three drugs. Based on this data, the sponsor decided to use MYL-1041H in the confirmatory assay for the detection of ADA against MYL-1041H, US-licensed and EU-approved Neulasta. This is acceptable.

1.5.3 Screening Cut Point (SCP) Determination

BCHS

A total of 48 drug naïve BCHS samples were divided into 3 groups of 16 samples per group. Each group was analyzed on a single plate in 6 independent runs by 2 analysts on 3 different days following the balanced design shown below. Each run contain 4 sets of NC samples in duplicate and 2 sets of HPC and LPC samples in duplicate.

Plate Order	Analyst 1			Analyst 2		
	Run 1/Day 1	Run 2/Day 2	Run 3/Day 3	Run 4/Day 1	Run 5/Day2	Run 6/Day 3
1	Group A	Group B	Group C	Group C	Group A	Group B
2	Group B	Group C	Group A	Group A	Group B	Group C
3	Group C	Group A	Group B	Group B	Group C	Group A

Group A = individuals 1-16, Group B = individuals 17 – 32 and Group C = individuals 33-48.

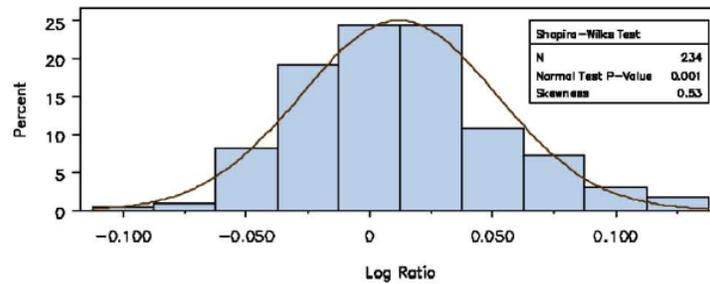
A floating cut-point approach was used to determine the SCP. ECL values for NC (n=72), HPC (n=36), LPC (n=36), and 48 BCHS samples (n=288) were provided in Study Report 8310-739, Appendix 5, Table 2 and 3. S/N ratio values were generated by

dividing the mean sample ECL value by the plate-specific mean negative control ECL value for each test samples (Refer to Study Report 8310-739, Appendix 5, Table 4 below). ECL and S/N ratio values were log-transformed and analyzed by statistical methods to assess for outliers and data distribution normality. The linear mixed effects ANOVA of log-transformed S/N ratio values identified 53 outliers, which were excluded from further analysis, resulting in 234 values for cut-point calculation.

Total number of assay values (Samples x Runs)	288
Values with High CV (CV% >25%)	1
Values identified as statistical outliers	53
Analytical outliers	14
Biological outliers (8 samples)	39
Total Values used in Cut Point Analysis	234

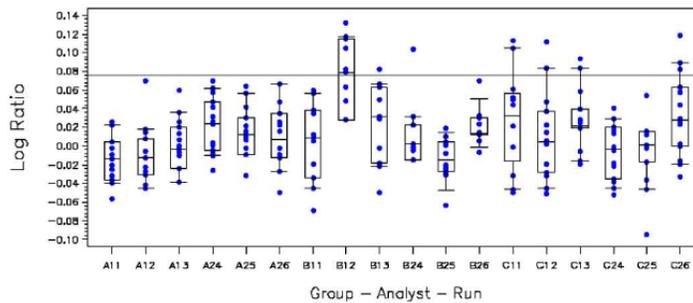
Although tests for normality of the log-transformed S/N ratio values were not confirmed (Shapiro-Wilk test, $p=0.001$), the skewness-coefficient was low (0.53), indicating that the distribution was symmetric (Figure 7 below).

Figure 7: Histogram of Human Serum Log transformed S/N Ratio Values after Removing Outliers



Levene’s test did not confirm the homogeneity of intra-plate sample variances across plates ($p =0.019$) and a statistical difference was observed among the assay plate mean values ($p<0.001$, Table 8 and Figure 2 below). Collectively, these results suggest that a parametric floating cut-point approach to determine the SCP is appropriate.

Figure 2: Plot of Human Serum Log-transformed S/N Ratio Values Versus the Assay Group, Analyst and Run Excluding Outliers



The horizontal reference line at 0.0752 corresponds to the parametric log-transformed floating cut point factor of 1.19

Table 8: Analysis of Variance Summary for NC Log ECL Values and HS Log S/N Ratio Values

ANOVA Factor	NC Log ECL (n=71)		HS Log S/N Ratio (n=234)	
	p-value	Effect	p-value	Effect
Fixed Effects:				
Group	N/A	N/A	0.546	NS
Analyst	0.190	N/A	0.618	NS
Plate Order	0.352	N/A	0.676	NS
Location	<.001*	Front < Back	N/A	N/A
Random Effects:	Variance	% of Total	Variance	% of Total
Sample (Group)	N/A	N/A	0.000774	44.1
Run (Analyst)	0.000075	5.2	0.000000	0.0
Assay Number	0.000297	20.8	0.000473	26.9
Residual	0.001056	74.0	0.000510	29.0
Total	0.001428	100.0	0.001756	100.0
Diagnostic Tests:	p-value	Effect	p-value	Effect
Normality Conditional Residuals (a)	0.418	NS	0.218	NS Figure 5
Normality Sample Number BLUP (a)	N/A	N/A	0.692	NS
Variance homogeneity Plate (b)	0.030*	See Figure 1	0.019*	See Figure 2
Difference in Plate Means (c)	0.024*	See Figure 1	<.001*	See Figure 2

a - Shapiro-Wilk Test
b - Levene's Test - Comparison of Rans for Negative Control
c - ANOVA - Comparison of Rans for Negative Control
* - Statistically significant at the 0.050 nominal level
BLUP - Best Linear Unbiased Predictor
NS - Not Significant
N/A - Not Applicable

A parametric method with Tukey's biweight procedure was used to calculate estimates of the mean and standard deviation of all log-transformed S/N ratios. The parametric floating cut-point factor was then determined by multiplying the SD value by the 95th quantile of the t-distribution (with degrees of freedom equal to the number of log-transformed ratio values) and adding that value to the mean value before performing an inverse log transformation. **The parametric cut point factor of 1.19 was used as Normalization Factor (NF) for the in-study SCP calculation, by multiplying a NF of 1.19 to the mean ECL values for NC obtained during the in-study plate.** The false positive rate was shown to be 7.3% (17/234 samples).

Method	Parametric (Biweight) Estimate	Non-parametric (95 th Percentile) Estimate
Screening Floating Cut Point Multiplicative Factor Estimates	1.19	1.22

NHS

A total of 48 drug naïve NHS samples were divided into 3 groups of 16 samples per group. Each group was analyzed on a single plate in 6 independent runs by 2 analysts on 3 different days following the same balanced design shown above. The SCP was determined by the same statistical methods, such as evaluating distribution of assay values, outlier analysis, comparison of means and variances between assay runs, used to determine SCP factor for BCHS shown above. **The parametric cut point factor of 1.17 was used as Normalization Factor (NF) for the in-study SCP calculation, by multiplying a NF of 1.17 to the mean ECL values for NC obtained during the in-study plate.** The false positive rate was shown to be 4.4% (8/182 samples).

Method	Parametric (Biweight) Estimate	Non-parametric (95 th Percentile) Estimate
Screening Floating Cut Point Multiplicative Factor Estimates	1.17	1.17

In response to an IR (June 16, 2017), Mylan stated that the panel of 48 drug naïve BCHS samples used for determination of NF were pre-dose samples collected from clinical study MYL-1401H-3001 and thus the pre-study NF of 1.19 does not need to be confirmed. However, the panel of 48 drug naïve NHS samples used for determination of NF was obtained commercially from (b) (4). Mylan confirmed the pre-study NF of 1.17 using 216 pre-dose samples collected from clinical study MYL-1401H-1001 and 50 samples collected from clinical study MYL-1401H-1002.

Reviewer Comments: The assay design is balanced. The sponsor provided the results from these analyses and outliers were appropriately determined and eliminated for the normalization factor calculations. Based on a review of the pre-study and in-study data, the normalization factors are acceptable.

1.5.4 Confirmatory Cut Point (CCP) Determination

BCHS

The confirmatory assay is based on competition with excess, unlabeled drugs or PEG. To determine confirmatory cut points, the same 48 drug naïve BCHS samples used in the SCP determination were spiked with excess competitor. Three competitors were assessed in the spiking exercises: 200 µg/mL of MYL-1401H (MYL), 100 µg/mL of GCSF (Neupogen, NEU), and 16 mg/mL of PEG. The analysis was performed by 2 analysts on 3 different days using a balanced design.

Different CCPs were established separately for each competitor based on % inhibition values (288 values for each competitor): % inhibition = $100 \times [1 - (\text{Response with excess drug} / \text{Response with buffer})]$. The same statistical methods, such as evaluating distribution of assay values, outlier analysis, comparison of means and variances between assay runs, used for SCP determination were performed to determine CCPs. Both parametric and non-parametric CCPs were determined at the 1% and 0.1% false positive rates for each competitor (shown in Table below). **The parametric cut-point approach based on the 0.1% false positive rate was chosen to analyze the clinical samples.** None of the % inhibition values were shown to be above the 99.9% parametric CCPs for MYL, NEU, and PEG.

Description	False Positive Error Rate	Parametric Estimate	Non-parametric Estimate
Confirmation Cut Point for Percent Inhibition for MYL	1.0% 0.1%	18.5% 24.4%	22.4% NR
Confirmation Cut Point for Percent Inhibition for NEU	1.0% 0.1%	23.4% 30.3%	23.6% NR
Confirmation Cut Point for Percent Inhibition for PEG	1.0% 0.1%	20.5% 27.5%	20.5% NR

NHS

The same 48 drug naïve NHS samples used in the SCP determination were spiked with excess competitors (3 types described above). Different CCPs were established using the same statistical methods shown above and summarized below. **The parametric cut-point approach based on the 0.1% false positive rate was chosen to analyze the clinical samples.**

Description	False Positive Error Rate	Parametric Estimate	Non-parametric Estimate
Confirmation Cut Point for Percent Inhibition for MYL	1.0% 0.1%	19.4% 24.8%	16.9% NR
Confirmation Cut Point for Percent Inhibition for NEU	1.0% 0.1%	14.9% 19.3%	11.0% NR
Confirmation Cut Point for Percent Inhibition for PEG	1.0% 0.1%	12.7% 17.0%	10.6% NR

In response to an IR (June 16, 2017), Mylan stated that the panel of 48 drug naïve BCHS samples used for determination of CCPs were pre-dose samples collected from clinical study MYL-1401H-3001 and thus the pre-study CCPs do not need to be confirmed. However, the panel of 48 drug naïve NHS samples used for determination of CCPs was obtained commercially from (b) (4). Mylan stated that they could not confirm the pre-study CCPs using pre-dose clinical samples because only 35 screened positive pre-dose clinical samples underwent confirmatory assay and this number is not suitable for statistical determination of in-study CCPs.

Reviewer Comments:

- a) *FDA guidance recommends that a 1% false positive rate be used to set the CCP; the use of a CCP based on a 0.1% false positive rate increases the risk of false negatives (difference of 5-7% of signal inhibition between cut-points). The sponsor should use CCPs at the 1% false positive rate to analyze the clinical data or provide a summary of data to support that the ADA incidence is comparable when using CCPs based on 1% and 0.1% false positive rates. In response to an IR (June 16, 2017), Mylan revised ADA analysis using CCPs at 1% false positive rate. Refer to “Section 3 Analysis of Clinical Immunogenicity Results” below for detailed information.*
- b) *FDA guidance also recommends that cut point be confirmed with appropriate sample in-study. However, the sponsor did not provide data to confirm the CCPs using pre-treatment samples for NHS. This is acceptable in this case because the validation study using NHS was conducted to support clinical studies MYL-1401H-1001 and -1002. Since these two studies provide limited additional immunogenicity data, verification of cut-points for NHS is not needed.*

1.5.5 Titer Cut Point (TCP) Determination

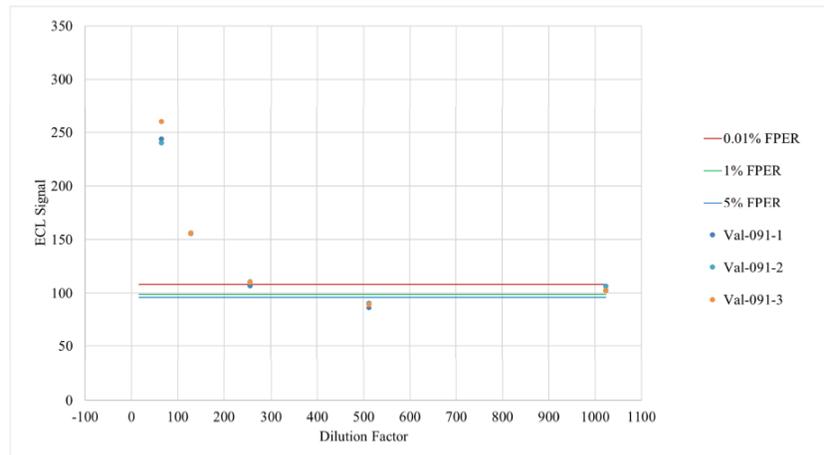
The titer cut point factor was determined based on the same data and statistical methods used to establish the parametric SCP factor but with more extreme probability levels (99.9% and 99.99% percentile). **The titer cut point factor at the 0.01% false positive rate was chosen to analyze the clinical samples.**

	99.9%	99.99%
BCHS	1.36	1.45
NHS	1.27	1.32

Table prepared by OBP immunogenicity reviewer

Reviewer Comments: The TCP factor at a 0.01% false positive rate was chosen to analyze clinical samples. Using this TCP, clinical samples that confirmed positive would be reported as “no titer” because a higher false-positive rate (1%) was used to determine the CCPs. In an IR dated June 16, 2017, we asked the sponsor to revise their TCP and re-calculate titers for clinical samples based on a revised TCP. To defend their original TCP determination, in the IR response, the sponsor provided titration curves and compared the TCPs at 0.01%, 1.0% and 5% false-positive rates (one representative figure is shown below).

Figure 1: Titration Curves from VAL-091



The sponsor observed that the titer positive control samples failed to cross the screening cut point (5% FPER) or a higher TCP (1% FPER) even after multiple dilutions. Based on these observations, the sponsor decided to use a higher TCP at a 0.01% false-positive rate to analyze clinical samples. To further support the TCP at a 0.01% false-positive rate, the sponsor stated that this TCP produced better titer precision than other TCPs at 1% and 5% false-positive rates and they reported “1×MRD” as the titer instead of “no titer” for those confirmed positive samples whose responses fell between the SCP and TCP. It is a common problem that the SCP lays in the lower plateau of the dilution curve. Using a higher TCP at a lower false-positive rate is an approach to resolve this issue per (USP <1106>) Immunogenicity assay design and validation of immunoassays to detect anti-drug antibodies and “Cut points and performance characteristics for anti-drug antibody assays” (Devnarayan, 2011). Thus, the sponsor’s response is acceptable.

Regardless, as described below, because the sensitivity of the assay at the TCP at a 0.01% false positive rate is 7.9 ng/mL (for bulk ADA) with an acceptable amount of variability ($\leq 14\%$ CV), the approach used to establish TCP is acceptable.

1.5.6 Assay Sensitivity

BCHS

To determine the assay sensitivity, ten 2-fold serial dilutions of HPC samples (bulk ADA and anti-PEG ADA) spanning the 0.01% titer cut point were tested in totally 4 runs by 2 analysts on 2 days. Three independent serial dilutions prepared from frozen HPC aliquots were tested in each run. Sensitivity was calculated using the following approach:

1. Calculate the fraction (f) of a dilution step between the first dilution above the titre cut point and the plate specific titre cut point as follows:

$$f = \frac{S_T - S_{PSTCP}}{S_T - S_{FND}}$$

Where: S_T = ECL signal at the first dilution above the titre cut point

S_{PSTCP} = Plate specific titre cut point

S_{FND} = ECL signal at the first dilution below the titre cut point

2. Calculate the log end point titre (EPT) as follows:

$$\log_{10}(EPT) = \log_{10}(T) + f \log_{10}(2)$$

Where: T = first serial dilution above the titre cut point

3. Calculate the antilog of the result and report the end point titre (EPT).

The end-point titer (EPT) determined from each run was converted to an end point concentration (EPC= HPC concentration/EPT). The mean of EPC from 12 dilution curves was calculated and defined as the assay sensitivity. Sensitivity was calculated as 7.9 ng/mL for bulk ADA (Table 21 below) and 6.1 ng/mL for anti-PEG ADA (Refer to Study Report 8310-739, Appendix II, Table 22).

Table 21: Intra and Inter-Assay Precision for Titration Assay Using Bulk ADA

Analytical Run (b) 8310-739	Plate Specific Titre Cut Point (Spccr)	Duplicate s	1 in X *												S_T	T	S_{PSTCP}	Fraction (f) (2 d.p.)	Log End Point Titre (EPT) (2 d.p.)	EPT Intra- assay Mean Sidev %CV	Sensi- tivity
			1 in 1	1 in 2	1 in 4	1 in 8	1 in 16	1 in 32	1 in 64	1 in 128	1 in 256	1 in 512	1 in 1024	Observed Response (RLU)							
Val-076	92	1	7083	3414	1814	954	533	290	172	120	91	81	65	120	128	91	0.97	2.40	2.52	8.0	
		2	6625	3400	1712	929	531	293	174	120	94	89	73	94	256	89	0.36	2.52	0.12	6.1	
		3	6785	3505	1786	991	545	307	180	132	99	90	77	99	256	90	0.74	2.63	4.6	4.7	
Mean (RLU)			6831	3440	1770	958	536	297	175	124	95	86	72	-	-	-	-	-	-	-	
Stdev			232.2	57.2	52.4	31.2	7.9	9.3	4.2	7.1	4.3	4.6	6.1	-	-	-	-	-	-	-	
%CV			3.4	1.7	3.0	3.3	1.5	3.1	2.4	5.7	4.5	5.3	8.5	-	-	-	-	-	-	-	
Val-079	105	1	8419	4416	2272	1175	861	386	210	145	115	82	76	115	256	82	0.30	2.50	2.54	6.3	
		2	10213	4811	2472	1295	680	455	215	155	125	93	86	125	256	93	0.63	2.60	0.05	5.0	
		3	10400	4948	2418	1342	695	397	239	159	114	88	82	114	256	88	0.35	2.51	2.1	6.1	
Mean (RLU)			9677	4725	2387	1271	745	413	221	153	118	87	81	-	-	-	-	-	-	-	
Stdev			1,093.6	276.3	103.3	85.9	100.5	37.2	15.5	6.9	6.1	5.5	5.3	-	-	-	-	-	-	-	
%CV			11.3	5.8	4.3	6.8	13.5	9.0	7.0	4.5	5.2	6.3	6.5	-	-	-	-	-	-	-	
Val-082	85	1	6141	2146	1146	610	360	209	136	96	76	69	68	96	128	76	0.55	2.27	2.28	10.7	
		2	6726	2058	1130	641	354	208	133	93	77	68	64	93	128	77	0.50	2.26	0.03	11.0	
		3	6849	2275	1197	719	377	224	135	105	76	72	70	105	128	76	0.69	2.31	1.3	9.7	
Mean (RLU)			6572	2159	1157	657	364	214	133	98	76	69	67	-	-	-	-	-	-	-	
Stdev			378.0	109.4	34.8	36.2	12.1	9.0	1.8	6.0	0.5	2.0	3.1	-	-	-	-	-	-	-	
%CV			5.8	5.1	3.0	8.6	3.3	4.2	1.3	6.1	0.7	2.9	4.6	-	-	-	-	-	-	-	
Val-085	99	1	5875	2683	1339	702	435	254	166	116	93	74	68	116	128	93	0.74	2.33	2.35	9.4	
		2	6389	2874	1663	787	444	251	170	116	91	74	68	116	128	91	0.68	2.31	0.04	9.8	
		3	6366	2912	1536	925	485	253	158	121	98	85	80	121	128	98	0.96	2.40	1.9	8.0	
Mean (RLU)			6210	2823	1512	804	454	253	164	117	94	77	72	-	-	-	-	-	-	-	

Stdev			290.5	122.7	163.5	112.3	26.9	1.3	6.2	3.2	3.4	6.4	6.9							
%CV			4.7	4.3	10.8	14.0	5.9	0.5	3.8	2.7	3.6	8.3	9.6							
Mean (RLU)																			2	7.9
Stdev																				0.1
%CV																				5.3
Mean + log2																				3.7
Mean - log2																				1.1
t																				2.201
SQRT (Dilution)																				1.414
MSR**																				3

* Dilution includes the

MRD

Underlined = %CV

>25%

S_T = RLU signal at the sample titre

T = Sample Titre

S_{END} = RLU signal at the first dilution below the titre cut point

t = threshold from a two-sided Student's t-distribution with n-1 degrees of freedom and 5% error rate.

SQRT (Dilution) = the square root of the dilution factor

MSR** = MSR =

$10^{(t^2/(n-2))}$

NHS

Similarly, sensitivity was calculated as 5.2 ng/mL for bulk ADA (Refer to Study Report 8308-904, Appendix II, Table 33) and 4.3 ng/mL for anti-PEG ADA (Refer to Study Report 8308-904, Appendix II, Table 34).

Reviewer Comments: The sensitivity of the assay is well below the sensitivity of 100 ng/mL recommended in the FDA Draft Guidance for Industry (April 2016) and thus it is acceptable. It should be noted that the sensitivity was determined based on the TCP at a 0.01% false-positive rate instead of the SCP at 5% false-positive rate. The assay sensitivity is defined as the lowest concentration of the positive control antibody that tests positive in the assay or the concentration of the positive control antibody that intersects the SCP on the titration curve. It is often recommended that a positive control be diluted cross the SCP at 5% false positive rate. However, the assay sensitivity based on the titer assay data using a lower false positive rate provides an acceptable sensitivity value (<10 ng/mL for both positive control antibodies), well below the sensitivity of 100 ng/mL recommended in the FDA Draft Guidance for Industry (April 2016). Thus, it is acceptable and not necessary to ask the sponsor to re-determine the sensitivity of the assay based on a higher false positive rate.

1.5.7 LPC Concentration Determination

A LPC concentration of 30 ng/mL was chosen for the bulk ADA control for both validation studies in BCHS and NHS. A LPC concentration of 150 ng/mL and 50 ng/mL were chosen for the anti-PEG ADA control for validation studies in BCHS and NHS, respectively. The sponsor stated they were chosen because they yield a signal to noise ratio (LPC response/NC response) of approximately 3 in the screening assay. The LPCs generated no false negative results in the screening and confirmatory cut point runs and the false negative error rate was determined to be <0.01%.

Reviewer Comments: The concentration of the LPC is recommended be determined using data obtained from the sensitivity exercise and 1% false positive rate. However, the LPC concentrations in this assay validation study were not determined in this way. The chosen LPC concentrations were shown to produce a 0.01% rejection rate, which is not the

recommended 1% rejection rate to ensure proper assessment of assay performance near the cut-point level. Because the assay is very sensitive and within the recommended sensitivity range (1-100 ng/mL), it's unnecessary to lower the LPC concentration to provide a greater rejection rate (i.e., 1%). Therefore, the LPC at a concentration of 30 ng/mL for bulk ADA is acceptable as a system suitability control. Similarly, the LPC of 150 ng/mL for anti-PEG ADA is acceptable because the assay sensitivity for detecting anti-PEG is within 100 ng/mL (6.1 ng/mL). In addition, main clinical concerns with anti-PEG antibodies are loss of efficacy and hypersensitivity responses. This is in contrast to anti-G-CSF antibodies, where cross-reactivity to an endogenous protein is also a concern.

1.5.8 Assay Precision

Intra- and inter-assay precision of screening and confirmatory assays were assessed by evaluating PC samples prepared using both bulk ADA and anti-PEG ADA in the same run. Three sets of HPC, LPC, and NC samples were run on 6 different plates by 2 analysts on different days for each competitor drug (MYL-1401H, EU-approved Neulasta, GCSF, PEG). Precision of PC samples were calculated using both response and ratio to NC. The intra- and inter- assay precision results for BCHS are summarized in the table below.

	Screening (Bulk ADA)		Screening (anti-PEG ADA)	
	Intra-assay	Inter-assay	Intra-assay	Inter-assay
MYL-1401H	≤8.6% (with exception of 30% for LPC in VAL-68, 54.3% for HPC in VAL-069, and 35.0% for LPC in VAL-069)	<u>HPC:</u> 22.2% (response) 18.9% (HPC/NC) <u>LPC:</u> 24.4% (response) 20.3% (LPC/NC)	≤18.4% (with exception of 29.2% for HPC in VAL-68, 35.4% for HPC in VAL-073)	<u>HPC:</u> 20.9% (response) 21.5% (HPC/NC) <u>LPC:</u> 16.9% (response) 17.7% (LPC/NC)
EU-approved Neulasta	≤22.8 % (with exception of 35% for LPC in VAL-71)	<u>NC:</u> 8.2% (response)	≤17.1 % (with exception of 25.6% for LPC in VAL-71)	<u>NC:</u> 9.5% (response)
GCSF	≤11.1 %		≤12 %	
PEG	≤17.5 %		≤15 %	

Table prepared by OBP immunogenicity reviewer

	Confirmatory (Bulk ADA)		Confirmatory (anti-PEG ADA)	
	Intra-assay	Inter-assay	Intra-assay	Inter-assay
MYL-1401H	≤20.7%	≤11.2%	≤2.0%	≤1.6%
EU-approved Neulasta	≤21.6 % (with exception of 26.4% for LPC in VAL-71)	≤19.8%	≤1.3%	≤1.4%
GCSF	≤9.3 %	≤11.0%	No confirmation	No confirmation
PEG	No confirmation	No confirmation	≤2.1%	≤1.3%

Table prepared by OBP immunogenicity reviewer

Reviewer Comment: Most of the intra-assay and inter-assay precision values are within the plate acceptance criteria of <25%CV for HPC, LPC and NC samples. Thus, the binding ADA assay precision is acceptable.

Intra- and inter-assay precision of the titration assay was evaluated across 4 runs by 2 analysts on 2 different days. Three independent sets of ten 2-fold serial dilutions were evaluated in each run. The intra- and inter- assay precision data is provided in Appendix 5, Table 21 through Table 22. Results are summarized in the below Table.

	Titration (Bulk ADA)	Titration (Anti-PEG ADA)
Intra-assay (response)	≤14.0%	≤8.8%
Inter-assay [Log(EPT)]	5.3%	3.3%

Table prepared by OBP immunogenicity reviewer

Reviewer Comment: All intra- and inter-assay precisions are within the assay acceptance criteria of <25%CV. Thus, the assay precision is acceptable for titration assay.

1.5.9 Drug Tolerance

Drug tolerance was performed to determine the highest level of drug that could be added to a sample spiked with the positive control antibody without interfering with its detection as a positive antibody response. Drug tolerance was assessed by using Bulk ADA, primate anti-Neulasta/PEG GCSF antibody², and anti-PEG ADA. The results were provided in Study Report 8310-739, Appendix II, Table 23 and Study Report 8308-904, Appendix II, Table 35.

	BCHS Detectable in the presence of MYL-1401H (µg/mL)	NHS Detectable in the presence of MYL-1401H (µg/mL)
Bulk ADA 31.25 ng/ml	1.00	1.00
Primate anti-Neulasta/PEG GCSF ADA 62.5 ng/ml 125 ng/ml	0.75 1.00	0.50 0.75
Anti-PEG ADA 31.25 ng/ml	1.00	1.00

Table prepared by OBP immunogenicity reviewer

Reviewer Comments: The results presented above suggest that the assay can tolerate residual serum drug concentration of 1 µg/mL for detection of 31.25 ng/mL of bulk ADA and anti-PEG ADA.

- a) *In clinical study MYL-1401H-3001, pegfilgrastim serum concentration in breast cancer patients were below the lower limit of quantification (300 pg/mL) at sample collection time points. Thus, it is unlikely that on-board levels of drugs will interfere with ADA detection in breast cancer patients.*

² ***Primate Anti-Neulasta/PEG GCSF Antibody:*** This ADA was produced by purifying hyper-immune sera from cynomolgus monkey immunized with Neulasta using an affinity column prepared with MYL-1401H.

b) PK data from healthy subjects from clinical study MYL-1401H-1001 showed that the maximum MYL-1401H serum concentration (C_{max}) was 36.7 ng/mL and $T_{1/2}$ was 49.3 hours³. Thus, the assay should be able to tolerate on-board levels of drugs at a wide concentration range of ADA in health subjects.

1.5.10 Selectivity

BCHS

Selectivity was evaluated using 15 BCHS samples spiked with Bulk ADA and anti-PEG ADA at their LPC levels and analyzed in the screening and confirmatory assays. Confirmations were performed using excess MYL-1401H and PEG, respectively. The data were provided in Study Report 8310-739, Appendix II, Table 24 and 25.

Bulk ADA (Confirmed with MYL-1401H)	Total number	Screening positive number	Confirmatory positive number
Blank	15	6	2
LPC	15	14	14

Table prepared by OBP immunogenicity reviewer

Anti-PEG ADA (Confirmed with MYL-1401H)	Total number	Screening positive number	Confirmatory positive number
Blank	15	5	1
LPC	15	15	15

Table prepared by OBP immunogenicity reviewer

Anti-PEG ADA (Confirmed with PEG)	Total number	Screening positive number	Confirmatory positive number
Blank	15	4	2
LPC	15	15	15

Table prepared by OBP immunogenicity reviewer

NHS

A total of 15 NHS samples were spiked with Bulk ADA and anti-PEG ADA at their LPC levels and analyzed in the screening and confirmation assays. Confirmations were performed using excess MYL-1401H. The data were provided in Study Report 8308-904, Appendix II, Table 36.

Bulk ADA	Total number	Screening positive number	Confirmatory positive number
Blank	15	2	1
LPC	15	15	15

Table prepared by OBP immunogenicity reviewer

Anti-PEG ADA	Total number	Screening positive number	Confirmatory positive number
Blank	15	4	1
LPC	15	15	15

Table prepared by OBP immunogenicity reviewer

³ BLA 761075 Section 2.7.2 Summary of Clinical Pharmacology Studies.

In addition, the potential for lipemic or hemolyzed serum interference were assessed using 5 samples for each condition spiked with bulk ADA and anti-PEG at their LPC levels and analyzed in screening and confirmatory assays. Confirmations were performed using excess MYL-1401H. The data were provided in Study Report 8308-904, Appendix II, Table 37 and 38. The results show that there was no interference on the method.

Reviewer Comment: The data for blank (unspiked) samples suggest that there are pre-existing antibodies and the data for “Anti-PEG ADA” indicate that the pre-existing antibodies in both sera are anti-PEG antibodies. This is expected as anti-PEG antibodies are known to be present in the general population. The data for LPC spiked samples, most were tested positive and CV% were <25%, suggest that components in both sera do not interfere with assay performance.

1.5.11 Prozone Effect

To determine whether high concentration of positive controls interfere with the screening assay performance to produce false negatives (prozone effect), samples with concentration of positive controls above the HPC level (i.e., 20000 ng/mL and 10000 ng/mL) were evaluated in the assay. The results are presented in Table 26a and Table 26b below.

Table 26a: Prozone (Hook Effect) BULK ADA

Analytical Run Number (b) (4) 8310-739-VAL-107				
UHPC (20000 ng/mL)	Plate Specific Cut Point	UHPC	UHPC2	UHPC3
		Concentration (ng/mL)		
		20000 (Neat)	10000 (1 in 2)	2000 (1 in 10)
Observed Response (RLU)				
	71	51403	28861	6367

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Table 26b: Prozone (Hook Effect) anti-PEG ADA

Analytical Run Number (b) (4) 8310-739-VAL-107				
UHPC (20000 ng/mL)	Plate Specific Cut Point	UHPC1	UHPC2	UHPC3
		Concentration (ng/mL)		
		20000 (Neat)	10000 (1 in 2)	2000 (1 in 10)
Observed Response (RLU)				
	71	4123	3855	3816

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Reviewer Comment: The data suggest that there is no hook effect observed in the assay with ADA concentration as high as 20000 ng/mL. Therefore, patient samples with concentration of ADAs as high as 20000 ng/mL are not expected to impact the assay performance.

1.5.12 Specificity

Specificity was assessed by spiking an irrelevant anti-drug antibody (Anti-BMO-2/Humira) at the HPC and LPC levels. Both samples were screened negative supporting that the method is specific for detection of anti-PEG-GCSF antibodies. The data is presented in Table 27 below.

Table 27: Specificity

Analytical Run Number (b) (4) 8310-739-VAL-107

Sample (Mean on replicates)	Observed Response (RLU)	Plate Specific Cut Point	Result
Irrelevant Anti-Drug Ab at HPC level	51	71	Negative
Irrelevant Anti-Drug Ab at LPC level	50		Negative

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Reviewer Comment: The data suggest that this assay is specifically detecting ADA against PEG GCSF.

1.5.13 Cross Reactivity

Cross Reactivity was assessed with non-specific drug (Humira) using LPC and HPC samples prepared using the Bulk ADA and the anti-PEG ADA. Samples were also evaluated with the relevant drug MYL1401H. Both Bulk ADA PCs and the anti-PEG ADA PCs were confirmed positive when analyzed with excess MYL1401H drug and did not confirm positive with nonspecific drug (Humira EU). The data is presented in Table 28a and Table 28b.

Table 28a: Cross Reactivity – Bulk ADA

Analytical Run Number (b) (4) 8310-739-VAL-107

PC level (ng/mL)	Plate Specific Cut Point	Conf-Cut Point (%)	Without Drug	With Relevant Drug-MYL-1401H (200 µg/mL)	% Inhibition	Confirmatory Results
			Observed Response (RLU)			
HPC (2000.00)	71	24.4	6659	62	99.1	Positive
LPC (30.00)			128	55	57.4	Positive
PC level (ng/mL)	Plate Specific Cut Point	Conf-Cut Point (%)	Without Drug	With Non Specific Drug-Humira EU (200 µg/mL)	% Inhibition	Confirmatory Results
			Observed Response (RLU)			
HPC (2000.00)	71	24.4	6605	6600	0.1	Negative
LPC (30.00)			114	130	-13.6	Negative

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Table 28b: Cross Reactivity – Anti-PEG ADA

Analytical Run Number (b) (4) 8310-739-VAL-107

PC level (ng/mL)	Plate Specific Cut Point	Conf-Cut Point (%)	Without Drug	With Relevant Drug-MYL-1401H (200 µg/mL)	% Inhibition	Confirmatory Results
			Observed Response (RLU)			
HPC (2000.00)	71	27.5	4153	58	98.6	Positive
LPC (150.00)			757	59	92.3	Positive
PC level (ng/mL)	Plate Specific Cut Point	Conf-Cut Point (%)	Without Drug	With Non Specific Drug-Humira EU (200 µg/mL)	% Inhibition	Confirmatory Results
			Observed Response (RLU)			
HPC (2000.00)	71	27.5	3791	4025	-6.2	Negative
LPC (150.00)			691	713	-3.1	Negative

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Reviewer Comment: The results suggest that this assay does not have cross reactivity issue. Although US-licensed Neulasta or EU-approved Neulasta were not used here, data from the antigenic equivalence experiment demonstrate that unlabeled US-licensed Neulasta, EU-approved Neulasta and MYL-1401H inhibit ADA responses at a comparable level with comparable precision.

1.5.14 Stability: antibody

Freeze Thaw

Freeze thaw stability were assessed at -60 to -80°C (Table 29 below) and -15 to -30°C (Study Report 8310-739, Appendix II, Table 30) for both Bulk ADA and anti-PEG ADA up to 6 freeze/thaw cycles.

Table 29a: Freeze/Thaw (F/T) Stability: Bulk ADA PC samples subjected to 2, 4 and 6 additional freeze/thaw cycles at -60 to -80°C prior to analysis

Analytical Run Number (b) (4) 8310-739-Val-105

Duplicate	NC	Plate Specific Cut Point	LPC (30.00 ng/mL)				HPC (2000.00 ng/mL)			
			Baseline*	2 F/T	4 F/T	6 F/T	Baseline*	2 F/T	4 F/T	6 F/T
			Ratio				Ratio			
1			2.3	2.0	2.0	2.0	98.0	99.3	98.2	103.1
2	62	74	2.4	2.2	2.2	2.4	107.9	110.6	105.2	90.5
3			NA	2.1	2.2	2.3	NA	100.0	101.6	86.7
4			NA	2.2	2.3	2.4	NA	102.0	100.6	100.3

*Baseline used for information monitoring the trend.

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Table 29b: Freeze/Thaw (F/T) Stability: Anti-PEG ADA PC samples subjected to 2, 4 and 6 additional freeze/thaw cycles at -60 to -80°C prior to analysis

Analytical Run Number (b) (4) 8310-739-Val-106

Duplicate	NC	Plate Specific Cut Point	LPC (150.00 ng/mL)				HPC (2000.00 ng/mL)			
			Baseline*	2 F/T	4 F/T	6 F/T	Baseline*	2 F/T	4 F/T	6 F/T
			Ratio				Ratio			
1			11.9	12.0	10.7	11.3	45.6	51.5	48.2	36.5
2	63	75	10.6	10.0	10.4	9.7	50.3	42.5	43.4	56.1
3			NA	11.2	10.3	10.2	NA	54.7	50.8	42.4
4			NA	11.1	11.0	9.2	NA	43.1	46.8	53.6

*Baseline used for information monitoring the trend.

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Bold = Outside established PC range

Bench Top

Bench top stability was assessed for 24 hours for both Bulk and anti-PEG ADA (Table 31 below).

Table 31a: Bench Top Stability - BULK ADA PC Samples Stored for 24 (± 4) Hours at Room Temperature Prior to Analysis

Analytical Run Number (b) (4) 8310-739-Val-105

Duplicate	NC	Plate Specific Cut Point	LPC (30.00 ng/mL)		HPC (2000.00 ng/mL)	
			Baseline*	T = 24 Hours	Baseline*	T = 24 Hours
			Ratio			
1			2.3	2.3	82.1	85.4
2	62	74	2.4	2.1	90.4	88.8
3			NA	2.3	NA	91.4
4			NA	2.3	NA	87.4

*Baseline used for information monitoring the trend.

Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Table 31b: Bench Top Stability - Anti-PEG ADA PC Samples Stored for 24 (± 4) Hours at Room Temperature Prior to Analysis

Analytical Run Number (b) (4) 8310-739-Val-106

Duplicate	NC	Plate Specific Cut Point	LPC (150.00 ng/mL)		HPC (2000.00 ng/mL)	
			Baseline*	T = 24 Hours	Baseline*	T = 24 Hours
			Ratio			
1			11.9	11.0	45.6	47.8
2	63	75	10.6	11.0	50.3	45.0
3			NA	10.8	NA	47.8
4			NA	11.6	NA	50.5

*Baseline used for information monitoring the trend.

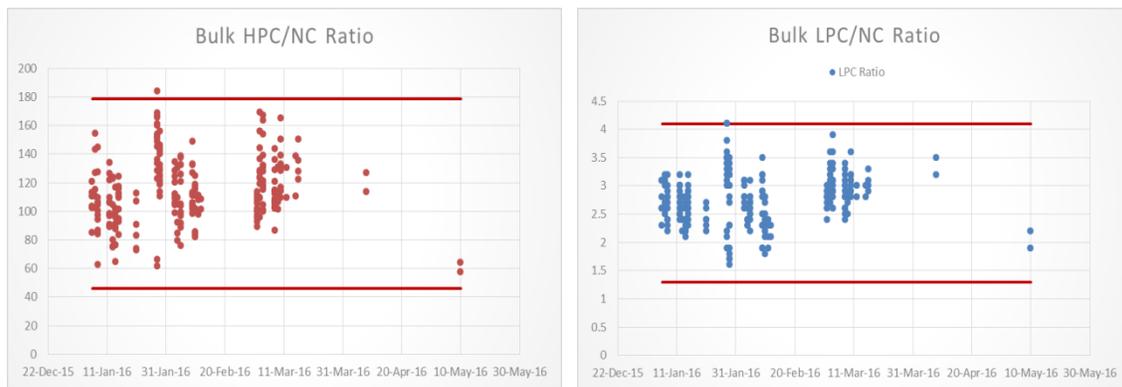
Underlined = %CV >25%; if no underlined values, data reviewed and all CVs ≤ 25%

Reviewer Comment: The stability data support that both LPCs and HPCs for bulk ADA and anti-PEG ADA are stable for up to 6 freeze/thaw cycles and for 24 hours at bench top conditions. This is acceptable.

1.5.15 Stability: Biotin- and Sulfo-Tag labelled MYL-1401H

In response to an IR (June 16, 2017), Mylan stated that the stability of biotin- or Sulfo-Tag labeled MYL-1401H was not assessed in the validation. However, they contended that performance of PC samples during assay validation and sample analysis can be stability indicating for biotin- and Sulfo-Tag labeled MYL-1401H. They provided figures (one representative figure is shown below) showing that both HPC and LPC responses were within the system suitability ranges in the period between July-31-2015 and May-10-2016 for all 3 clinical studies.

Figure 1: Performance of HPC and LPC Through Assay Validation and Sample Analysis Studies for MYL-1401H-3001



Reviewer Comment: I agreed that stability of biotin- and Sulfo-Tag labeled MYL-1401H can be indicated by PC performance in the ECL assay where they form a bridge with PC antibodies to elicit response. The provided data on PC performance support that the biotin- and Sulfo-Tag labeled MYL-1401H reagents are stable during method validation and sample analysis phases.

1.6 Facility Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of studies 8308-902, 8308-482, 8331-647 and 8329-463 conducted at (b) (4). Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI). Based upon the results of this inspection, OSIS recommend that bioanalytical data from all inspected studies be accepted for Agency review, but with several considerations (Refer to (b) (4) OSIS inspection report dated July 27, 2017). OSIS recommendations have been taken into consideration.

2. VALIDATION OF CELL-BASED NEUTRALIZING ANTIBODY ASSAY

2.1 Background

A cell-based assay to test for neutralizing ADA was developed and validated at (b) (4). Two cell-based neutralizing assay validation reports for two populations (healthy subjects and breast cancer patients) were submitted to the 351(k) BLA. An initial neutralizing ADA validation study (b) (4) was performed in support of comparative immunogenicity testing in healthy volunteers for clinical studies MYL-1401H-1001 and MYL-1401H-1002. A subsequent neutralizing ADA validation study (b) (4) was performed in support of comparative immunogenicity testing in breast cancer patients for clinical study MYL-1401H-3001. The Table below provides information on these two method validation reports.

Validation Report	Relevant clinical study	Completion date	Amended date
(b) (4)	MYL-1401H-1001 MYL-1401H-1002 (Healthy subjects)	19 October 2016	18 August 2017
(b) (4)	MYL-1401H-3001 (patients with breast cancer)	14 June 2016	08 September 2017

Table prepared by OBP immunogenicity reviewer

Validation report (b) (4) is more relevant because the method was used to assess NAb in the indicated patient population. In this section, information in (b) (4) was reviewed with reference to Report (b) (4) where appropriate.

• Method Principle

This method is a direct qualitative neutralizing cell-based assay with an evaluation of NFS-60 cell proliferation as the functional endpoint. These cells, normally cultivated with murine interleukin-3 (mIL-3), are capable of growth in the presence of recombinant GCSF (such as MYL-1401H). Pre-incubation of serum samples containing antibodies with neutralizing activity with the fixed concentration of MYL-1401H, before adding to the cells, will inhibit cell proliferation which is measured using the Cell Titer-Glo 2.0 viability reagent (luminescence). The measured luminescent signal is proportional to the amount of intracellular ATP, which is proportional to the number of cells present. Relative light units (RLU) are the raw data from the assay.

All samples are subjected to three tiers of analyses, which are performed in parallel.

- 1) The no inducer assay eliminates samples that demonstrate non-specific cell growth and that could be identified as false negative. Samples for which the no inducer assay value (NOAV) is above the no inducer cut point are reported as 'not reportable'. Samples for which the no inducer assay value (NOAV) is below the no inducer cut point are evaluated in the screening assay.

- 2) The screen assay is to screen for the presence of neutralizing antibodies against PEG GCSF based on a statistically determined assay cut point. Samples for which the screening assay value (SAV) is above the screening cut point are reported as ‘screened negative’ and those below or equal to the screening cut-point are reported as ‘screened positive’ for neutralizing activity.
- 3) The confirmatory assay is similar to the above screen assay except that samples are pre-incubated with a fixed concentration of mIL-3, instead of MYL-1401H. The confirmatory assay is used to determine whether the neutralizing activity is specific to PEG GCSF due to non-specific growth inhibition. Samples that result positive (for which the CAV is below the confirmatory cut point) for non-specific mIL-3 neutralization are reported as ‘confirmed negative’. Samples that result negative confirmatory assay value (CAV) above the confirmatory cut point for non-specific mIL-3 neutralization are reported as ‘confirmed positive’ for neutralizing activity against PEG GCSF.

The assay characteristics are summarized in Table A below.

Table A Assay Characteristics

Assay characteristic		Description
In vitro cell system		NFS-60 cells in culture
Assay endpoint		Proliferative response of NFS-60 cells in presence of 500.0 pg/mL of MYL-1401H inducer (final concentration)
Unit of measurement (reading)		Relative Luminescence Unit (RLU)
Data analysis and calculation softwares		Microsoft Excel® 2010 and GraphPad Prism® v5.01
Testing matrix		Normal human serum (NHS)
Assay MRD		1/40 dilution (final sample dilution including all reagents and cells)
Drugs (cell proliferation inducers)		MYL-1401H (500.0 pg/mL final concentration) for screening assay or mIL-3 (40.0 pg/mL final concentration) for confirmatory assay
Positive control samples	LPC	650.0 (LPC1) or 1300.0 ng/mL (LPC2) ^a of Rabbit Anti-Neulasta / PEG GCSF Antibody in NC pool (+ MYL-1401H or mIL-3 + NFS-60 cells)
	HPC	2000.0 ng/mL of Rabbit Anti-Neulasta / PEG GCSF Antibody in NC pool (+ MYL-1401H or mIL-3 + NFS-60 cells)
Viability control (VC)		NC pool + MYL-1401H or mIL-3 + NFS-60 cells
Negative control (NC)		NC pool + NFS-60 cells
Screening Assay Value (SAV)		Mean RLU of sample in presence of MYL-1401H inducer / mean RLU of VC in presence of MYL-1401H inducer
Confirmatory Assay Value (CAV)		Mean RLU of sample in presence of mIL-3 inducer / mean RLU of VC in presence of mIL-3 inducer
No Inducer Assay Value (NOAV)		Mean RLU of sample in absence of inducer / mean RLU of VC in presence of MYL-1401H inducer

^a Initial LPC level of 650.0 ng/mL was updated to 1300.0 ng/mL in protocol amendment 01 following event investigation #100 (refer to section 17.3). Initial assessments were performed with LPC at 650.0 ng/mL (identified as LPC1) and assessments needing to be repeated were performed with LPC at 1300.0 ng/mL (identified as LPC2).

- **Testing Facility**

(b) (4)



2.2 Reagents and Controls

- **Reagents**

Reagents	Supplier	Storage
Rabbit Anti-Neulasta/PEG GCSF antibody (Bulk ADA)	(b) (4)	-80.0 °C nominal, 2.0-8.0 °C after thawing
Anti-BMO-02/Humira polyclonal antibody	(b) (4)	-80.0 °C nominal, 2.0-8.0 °C after thawing
MYL-1401H	(b) (4)	5.0 °C nominal
EU-approved Neulasta	Mylan	5.0 °C nominal
US-licensed Neulasta	Mylan	5.0 °C nominal
NFS-60 Cell Line	(b) (4)	Liquid nitrogen
Murine Interleukin-3 (mIL-3)	(b) (4)	-20.0°C nominal until reconstitution

Table prepared by OBP immunogenicity reviewer

- **Matrix**

Three (3) different matrixes were used in the above two validation studies and stored at -80 °C.

Matrix	Made of	Supplier
Pre-dose BCHS pool	Individual pre-dose breast cancer human serum (BCHS) samples from clinical study MYL-1401H-3001	Mylan
Commercial NHS pool	Individual commercial NHS samples	(b) (4)
Pre-dose NHS pool	Individual pre-dose NHS samples from clinical study MYL-1401H-1001 and MYL-1401H-1002	Mylan

Table prepared by OBP immunogenicity reviewer

- **Negative and Positive Controls:**

The above three serum pools were used to prepare the negative and positive controls (see Table A above for concentrations of positive controls).

2.3 Validation Parameters

Table C below summarizes the validation parameters the sponsor did in this study.

Table C List of Validation Assessments

<i>Assessment</i>
<ul style="list-style-type: none"> • MYL-1401H and mIL-3 titrations • Screening, confirmatory and no inducer cut-points • Assay precision • Assay sensitivity (LOD) and hook effect assessments • Assay specificity • Matrix selectivity • MYL-1401H drug tolerance • Hemolyzed and lipemic serum Interference • Bioanalytical similarity • mIL-3 stock 1 stability
<ul style="list-style-type: none"> • Stability of Rabbit Anti-Neulasta / PEG GCSF positive control antibody in NC pool

2.4 Assay Acceptance Criteria

System suitability ranges were calculated for NC, VC/NC, and PC samples using data from all acceptable runs, based on 1% failure rate. For PC samples, instead of the response values, ratio to mean VC values were calculated and used for computing the system suitability ranges. The data is presented in Validation Report (b) (4), Appendix I, Table 14, 15, 16, 17 and in validation report (b) (4), Appendix I, Table 17, 23, 24, 25, and 30. The control ranges were summarized in the Table below.

Controls	Pre-dose BCHS Matrix	Pre-dose NHS Matrix	Commercial NHS Matrix
NC threshold	744082 (RLU)	929373 (RLU)	NR
VC (MYL-1401H)/NC threshold	2.44	2.76	NR
VC (mIL-3)/NC threshold	2.34	2.02	NR
LPC1/VC	NR	NR	0.52-0.71
LPC2/VC	0.24-0.56	0.31-0.55	0.35-0.64
HPC/VC	0.25-0.45	0.25-0.43	0.30-0.43

Table prepared by OBP immunogenicity reviewer

Reviewer Comments: The NC indicates the assay background; therefore, the NC threshold controls the maximum background on each plate. The VC/NC ratio indicates cell proliferation under the fixed amount of inducer, i.e. whether the cells proliferate as expected under 500 pg/mL of MYL-1401H or 40 pg/mL of mIL-3; therefore, the VC/NC threshold control the maximum cell proliferation on each plate. The PC/VC ratio indicates neutralizing activity of NAb on cell proliferation and thus the PC/VC ranges control the suitability of different levels of PCs on each plate. It is noted that the ranges for LPC2 and HPC have overlaps indicating that PC concentrations may not be selected appropriately. However, the raw data show that LPC2/VC ratios were higher than HPC/VC ratios for corresponding sets in all runs. Thus, this flaw in system suitability ranges could be neglected. Overall, the established control thresholds and ranges are acceptable.

To accept a run, the acceptance criteria described below were used unless otherwise specified in the following subsections.

- The precision (%CV) of the NC, VC and PC sample readings must be $\leq 25.0\%$ for at least 2 out of 3 sets. The run is rejected if both the NC and VC samples at the same place of the plate do not meet %CV acceptance criteria.
- The NC, VC/NC ratio, and PC/VC ratios must be within their corresponding acceptance ranges (shown above) for at least 2 out of 3 sets.

Reviewer Comment: The established assay acceptance criteria are acceptable.

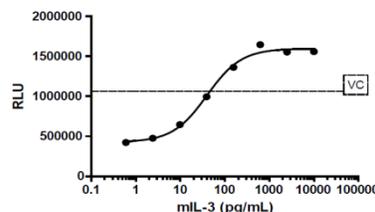
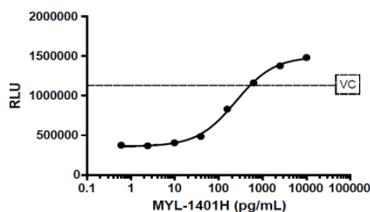
2.5 Validation Exercise

For the validation study (b) (4) in support of comparative immunogenicity testing in patients with breast cancer for clinical study MYL-1401H-3001, Mylan performed the validation study using the pre-dose BCHS matrix. For the validation study (b) (4) in support of comparative immunogenicity testing in healthy volunteers for clinical study MYL-1401H-1001 and MYL-1401H-1002, Mylan originally validated the assay using the commercial NHS matrix. Due to the failure of the matrix selectivity assessment, Mylan conducted an investigation and concluded that the commercial NHS matrix used in the initial validation study was not representative of the pre-dose NHS clinical matrix. Thus, they re-assessed selected performance parameters using the pre-dose NHS matrix. The above mentioned three matrixes are reviewed under annotated sub-heading for each validation parameter unless they were not reported.

2.5.1 MYL-1401H and mIL-3 Titrations

The MYL-1401H and mIL-3 concentrations used as inducers in the assay were selected based on their titration data. Eight 4-fold serial dilutions (ranging from 10000.0 to 0.6 pg/mL, prepared in basic medium) of MYL-1401H and mIL-3 were tested for a total of 3 times each. The titration data was provided in the submission (Appendix I, Table 2 and 3). 500 pg/mL of MYL-1401H and 40 pg/mL of mIL-3 were selected as the inducer concentrations.

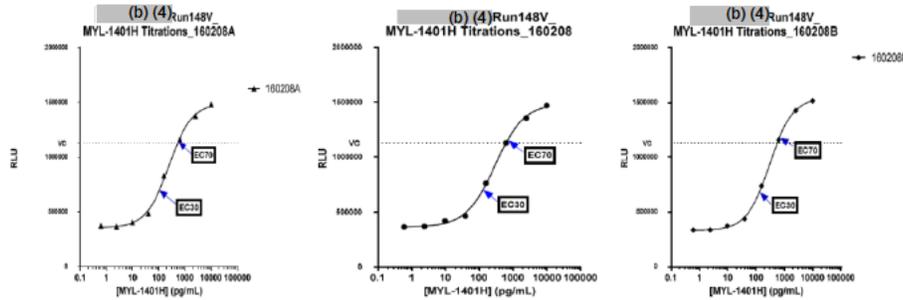
Figure 1 Representative MYL-1401H Titration Curve (Titration ID 160208A) (Commercial NC Pool) Figure 2 Representative mIL-3 Titration Curve (Titration ID 160208A) (Commercial NC Pool)



Reviewer Comment: The selected inducer concentrations for MYL-1401H and mIL-3 are acceptable because their response lay within the linear portion of the titration curves (between EC₃₀ and EC₇₀) and they yield similar RLU outcomes. It should be noted that the VC response at the selected concentration of 500 pg/mL for MYL-1401H is near the upper plateau of the titration curve, which may indicate that the cell growth may be insensitive to the neutralizing effect of anti-PEG GCSF antibody in the assay. In response

to an IR (June 16, 2017), the sponsor provided two additional titration curves and statistical results as below. The sponsor contended that all 3 responses at 500 pg/mL of MYL-1401H fell within the linear region (EC₃₀ - EC₇₀) and thus the selected inducer concentration for MYL-1401H is feasible for this assay. This is acceptable.

Figure 8: MYL-1401H Titration Curves During Assay Validation



Assay response (RLU) of VC control at 500 pg/mL, EC30, and EC70 were denoted.

Table 8: Titration Curve Statistics and Interpolated EC at 500pg/mL

Phase	Titration	Overall Mean VC Response	Response at EC30	Response at EC70	Interpolated EC at 500 pg/mL
Feasibility	150816	1485675	953333	1554285	65.4
Validation	160208	1131911	704009	1153718	68.1
Validation	160208A		699346	1153434	68.3
Validation	160208B		696805	1178631	66.1

1.6.1 Cut Points Determination

The table below summarizes the experimental design for determination of screening cut point (SCP), confirmatory cut point (CCP), and no inducer cut point (NICP).

	Experimental Design
Pre-dose BCHS matrix	Thirty-two (32) pre-dose BCHS samples from clinical studies MYL-1401H-3001 were tested 4 times in a total of 4 runs by 2 analysts on 2 different days (totally 144 assay values). Three (3) sets of NC, 3 sets of VC (MYL-1401H inducer), 4 sets of LPC and HPC were included on each plate. The pre-dose BCHS NC pool was used to prepare all control samples.
Commercial NHS matrix	Sixty-four (64) pre-dose NHS samples were tested at least 6 times in a total of 9 runs by 3 analysts on 3 different days using a balanced experimental design. Three (3) sets of NC, 3 sets of VC (MYL-1401H inducer), 4 sets of LPC and HPC were included on each plate. The commercial NHS NC pool was used to prepare all control samples.
Pre-dose NHS matrix	Over thirty (36 for SCP; 32 for CCP and NICP) pre-dose NHS samples from clinical studies MYL-1401H-1001 and MYL-1401H-1002 were tested 4 times in a total of 4 runs by 2 analysts on 2 different days. Three (3) sets of NC, 3 sets of VC (MYL-1401H inducer), 3 sets of LPC and HPC were included on each plate. The pre-dose NHS NC pool was used to prepare all control samples.

Table prepared by OBP immunogenicity reviewer

Note: Since statistical analyses were performed on SAVs, CAVs, and NOAVs (S/VC ratio values) for each tier of the cell-based assay, the floating cut point factors were determined as follows.

1.6.1.1 Screening Cut Point (SCP) Factor Determination

The SCP is defined as the level of assay response that identifies a clinical sample as positive or negative for the presence of NABs in the cell-based assay. The SCP factor was calculated using the following formula:

$$SAV = \text{MEAN RLU (Sample + MYL-1401H + cells)} / \text{MEAN RLU (NC pool + MYL-1401H + cells)}$$

$$\text{SCP factor} = \text{MEAN (SAV)} - t_{0.01 \text{ or } 0.05, df} \times \text{SD (SAV)}$$

	SCP factor
Pre-dose BCHS matrix	0.59 (parametric at 5% false positive rate)
Commercial NHS matrix	0.71 (non-parametric at 1% false positive rate)
Pre-dose NHS matrix	0.82 (parametric at 1% false positive rate)

**Table prepared by OBP immunogenicity reviewer*

Pre-dose BCHS Matrix

One (1) of SAV had a high %CV (>25%) and was removed. The linear mixed effects ANOVA of SAVs identified 10 assay values as outliers and were removed from further analysis, resulting in 117 assay values analyzed for SCP factor assessment. The normality of the outlier-excluded data distribution was not confirmed by the Shapiro-Wilk test ($p < 0.001$; Table 4 below). However, the skewness was low (-0.89). The sponsor contended that the parametric cut point estimate could be used since the distribution of SAVs was somewhat symmetric. Figure 3 provides a bivariate scatter plot of the plate-specific sample RLU values versus the VC RLU values. The linear relationship between mean values with a slope of 0.8401 supports the application of a floating cut point factor. Parametric approaches at the 0.1%, 1%, and 5% false positive rates were used to determine the SCP factor. **The parametric SCP factor of 0.59 at 5% false positive rate was applied in the following validation exercise in which the pre-dose BCHS NC pool was used, and will be used for the related clinical samples analysis study.** Samples with SAV values at or below 0.59 are designated as “screen positive”. Note the false positive rate was shown to be ~11.1% (13/117 samples with SAVs below 0.59).

Figure 4: Histogram of Human Serum S/VC Ratio Values after Removing Outliers

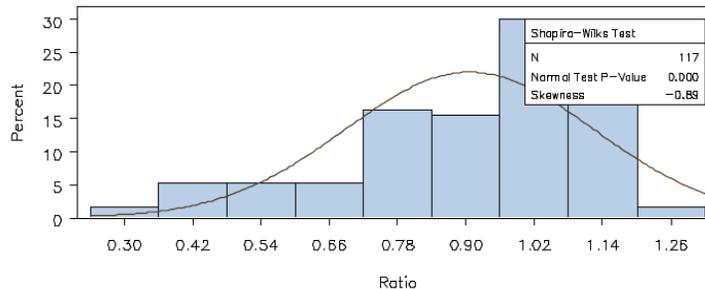
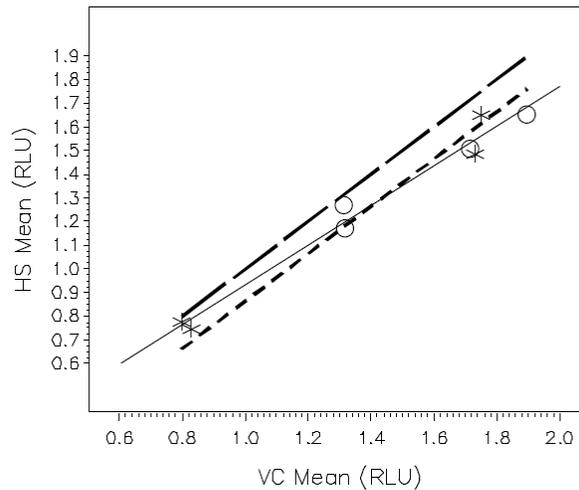


Figure 3: Scatter Plot of the Biweight Mean Value for Human Serum Samples versus the VC Mean Value for the Assay Group and Analyst



Regression Equation:
 $HS_Mean = 0.090563 + 0.840086 * VC_Mean$

Legend: Analyst 1 =Circle 2=Star

Table 6: Parametric and Non-parametric Cut Point Estimates

No. Values	FPER	Biweight Mean	Biweight SD	Log Transformed		Parametric Cut Point	Non-parametric Cut point	Normality Test ^b (Skewness)
				Parametric Cut Pt	Non Parametric Cut Pt			
Screening Floating Cut Point Factor Estimates (SVC Ratio)								
117	5%	0.9389 ^a	0.2097 ^a	--	--	0.59	0.45	p<0.001 (-0.89) (Figure 4)
	1%	--	--	--	--	0.44	0.30	
	0.1%	--	--	--	--	0.28	NR	

Parametric: Tukey Biweight
 Non-parametric: Empirical Percentiles
 NR: Not Reported
^aLog-transformed
^bShapiro Wilk Normality Test

Commercial NHS Matrix

Three (3) of SAV had a high %CV (>25%) and were removed. The linear mixed effects ANOVA of SAVs identified 52 assay values as outliers and were removed from further analysis, resulting in 377 assay values analyzed for SCP factor assessment. The normality of the outlier-excluded data distribution was not confirmed by the Shapiro-Wilk test (p=00000; Table 4 below) and skewness was above 1 (-1.16; Table 4 below) indicating that the distribution of SAVs was not symmetric. Thus, a non-parametric SCP factor was determined at 1%, and 5% false positive rates. **The non-parametric SCP factor of 0.71 at 1% false positive rate was applied in the following validation exercise in which the commercial NHS NC pool was used.** Samples with SAVs at or below 0.71 are designated as “screen positive”. Note the false positive rate was shown to be ~1.1% (4/377 samples with SAVs below 0.71), which is close to the desired 1% level.

Figure 4: Histogram of Human Serum S/VC Ratio Values after Removing Outliers

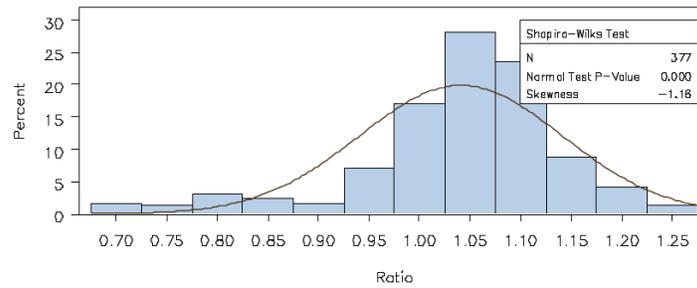


Table 6: Parametric and Non-parametric Cut Point Estimates

Log Transformed							
No. Values	Error Rate	Biweight Mean	Biweight SD	Parametric Cut Pt	Non Parametric Cut Pt	Parametric Cut Point	Non-parametric Cut point
Screening Floating Cut Point Multiplicative Factor Estimates (S/VC Ratio)							
377	5%	1.0595 ^a	0.0777 ^a	--	--	0.93	0.81
	1%			--	--	0.88	0.71
	0.1%			--	--	0.82	NR

Parametric: Tukey Biweight
 Non-parametric: Empirical Percentiles
 NR: Not Reported
^aLog-transformed
^bShapiro Wilk Normality Test

Pre-dose NHS Matrix

Three (3) of SAV had a high %CV (>25%) and were removed. The linear mixed effects ANOVA of SAVs identified 16 assay values as outliers and were removed from further analysis, resulting in 125 assay values analyzed for SCP factor assessment. The normality of the outlier-excluded data distribution was not confirmed by the Shapiro-Wilk test (p=0.032; Table 4 below). However, the skewness was low (-0.46). The sponsor contended that the parametric cut point estimate could be used since the distribution of SAV was somewhat symmetric. Figure 3 provides a bivariate scatter plot of the plate-specific sample RLU values versus the VC RLU values. The linear relationship between mean values with a slope of 0.9627 supports the application of a floating cut point factor. Parametric approaches at the 0.1%, 1%, and 5% false positive rates were used to determine the SCP factor. **The parametric SCP factor of 0.82 at 1% false positive rate was applied in the following validation exercise in which the pre-dose NHS NC pool was used, and will be used for the related clinical samples analysis study.** Samples with SAV values at or below 0.82 are designated as “screen positive”. Note the false positive rate was shown to be ~0.8% (1/125 samples with SAV s below 0.82), which is close to the desired 1% level.

Figure 4: Histogram of Human Serum S/VC Ratio Values after Removing Outliers

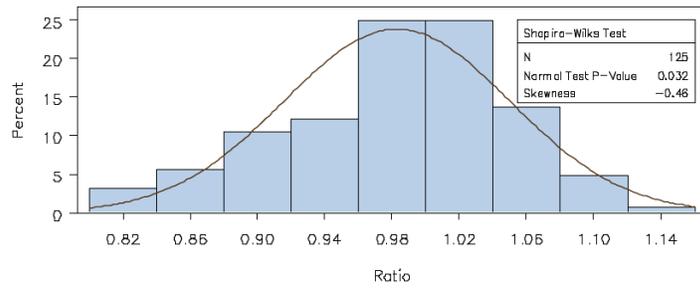
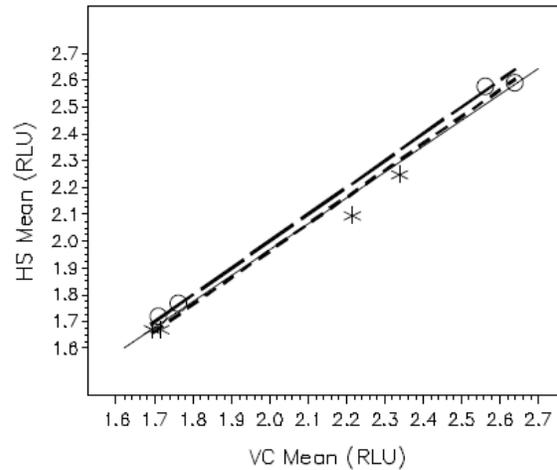


Figure 3: Scatter Plot of the Biweight Mean Value for Human Serum Samples versus the VC Mean Value for the Assay Group and Analyst



Regression Equation:
 $HS_Mean = 0.041375 + 0.962673 * VC_Mean$

Legend: Analyst 1=Circle 2=Star

Mean values are for RLU values

Solid line: Least squares regression line fit to Run mean values (slope 0.9627 and intercept 0.0414)

Short dashed line: Least squares regression line fit to Run mean values with the constraint that the slope = 1 (calculated intercept = -0.363)

Long dashed line: Linear function with slope = 1 and intercept = 0

Table 6: Parametric and Non-parametric Cut Point Estimates

No. Values	Error Rate	Biweight Mean	Biweight SD	Log Transformed		Parametric Cut Point	Non-parametric Cut Pt	Parametric Cut Point	Non-parametric Cut point	Normality Test ^b (Skewness)
				Parametric Cut Pt	Non-parametric Cut Pt					
Screening Floating Cut Point Factor Estimates (S/VC Ratio)										
125	5%	0.9879 ^a	0.0700 ^a	--	--	--	--	0.87	0.85	p=0.032 (-0.46) (Figure 4)
	1%			--	--	--	--	0.82	0.82	
	0.1%			--	--	--	--	0.77	NR	

Parametric: Tukey Biweight

Non-parametric: Empirical Percentiles

NR: Not Reported

^aLog-transformed

^bShapiro Wilk Normality Test

Reviewer Comments: The experimental design for determining the NAb SCP follows the current guidance. The sponsor provided the raw data and statistical analysis results.

Based on a review of the data, the established SCP factors for each matrix are acceptable.

It is noted that the NAb SCPs were determined using a 5% and 1% false-positive rate for BCHS and NHS, respectively. Because serum samples were screened using a 5% false-positive rate and confirmed using a 1% false-positive rate for binding ADAs, the NAb SCP should be calculated based on a 1% false-positive rate. It is inappropriate to calculate the NAb SCP based on a 5% false-positive rate. In response to an IR (June 16, 2017), the sponsor explained that their approach was based on the recommendations for cell-based NAb assay validation (Gupta et al., 2011) which states “In cases where the NAb testing strategy includes a confirmatory step, the cut point of the NAb screening assay could be calculated as the mean plus or minus $1.645 \times SD$ (5% false-positive rate), if desired. However, if this approach is used, it is important that the confirmatory assay cut point calculation target no more than a 1% false-positive rate.” In addition, if the cut point at 1% false-positive rate is applied (0.44) instead of the 5% false-positive rate cut point originally used (0.59) the number of screen positive sample will be reduced from 9 to 6. This change of results in screening tier does not affect the overall reported NAb results with confirmatory assay cut point at 1% false-positive rate. In terms of using 1% false-positive rate to calculate NAb SCP for NHS, the sponsor explained that the NAb confirmatory assay was not validated at the time of testing clinical samples. They applied a SCP at a 1% false-positive rate and reported screening data. After validation of the confirmatory assay, the screen positive samples were further analyzed in the confirmatory assay using a 1% false-positive rate. The response is acceptable.

1.6.1.2 Confirmatory Cut Point (CCP) Factor Determination

The CCP was defined as the level of assay response that identifies a clinical sample as positive or negative for NAb specific to PEG GCSF. Since both GCSF and mIL-3 can induce NFS60 cell proliferation, using mIL-3 as an alternative inducer to show that the screened positive NAb would not block the mIL-3-induced cell growth. The CCP factor was calculated using the following formula:

$$\text{CAV} = \text{MEAN RLU (Sample + mIL-3 + cells)} / \text{MEAN RLU (NC pool + mIL-3 + cells)}$$

$$\text{CCP factor} = \text{MEAN (CAV)} - t_{0.01, df} \times \text{SD (CAV)}$$

The same statistical methods used for SCP determination were performed for CCP determination. The table below summaries the CCPs determined for each matrix.

	CCP factor	False Positive Rate
Pre-dose BCHS Matrix	0.67 (parametric at 1% false positive rate)	13% (16/123 samples with CAVs below 0.67)
Commercial NHS Matrix	NR (not reported due to bimodal distribution of NOAVs)	N.A.
Pre-dose NHS Matrix	0.87 (parametric at 1% false positive rate)	1.2% (1/85 samples CAVs value below 0.87)

Table prepared by OBP immunogenicity reviewer

Samples with CAVs equal or above CCP were considered as ‘confirmed positive’ for neutralizing antibody against PEG GCSF, samples with CAVs below CCP were considered as ‘confirmed negative’.

Reviewer Comments:

- a) *A NAb confirmatory assay cut-point based on a 1% false positive rate is acceptable. The sponsor provided the results from these analyses and outliers were appropriately determined and eliminated for the CCP calculation.*
- b) *A high false positive rate (13%) was observed in the pre-dose BCHS samples. Based on their statistical report ((b) (4) Appendix I), the CAVs was not normally distributed as per the Shapiro-Wilk test ($p < 0.001$) and skewness was -1.14, suggesting that the non-parametric cut point estimated should be used. The sponsor also state that “For the non-parametric cut point estimates, 6/123 (4.9%) were below the 5% FPER cut point of 0.57 and 1/123 (0.8%) were below the 1% FPER cut point of 0.42. The non-parametric cut points are closer to the desired 5% and 1% FPER levels”. Thus, the sponsor should consider using the non-parametric 1% cut point factor of 0.42. In response to an IR (June 16, 2017), the sponsor provided the following justifications for using the parametric estimate:*
- *The non-parametric cut point estimates will always fall closer to the FPER levels when compared to the parametric estimates since the non-parametric cut point are estimated as assay values at the 5th and 1st percentiles for the 5% and 1% FPER.*
 - *When there is a small sample size ($n=123$) the non-parametric estimates are not very accurate since there are few values that are used in the non-parametric estimate. Although in this study the application of CPs on the validation data suggest non-parametric estimates are closer to the target FPER levels, this should not be considered reliable due to the small sample size.*

These justifications are acceptable.

1.6.1.3 No Inducer Cut Point (NICP) Factor Determination

The NICP is defined as the level of assay response that identifies a clinical sample capable of inducing non-specific cell growth in the cell-based assay. The NICP factor was calculated using the following formula:

$$\text{NOAV} = \text{MEAN RLU (Sample + cells)} / \text{MEAN RLU (NC pool + MYL-1401H + cells)}$$

$$\text{NICP factor} = \text{MEAN (NOAV)} + t_{0.001, df} \times \text{SD (NOAV)}$$

The same statistical methods used for SCP determination were performed for NICP determination. The Table below summaries the NICPs determined for each matrix.

	NICP factor	False Positive Rate
Pre-dose BCHS Matrix	0.48 (parametric at 0.1% false positive rate)	0% (0/116 samples with NIAV above 0.48)
Commercial NHS Matrix	NR (not reported due to bimodal distribution of NOAVs)	N.A.
Pre-dose NHS Matrix	0.42 (parametric at 0.1% false positive rate)	0% (0/115 samples with NIAV above 0.42)

Table prepared by OBP immunogenicity reviewer

Samples with NOAVs equal or above the NICP were considered as interfering with the method and designated as ‘non reportable’; Samples with NOAVs below the NICP were reported in the screening and confirmatory assays.

Reviewer Comment: The sponsor provided the results from this analysis and outliers were appropriately determined and eliminated for the NICP calculation. A no inducer assay cut-point based on a 0.1% false positive rate is acceptable since the false positive rate was shown to be 0% in pre-dose samples. Based on a review of the data, the NICPs for each matrix are acceptable.

1.6.2 Assay Precision

Pre-dose BCHS Matrix

LPC (1300.0 ng/mL) and HPC (2000.0 ng/mL) samples prepared using pre-dose BCHS NC pool tested in no inducer assay cut point runs as 4 sets/run (total of 8 runs, refer to Study Report (b) (4) Appendix I, Table 5).

- Intra-assay precision $\leq 7.2\%$,
- Inter-assay precision of 10.5% at LPC and 11.1% at HPC.

Commercial NHS Matrix

LPC1 (650.0 ng/mL) and HPC (2000 ng/mL) samples prepared using commercial NHS NC pool tested in the screening assay cut point runs as 4 sets/plate (total of 27 runs, refer to Study Report (b) (4), Appendix I, Table 7).

- Intra-assay precision %CVs $\leq 20.7\%$,
- Inter-assay precision %CVs of 8.0% at LPC1 and 4.4% at HPC.

Pre-dose NHS Matrix

LPC2 (1300.0 ng/mL) and HPC (2000.0 ng/mL) samples prepared using pre-dose NHS NC pool tested in the screening assay cut point runs as 3 sets/run (total of 8 runs, refer to Study Report (b) (4), Appendix I, Table 20).

- Intra-assay precision %CVs $\leq 8.7\%$,
- Inter-assay precision %CVs of 10.4% at LPC2 and 9.9% at HPC.

Reviewer Comment: The reported assay precision is within the limit stated in the guidance (<20%) for PCs, with one exception of 20.7%, and is therefore acceptable.

1.6.3 Matrix Selectivity

Pre-dose BCHS Matrix

Fifteen (15) pre-dose BCHS samples from clinical study MYL-1401H-3001 were tested in the screening and confirmatory assays unspiked and spiked at LPC2 level (Refer to Study Report (b) (4) Appendix I, Table 9 and 10).

- Matrix selectivity met target acceptance criteria in the screening assay: 14/15 (93.3%) unspiked samples were screened negative (1 set failed due to %CV). All 14 qualified spiked samples (100.0%) were screened positive.
- Matrix selectivity met target acceptance criteria in the confirmatory assay: all 15 unspiked samples were confirmed negative. Fourteen of the 15 (93.3%) qualified spiked samples were confirmed positive for NAbs against PEG GCSF.

Commercial NHS Matrix

Fifteen pre-dose NHS samples from clinical studies MYL-1401H-1001 and MYL-1401H-1002 were tested in the screening assay unspiked and spiked with LPC1 (Refer to Study Report (b) (4) Appendix I, Table 11). The NC and VC samples in these runs were prepared by commercial NHS NC pool.

- Matrix selectivity failed acceptance criteria in the screening assay: Although 15/15 (100%) unspiked samples screened negative, only 3/15 (20%) spiked samples screened positive (acceptance criteria: PC samples must screen positive).

Due to this failure, the sponsor increased the LPC concentration from 650 ng/mL (LPC1) to 1300 ng/mL (LPC2) and repeated this matrix selectivity assessment.

- Matrix selectivity failed acceptance criteria in the screening assay: Although 14/15 (93.3%) unspiked samples screened negative, only 11/14 (78.6%) qualified spiked samples were screened positive (acceptance criteria: PC samples must screen positive).

Pre-dose NHS Matrix

Fifteen pre-dose NHS samples from clinical studies MYL-1401H-1001 and MYL-1401H-1002 were tested in the screening and confirmatory assays unspiked and spiked at LPC2 levels (Refer to Study Report (b) (4) Appendix I, Table 21 and 29). The NC and VC samples in these runs were prepared by pre-dose NHS NC pool.

- Matrix selectivity met target acceptance criteria in the screening assay: 14/15 (93.3%) unspiked samples screened negative. All 14 qualified spiked samples (100.0%) were screened positive.
- Matrix selectivity met target acceptance criteria in the confirmatory assay: 14/15 unspiked samples confirmed negative. All 14 qualified spiked samples (100%) confirmed positive for NAbs against PEG GCSF.

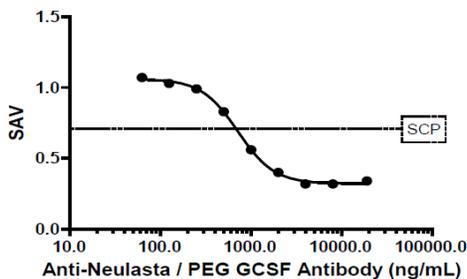
Reviewer Comments:

- a) *The data suggest that the assay has the capability to differentiate samples as positive or negative for NAbs in the pre-dose NHS and BCHS matrix.*
- b) *The failures to detect LPC spiked samples in commercial NHS matrix indicate that there might be interfering factors in either the individual pre-dose NHS samples or the control samples prepared by the commercial NHS NC pool. The sponsor performed the investigation and concluded that the commercial NHS NC pool accounted for these failures. This conclusion is supported by the matrix selectivity assessment using the control samples prepared by the pre-dose NHS NC pool. To address this issue, the sponsor repeated all method validation experiments using the pre-dose NHS matrix to support comparative immunogenicity testing in healthy volunteers for clinical studies MYL-1401H-1001 and -1002. Because the results from pre-dose NHS matrix are more relevant to the clinical samples this is acceptable.*

1.6.4 Assay Sensitivity (LOD)

The assay sensitivity is defined as the lowest concentration of the PC antibody that test positive in the assay and can be determined as the concentration of PC that intersects the SCP on the titration curve. Titration of the bulk ADA (ranging from 8000.0 to 62.5 ng/mL, 2-fold serial diluted in commercial NHS NC pool) was performed in 2 runs by 2 analysts. Each run consists of 2 titration curves. One titration curve/run also had an additional PC concentration of 19000 ng/mL to evaluate hook effect. The results were provided in Study Report (b) (4), Appendix I, Table 8. No hook effect was observed at PC concentration up to 19000 ng/mL (Figure 3 below).

Figure 3 Hook Effect Evaluation for Anti-Neulasta / PEG GCSF Antibody Measurements in Commercial NC Pool
(Representative Curve from Run 147V)



As presented in Table 9 below, the sensitivity was empirically determined based on the interpolation of the PC concentration at the SCP on PC titration curves and a 5% failure rate. The sensitivity was estimated at 898.8 ng/mL.

Table 9 LOD Estimation (Commercial NC Pool)

Run Number	Curve ID	Interpolated Anti-Neulasta / PEG GCSF Antibody Concentration at SCP (ng/mL)
147V	1	689.0
	2	629.8
153V	3	371.2
	4	403.2
Mean		523.3
SD		159.5
n		4
$t_{0.05,df}$		2.353
Estimated LOD		898.8

Underlined = %CV > 25.0%; if no underline, %CVs reviewed and \leq 25.0%.

Estimated LOD = mean + ($t_{0.05,df} \times$ SD)

Reviewer Comments: The reported assay sensitivity (898.8 ng/mL) using commercial NHS is reasonable. The sponsor confirmed this assay sensitivity using pre-dose NHS matrix and pre-dose BCHS matrix in two separate IR responses dated 08/18/2017 and 09/08/2017 (Refer to GlobalSubmit Sequence 0031 and 0037). The assay sensitivity is 506.0 ng/mL and 1483.5 ng/mL when the titration curves were prepared in pre-dose NHS matrix and pre-dose BCHS matrix, respectively. The estimated sensitivity using pre-dose BCHS matrix (1483.5 ng/mL) is higher than the LPC level (1300.0 ng/mL) due to high variability among runs; this indicates that LPC samples might have a failure rate higher than typically expected (1%). However, no runs were rejected due to failing LPC samples, suggesting that the sensitivity of 1483.5 ng/mL could have been overestimated.

1.6.5 Drug Tolerance

The drug tolerance was evaluated by testing PC samples prepared in all 3 different matrixes in the presence of MYL-1401H. The results were summarized in the following Tables.

Table H Drug Tolerance of PC Antibody in NC Pool

<u>PC antibody</u> ng/mL	<u>Tolerance to MYL-1401H drug</u> ng/mL
2600.0	\geq 20.0
2000.0	\geq 20.0
1300.0	\geq 20.0
650.0	N/AP ^a
325.0	N/AP ^a
162.5	N/AP ^a

^a not applicable since screened negative even without presence of drug.

Reviewer Comments: The results presented above suggest that the assay can tolerate residual serum drug concentration of 20 ng/mL.

- a) In clinical study MYL-1401H-3001, pegfilgrastim serum concentration in breast cancer patients were below the lower limit of quantification (300 pg/mL) at sample collection time points. Thus, it is unlikely that on-onboard levels of drugs will interfere with NAb detection in patients with breast cancer.

- b) *Based on PK data from the healthy subjects in clinical study MYL-1401H-1001, the maximum MYL-1401H concentration (C_{max}) was 36.7 ng/mL and $T_{1/2}$ was 49.3 hours⁴. Thus, the assay should be able to tolerate on-board levels of drugs at a wide concentration range of NAb in health subjects.*

1.6.6 Assay Specificity

The assay specificity was evaluated by testing an anti-BMO-02/Humira polyclonal antibody (non-specific antibody) LPC and HPC levels prepared in all three different matrices as 3 sets in the screening assay and confirmatory assays. Assay specificity was confirmed as all tested samples with the non-specific antibody at different levels were 'screened negative' in the screening assay or 'confirm negative' in the confirmatory assay (Refer to Study Report (b) (4), Appendix I, Table 10 and 28; Study Report (b) (4) Appendix I, Table 7 and 8.).

Reviewer Comment: The evaluation of the assay specificity is appropriate and the results are acceptable.

1.6.7 Hemolytic/Lipemic Serum Interference

The assay performance in hemolyzed or lipemic plasma was assessed. Results were provided in Study Report (b) (4), Appendix I, Table 13 and 14. In summary, moderate hemolytic levels do not interfere in the assay, but severe hemolytic levels do; neither moderate nor severe lipemia levels interfere in the assay.

Reviewer Comment: The results show that 2 out of 5 severe hemolyzed serum samples screened positive when they were not spiked with LPC, which indicates severe sample hemolysis may increase the risk of false positive detection in the neutralizing assay.

1.6.8 Stability of PCs

Pre-dose BCHS Matrix

LPC2 and HPC samples were analyzed in the screening assay at 3 sets/levels after 6 freeze-thaw cycles. Stability was confirmed for 6 freeze-thaw cycles as SAVs of all stability PC samples gave positive screening results and were within system suitability ranges (Refer to Study Report (b) (4) Appendix I, Table 13A).

LPC2 and HPC samples were analyzed in the screening assay at 3 sets/levels after 24 h 54 min at room temperature. Stability was confirmed for 24 h 54 min at room temperature as SAVs of all stability PC samples gave positive screening results and were within system suitability ranges (Refer to Study Report (b) (4) Appendix I, Table 13B).

Commercial NHS Matrix

LPC1 (650 ng/mL) and HPC were analyzed in the screening assay at 3 sets/levels after 2, 4, 6, and 10 freeze-thaw cycles. Due to the matrix selectivity issue observed in commercial NHS matrix, 2 of 3 sets of LPC1 samples were tested negative at baseline in one run, this

⁴ BLA 761075 Section 2.7.2 Summary of Clinical Pharmacology Studies

failed stability assessment criteria (at least 2 of 3 sets of each baseline PC samples must be tested positive). A protocol deviation was made to allow for interpretation of the stability data in case the stability assessment criteria were not met. This deviation added “calculating % differences in SAV values between baseline and stability PC samples” into the protocol. Stability was confirmed for 2, 4, 6 or 10 freeze-thaw cycles as per protocol deviation: differences in SAV values between baseline and stability PC samples were within $\pm 6.1\%$ under all 4 tested conditions (Refer to Study Report (b) (4), Appendix I, Table 16A).

LPC2 (1300 ng/mL) and HPC samples were analyzed in the screening assay at 3 sets/levels after 24 h 18 min at room temperature. Stability was confirmed for 24 h 18 min at room temperature as mean SAVs of all stability PC samples gave positive screening results and were within system suitability ranges (Refer to Study Report (b) (4), Appendix I, Table 16B).

Reviewer Comments:

- a) *The results show that all PC samples are stable under the tested conditions. The freeze/thaw stability assessment in commercial NHS matrix shows that PCs are stable after 10 freeze/thaw cycles as per protocol deviation. This is acceptable because 6.1% differences between the baseline and stability PC samples are within assay variability acceptance criterion of 25%.*
- b) *Long-term stability data were not provided for PC samples. However, this is acceptable because PC samples for NAb assay analysis are stored at -80°C and immunoglobulins are stable when stored frozen in serum or plasma matrix (Gorovits, 2009).*
- c) *The Office of Study Integrity and Surveillance (OSIS) performed an inspection of studies MYL-1401H-1001 and MYL-1401H-1002 conducted at (b) (4) and issued Form FDA 483 to (b) (4). Significant objectionable findings were observed during this inspection that impacted the reliability of a portion of the audited studies. Specifically, (b) (4)*

These stability results were submitted on September 08, 2017 (Refer to GlobalSubmit Sequence 0037). The results show that both LPC and HPC samples were stable after 6 freeze/thaw cycles and at room temperature for 29 h 12 min as all SAVs gave positive screening results and were within system suitability ranges. This response is acceptable.

1.6.9 Stability of mIL-3

The mIL-3 stock stored at -20°C nominal for 61 and 96 days was stable since VC/NC ratios and CAVs for all tested PC samples met respective acceptance criteria (\geq VC/NC threshold of 2.0 and $>$ confirmatory cut-point). Refer to Study Report (b) (4) Appendix I, Table 12.

Reviewer Comment: The results show that mIL-3 is stable for 96 days stored at -20 °C. The sponsor sets 96 days after reconstitution as expiry date. This is acceptable.

1.6.10 Inducer activity of MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta in the cell-based NAb assay

The sponsor evaluated the ability of the PC antibody to neutralize the inducer activity of MYL-1401H, US-licensed Neulasta and EU-approved Neulasta in 3 independent runs. The results were provided in Appendix I, Table 15 in the submission. Table 15A below shows the results from one run.

Table 15A Bioanalytical Similarity (MYL-1401H, Neulasta[®] EU, Neulasta[®] US), Run 1 (Commercial NC Pool)

Run Number	Screening Cut-Point (Ratio)	Inducer	Overall Mean VC Response (RLU)	Duplicate Set	LPC1 (650.0 ng/mL)				HPC (2000.0 ng/mL)				
					Observed Response (RLU)	SAV (Ratio)	Mean SD %CV (Intra Assay)	Screening Assay Result	Observed Response (RLU)	SAV (Ratio)	Mean SD %CV (Intra Assay)	Screening Assay Result	
150V	0.71	MYL-1401H	1408664	1	859919	0.61	0.64	Positive	528334	0.38	0.39	Positive	
				2	957467	0.68	0.04	Positive	568774	0.40	0.01	Positive	
				3	892825	0.63	5.5%	Positive	550205	0.39	3.7%	Positive	
		Neulasta [®] EU	1391293	1	858092	0.62	0.63	Positive	510948	0.37	0.38	Positive	
				2	886278	0.64	0.01	Positive	558111	0.40	0.02	Positive	
				3	898397	0.65	2.3%	Positive	528500	0.38	4.5%	Positive	
		Neulasta [®] US	1388719	1	890679	0.64	0.61	Positive	536003	0.39	0.40	Positive	
				2	886637	0.64	0.05	Positive	572363	0.41	0.01	Positive	
				3	771562	0.56	8.0%	Positive	550794	0.40	3.3%	Positive	
							Mean	0.63					
							SD	0.03					
							%CV	5.4%					
					Mean	0.39							
					SD	0.01							
					%CV	3.7%							

Underlined = %CV > 25.0%; if no underline, %CVs reviewed and ≤ 25.0%.

Reviewer Comments: The results from this experiment demonstrate that MYL-1401H, US-licensed Neulasta, or EU-approved Neulasta induce NSF60 cell proliferation at a comparable level with comparable precision. Thus, it is acceptable to use a single assay in which MYL-1401H was used as cell proliferation inducer to detect NAb against MYL-1401H, US-licensed and EU-approved Neulasta.

Additional Comments on NAb Assay Validation:

NFS-60 cells stored in liquid nitrogen are used in the assay and are critical in the performance of the assay; however, no control over the use of these cells is indicated in the validation report. Because the number of cell passages can impact the suitability of the NFS-60 cells to be used in the assay, the assay protocol should control the limits of cell passage number and this should be evaluated as part of assay development and/or validation. Additionally, the robustness of the assay to the use of different lots of cells, amongst other types of reagents, should also be included in the assay validation.

In response to an IR (June 16, 2017), the sponsor provided the cell passage numbers for all analytical runs in assay validation in breast cancer serum, and the cell passages employed in sample analysis for clinical study MYL-1401H-3001 (Table 10). The cell passages employed during MYL-1401H-3001 sample analysis ranged from P18 to P24, which were within the cell passage range (P8-P24) used during the assay validation.

Table 10: Cell Passage Numbers of All Analytical Runs in Validation With Breast Cancer Serum ((b) (4) and Sample Analysis ((b) (4) for MYL-1401H-3001

(b) (4)		(b) (4)	
(Sample Analysis MYL-1401H-3001)		(Validation Phase 3)	
Run #	Cell passage	Run #	Cell passage
08-10	P18	01V-02V	P19
11-14	P18	03V-04V	P19
15-16	P20	05V-06V	P21
17	P21	07V-08V	P21
18-20	P24	09V-11V	P8
High limit	P24	12V-14V	P8
Low limit	P18	15V-18V	P23
Run 01-07 were rejected for a technical error.		19V-21V	P23
		22V-24V	P9
		25V-27V	P9
		28V-30V	P24
		31V-33V	P24
		34V-37V	P11
		38V-41V	P12
		High limit	P24
		Low limit	P8

The sponsor also provided the NAb screening assay performance of VC, LPC and HPC throughout assay validation and sample analysis studies with cell passage numbers ranging from P8 to P24. All 3 controls remained within their validated ranges between P8 and P24 (Figure not shown), demonstrating that the cell passage numbers within P8 and P24 assure assay performance. The sponsor further stated that the same data was generated for the healthy subject validation (P8 to P33) and sample analysis (P9 to P18), and also supported assay performance across the cell passage range employed. This response is acceptable.

2.6 Facility Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies MYL-1401H-1001 and MYL-1401H-1002 conducted at (b) (4). Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI). The sponsor provided responses to Form 483 on (b) (4), in which they conveyed corrective plans (b) (4). Thus, the 483 observations issued by OSIS were addressed by the sponsor.

3. ANALYSIS OF CLINICAL IMMUNOGENICITY RESULTS

The clinical immunogenicity assessment of MYL-1401H, US-licensed Neulasta, and EU-approved Neulasta was derived from ADA data obtained from a comparative clinical study in patients with breast cancer who were receiving chemotherapy (MYL-1401H-

3001) and supportive PK similarity studies in healthy volunteers (MYL-1401H-1001 and MYL-1401H-1002).

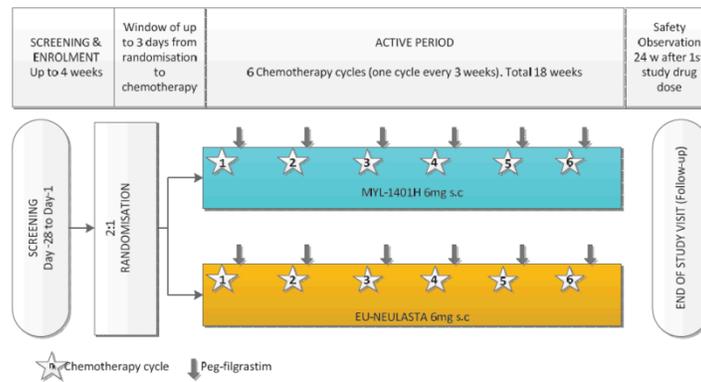
The sponsor originally evaluated ADA in the clinical samples using confirmatory cut-points at 0.1% false positive rate (see Section 1.5.4 above), which increases the risk of false negative results. The sponsor was asked to reanalyze the clinical data using confirmatory cut points at 1% false positive rate to maximize the detection of true positives (refer to FDA IR dated June 16, 2017). The data shown below are the revised results using CCPs at the 1% false positive rate.

3.1 Study MYL-1401H-3001

Study Design

Study MYL-1401H-3001 is a 6-dose (6 mg/dose), 2-arm parallel study in 194 patients with breast cancer aimed at comparing the safety, efficacy, and immunogenicity of MYL-1401H and EU-approved Neulasta. Of the 194 enrolled patients with breast cancer, 127 patients received MYL-1401H and 67 patients received EU-approved Neulasta. The study design is shown in Figure 3 below.

Figure 3: MYL-1401H-3001 Study Design



Abbreviations: mg = milligram; s.c. = subcutaneous; w = weeks
Source: CSR MYL-1401H-3001 Figure 9.1

Blood Sampling

Blood samples for immunogenicity assessment were collected in serum separator tubes at the time points shown in the table below.

Table 4: Sample Time Points and Blood Volumes for Immunogenicity Assessment

Assessments	Volume Collected (mL)		
	Day 1 of Cycle 1	Day 21 of Cycles 2, 4, and 6	Follow-up
Method optimization/validation	10	-	
Anti-Drug antibody (ADA)	5	5	5
Neutralizing antibody (NAb)	5	5	5
Study Drug Concentration	5	5	5

Follow-up: 168±15 days after the first exposure to the drug.

Immunogenicity Results

The ADA rates are summarized in the Table below. Pre-existing ADA rates were determined for patient samples with a positive result at baseline. In this study, 18.1% of the patients with breast cancer had pre-existing ADAs, which were primarily against the

PEG moiety and could be attributed to the exposure of these patients to various products in their daily usage that contain PEG. Post-dose ADA rates were determined for patient samples with a positive result at least once post-baseline. Treatment-induced ADA rates were determined for patient samples with a negative result at baseline and positive result at least once at any time post-baseline.

	MYL-1401H (n=126)	EU-Neulasta (n=67)
Pre-existing ADA+	21 (21/126=16.7%)	14 (14/67=20.9%)
	PEG+ =11 (8.7%)	PEG+ =12 (17.9%)
	GCSF+ =0 (0.0%)	GCSF+ =0 (0.0%)
	PEG+GCSF+ =6 (4.8%)	PEG+GCSF+ =0 (0.0%)
	PEG-GCSF- =4 (3.2%)	PEG-GCSF- = 2 (3.0%)
Post-dose ADA+	2 (2/126=1.6%)	2 (2/67=3.0%)
	PEG+ =0 (0.0%)	PEG+ =0 (0.0%)
	GCSF+ =0 (0.0%)	GCSF+ =1 (1.5%)
	PEG+GCSF+ =0(0.0%)	PEG+GCSF+ =0 (0.0%)
	PEG-GCSF- =2 (1.6%)	PEG-GCSF- =1 (1.5%)
Treatment-induced ADA+	0 (0/105=0.0%)	1 (1/53=1.9%)*
	PEG+ =0 (0.0%)	PEG+ =0 (0.0%)
	GCSF+ =0 (0.0%)	GCSF+ =1 (1.9%)
	PEG+GCSF+ =0 (0.0%)	PEG+GCSF+ =0 (0.0%)
	PEG-GCSF- =0 (0.0%)	PEG-GCSF- =0 (0.0%)
Pre-dose NAb+	0	0
Post-dose NAb+	0	0
Treatment-induced NAb+	0	0

Table prepared by OBP immunogenicity reviewer

*patient test positive for anti-GCSF at Cycle 2 Day 21 only

PEG+GCSF+: ADA recognizes both PEG and GCSF moieties

PEG-GCSF-: ADA recognizes a unique epitope of the PEGylated molecule

Reviewer Comments: Clinical study MYL-1401H-3001 is the most critical study for immunogenicity assessment because it has the appropriate design and power to allow for conclusions to be drawn about the comparative immunogenicity of MYL-1401H and EU-approved Neulasta. The sampling schedule is appropriate to minimize on-board drug interference. The difference in treatment-induced ADA incidence between groups is within 2% and no patients in either treatment group developed neutralizing ADA against PEG GCSF. These results indicate that there is no clinically meaningful difference between MYL-1401H and EU-approved Neulasta with respect to immunogenicity. The relevance of these data using EU-approved Neulasta as active comparator to support biosimilarity of MYL-1401H and US-licensed Neulasta is supported by the demonstration of a scientific bridge, including analytical and PK/PD components, between MYL-1401H, EU-approved Neulasta and US-licensed Neulasta (Refer to Product Quality and Clinical Pharmacology Review Memos, respectively).

3.2 Study MYL-1401H-1001

Study MYL-1401H-1001 is a single-dose (2 mg), 3-period, 3-arm crossover study in 216 healthy volunteers aimed at comparing the PK, safety, immunogenicity, and tolerability

of MYL-1401H, US-licensed Neulasta and EU-approved Neulasta. Blood samples were collected at predose, day 8 and 29 of period 1, and follow-up. The ADA rates are summarized in the Table below. In this study, 7.4% of the subjects had pre-existing ADAs, which were primarily against the PEG moiety and could be attributed to the exposure of these healthy volunteers to various products in their daily usage that contain PEG.

	MYL-1401H (n=72)	EU-Neulasta (n=72)	US-Neulasta (n=72)
Pre-dose ADA+	9 (9/72=12.5%)	4 (4/72=5.6%)	3 (3/72=4.2%)
	PEG+ =5 (6.9%)	PEG+ =1 (1.4%)	PEG+ =2 (2.8%)
	GCSF+ =1 (1.4%)	GCSF+ =0 (0.0%)	GCSF+ =0 (0.0%)
	PEG+GCSF+ =2 (2.8%)	PEG+GCSF+ =3 (4.2%)	PEG+GCSF+ =1 (1.4%)
	PEG-GCSF- =1 (1.4%)	PEG-GCSF- = 0 (0.0%)	PEG-GCSF- = 0 (0.0%)
Post-dose ADA+	21 (21/72=29.2%)	23 (23/72=31.9%)	28 (28/72=38.9%)
	PEG+ =12 (16.7%)	PEG+ =16 (22.2%)	PEG+ =14 (19.4%)
	GCSF+ =1 (1.4%)	GCSF+ =0 (0.0%)	GCSF+ =0 (0.0%)
	PEG+GCSF+ = 7 (9.7 %)	PEG+GCSF+ =4 (5.6%)	PEG+GCSF+ =8 (11.1%)
	PEG-GCSF- = 1 (1.4%)	PEG-GCSF- = 2 (2.8%)	PEG-GCSF- =3 (4.2%)
		PEG*GCSF- =1 (1.4%)	PEG*GCSF- =3 (4.2%)
Treatment-induced ADA+	14 (14/63=22.2%)	20 (20/68=29.4%)	25 (25/69=36.2%)
	PEG+ =8 (12.7%)	PEG+ =14 (20.6%)	PEG+ =13 (18.8%)
	GCSF+ =0 (0.0%)	GCSF+ =0 (0.0%)	GCSF+ =0 (0.0%)
	PEG+GCSF+ = 5 (7.9%)	PEG+GCSF+ = 3 (4.4%)	PEG+GCSF+ = 6 (8.7%)
	PEG-GCSF- = 1 (1.6%)	PEG-GCSF- = 2 (2.9%)	PEG-GCSF- =3 (4.3%)
		PEG*GCSF- =1 (1.5%)	PEG*GCSF- =3 (4.3%)
Pre-dose NAb+	3	0	0
Post-dose NAb+	4	1	1
Treatment-induced NAb+	2	1	1

Table prepared by OBP immunogenicity reviewer

*Insufficient volume for PEG domain characterization, but GCSF is negative.

3.3 Study MYL-1401H-1002

MYL-1401-1002 is a 2-period, 2-dose (6 mg/dose), 2-arm parallel study in 50 healthy volunteers aimed at comparing the PK, safety, immunogenicity, and tolerability of MYL-1401H and US-licensed Neulasta. Blood samples were collected during each period (Period 1 and Period 2) on Day -1, Days 8, 15, and 22, and at follow-up (in Period 2 only). The ADA rates are summarized in the Table below. In this study, 8% of the subjects had pre-existing ADAs and half of them are anti-PEG ADA.

	MYL-1401H (n=25)	US-Neulasta (n=25)
Pre-dose ADA+	3 (3/25=12%)	1 (1/25=4%)
	PEG+ =0 (0%)	PEG+ =1 (4%)
	GCSF+ =1 (4%)	GCSF+ =0 (0%)
	PEG+GCSF+ =1 (4%)	PEG+GCSF+ =0 (0%)
	PEG-GCSF- =1 (4%)	PEG-GCSF- = 0 (0%)

Post-dose ADA+	9 (9/25=36%)	7 (7/25=28%)
	PEG+ =5 (20%)	PEG+ =4 (16%)
	GCSF+ =1 (4%)	GCSF+ =0 (0%)
	PEG+GCSF+ = 2 (8%)	PEG+GCSF+ = 2 (8%)
	PEG-GCSF- = 1 (4%)	PEG-GCSF- = 1 (4%)
Treatment-induced ADA+	6 (6/22=27.3%)	7 (7/24=29.2%)
	PEG+ =4 (18.2%)	PEG+ =4 (16.7%)
	GCSF+ =0 (0.0%)	GCSF+ =0 (0.0%)
	PEG+GCSF+ = 1 (4.5%)	PEG+GCSF+ = 2 (8.3%)
	PEG-GCSF- = 1 (4.5%)	PEG-GCSF- = 1 (4.2%)
Pre-dose NAb+	1	0
Post-dose NAb+	1	0
Treatment-induced NAb+	0	0

Table prepared by OBP immunogenicity reviewer

Reviewer Comments: The results of these two studies show that there is no increase in ADA incidence for MYL-1401H as compared to US-licensed Neulasta. However, these two studies provided limited information for assessing comparative immunogenicity between the three products because the study design of the two studies is inadequate for immunogenicity assessment. The primary objective of study MYL-1401H-1001 was to compare the PK/PD of a single SC dose (2 mg) of MYL-1401H, EU-approved Neulasta, and US-licensed Neulasta. The study design included only a single dose in a cross-over manner which is insufficient to induce an immune response representative of actual use of the product. Although study MYL-1401H-1002 was conducted to compare the immunogenicity of two SC doses (6 mg each) between MYL-1401H and US-licensed Neulasta, the sample size is too small (25 samples per arm) to allow for meaningful conclusions to be drawn about the comparative immunogenicity of MYL-1401H and US-licensed Neulasta. Therefore, the comparative immunogenicity analyses from studies MYL-1401H-1001 and MYL-1401H-1002 are supportive of but not sufficient for a determination that there are no clinically meaningful differences in immunogenicity between MYL-1401H and US-licensed Neulasta. Results from study MYL-1401H-3001 are sufficient for a determination that there are no clinically meaningful differences in immunogenicity between MYL-1401H and US-licensed Neulasta.



Zhenzhen
Liu

Digitally signed by Zhenzhen Liu
Date: 9/19/2017 03:34:05PM
GUID: 555108d8007bb3724ef2a6d3413e2758



Maria
Gutierrez Lugo

Digitally signed by Maria Gutierrez Lugo
Date: 9/20/2017 01:26:16PM
GUID: 50757b3d000038f82ef48db08ba1ceea



Susan
Kirshner

Digitally signed by Susan Kirshner
Date: 9/19/2017 04:08:13PM
GUID: 508da6db000266b77da0ba4bfa620030

OFFICE OF DEVICE EVALUATION

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

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**



Date	August 30, 2017
To	Rachel Ershler, Medical Officer CDER/OND/OHOP/DHP
Requesting Division	Division of Hematology Products (DHP)
From	Steven Basile CDRH/ODE/DAGRRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # BLA 761075 ICCR# UCM013277 (Pre-SharePoint)
Recommendation	Device Constituents Parts of the Combination Product are Approvable.

Digital Signature Concurrence Table	
Reviewer	Steven Basile -S Digitally signed by Steven Basile -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Steven Basile -S, 0.9.2342.19200300.100.1.1=2002185460 Date: 2017.09.18 15:09:03 -04'00'
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	UCM013277 (Pre-SharePoint)
ICCR SharePoint Link	UCM013277
ICC tracking # (Lead)	ICC1700083
Submission Number	BLA 761075
Sponsor	Mylan GmbH
Drug/Biologic	MYL-1401H (a proposed biosimilar to pegfilgrastim)
Indications for Use	Decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Device Constituent	Prefilled Syringe (PFS) with Needle Safety Device (NSD)
Related Files	N/A

Table 2. Review Team	
CDER/CBER Lead Review Division	DHP
Submission RPM	Katie Chon
Lead Device Reviewer	Steven Basile
The CDRH review is being managed under ICC #: ICC1700083	

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2. PURPOSE/BACKGROUND

2.1. Scope

On Dec 9, 2016, Mylan GmbH (applicant) submitted a 351(k) for their product, MYL-1401H, a proposed biosimilar to pegfilgrastim. MYL-1401H is 6 mg in 0.6 mL Single-Dose Prefilled Syringe using the Ultra-Safe Plus Passive Needle Guard. Based on the modification using the Ultra-Safe Plus Passive Needle Guard, a consult is being requested whether the applicant has provided sufficient data/justification on the use-related risk and justification of a human factors study.

CDER is requesting confirmation from CDRH that the applicant has provided the regulatory requirements/data for a combination biologic and device (pre-filled syringe).

The goal of this memo is to evaluate the device (prefilled syringe + needle safety device) performance of the combination product (design control, verification/validation, and stability), and evaluate the use related risk of the Ultra-Safe Passive Needle guard. Drug-device compatibility is not covered under the scope of this review.

2.2. Prior Interactions

N/A

2.3. Indications for Use

Product	Indications for Use
MYL-1401H	Decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

2.4. Device Constituent

Device Name	Proposed Indications for Use
(b) (4) PFS	N/A, DMF

PMA/510(k) Number (if applicable):

Device Name	Cleared/Approved Indications for Use
(b) (4)	

	(b) (4)
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3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Document Number	Date - Version	Location
Container Closure System	N/A	N/A	eCTD 3.2.P.7
Container Closure System - Device Design and Development	N/A	N/A	eCTD 3.2.P.2.4
Stability Summary and Conclusion	N/A	N/A	eCTD 3.2.P.8.1
Device Functionality Data Obtained During Design Verification Testing of the MYL-1401H Device	GDD-DOC-2017-0114	V1.0	eCTD 3.2.P.2
Stability Data	N/A	N/A	eCTD 3.2.P.8.3
Functional Stability Report for Batch XXX	N/A	N/A	eCTD 3.2.P.8.3
Glide Force and Break Loose Stability Report for Batch XXX	N/A	N/A	eCTD 3.2.P.8.3

3.2. CDRH Review Team

Team Member	Role	Deficiencies
Steven Basile CDRH/ODE/DAGRID/GHDB	Lead Reviewer – {Engineering}	None.

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The MYL-1401H syringe with needle guard, henceforward referred to as the MYL- 1401H device, is a single-dose, disposable, prefillable syringe (PFS) with needle guard for subcutaneous administration and is nonreusable. The MYL-1401H device is designed to deliver a fixed dose (6 mg/0.6 mL) of MYL-1401H drug product to adult patients weighing 45 kg or greater.

The MYL-1401H device is composed of the (b) (4) glass PFS with 29 gauge half inch staked needle, the (b) (4) Plunger Stopper, the (b) (4) Plunger Rod (b) (4) and the (b) (4) UltraSafe Plus™ Passive Needle Guard (b) (4). The needle guard consists of a transparent (b) (4)

ICC1700083

BLA761075, MYL-1401H, PFS w/ Needle Guard

(b) (4)

body, a transparent (b) (4) guard, and a (b) (4) spring, and it undergoes passive activation (ie, automatically) post dose administration. The needle guard and plunger rod were cleared through the publicly available 510(k) number (b) (4). A Type III Drug Master File (DMF) is on file for the PFS describing the manufacturing and controls implemented.

Five of the individual components - the glass syringe barrel, needle, plunger stopper, needle shield skirt, and rigid shield - form the PFS component of the MYL-1401H device. (The needle is supplied staked to the glass syringe barrel.) These components are supplied by (b) (4). See components 1-5 below:

Component Part Number	Component Images (Not to Scale)	Component Name	Material Name	Function Related to the Operating Principles [<i>Reference to Component Part Number</i>]
-----------------------	---------------------------------	----------------	---------------	--

(b) (4)



ICC1700083

BLA761075, MYL-1401H, PFS w/ Needle Guard

(b) (4)

The 4 remaining individual components – the plunger rod, guard, body, and spring – together form part of the passive safety system of the MYL-1401H device. The guard, body, and spring are supplied preassembled as the UltraSafe Plus Passive Needle Guard as cleared through the publicly available 510(k) number (b) (4). See components 6-9 below:

Component Part Number	Component Images (Not to Scale)	Component Name	Material Name	Function Related to the Operating Principles [<i>Reference to Component Part Number</i>]
(b) (4)				



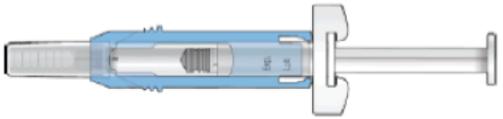
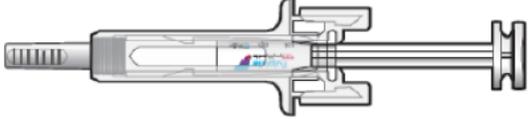
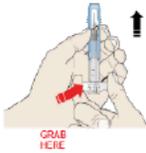
An overview of all the components of the PFS + NSD, material composition, sterilization method, and supplier are shown in Table 3.2.P.7/1 below:

Table 3.2.P.7/1: Overview of the MYL-1401H Container Closure/Device Components

Device Component	Constituent Component	Material	Reference	Sterilization Method	Sterilization Location	Supplier
(b) (4)						

Table 3.2.P.2.4/1 provides a comparison of the user interfaces for both the existing (Neulasta, Amgen) and proposed (MYL-1401H, Mylan Inc) products:

Table 3.2.P.2.4/ 1: Comparison of the User Interfaces for Neulasta and MYL-1401H

Company	Amgen	Mylan Inc
Name	Neulasta approved in United States in 2002	MYL-1401H
Composition	6 mg/0.6 mL pegfilgrastim, supplied in a 27-gauge, half inch staked needle syringe with an UltraSafe™ Needle Guard	6 mg/0.6 mL MYL-1401H drug product, supplied in a 29-gauge, half inch staked needle syringe with an UltraSafe Plus Passive Needle Guard
Component Color	A clear glass syringe with a transparent (clear) plastic blue needle guard and plunger rod	A clear glass syringe with a transparent (clear) plastic needle guard and white plunger rod
PFS	 Image representative of Neulasta device	 Image representative of MYL-1401H device
Needle Guard	Active needle guard. (ie, user required to manually activate needle guard after dose administration) From IFU (Revised 4/2016 v1) Step 4: Finish For your safety, pull the blue safety guard until it clicks and covers the needle.	Passive needle guard (ie, needle guard automatically activated after dose administration) From proposed IFU (b) (4). Once the entire dose has been delivered the needle safety guard will be triggered (b) (4) either of the following (b) (4) - Release the plunger until the entire needle is covered and then remove the needle from the injection site
Company	Amgen	Mylan Inc
	 Once extended, the blue safety guard will lock into position and will not slide back over the needle. Keep your hands away from the needle at all times.	Or - Gently remove the needle from the injection site and release the plunger until the entire needle is covered by the guard  After releasing the plunger, the prefilled syringe needle safety guard will safely cover the injection needle.
Packaging Configuration	Provided in a blister pack and carton containing 1 Neulasta Pre Filled Syringe with Needle Guard.	Provided in a blister pack and carton containing 1 MYL-1401H.
Package Insert	Combined labeling and IFU	Combined labeling and IFU

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

5.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	

Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		3.2.P.2.4 Container Closure System - Device Design and Development
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		3.2.P.2.4 Container Closure System - Device Design and Development
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.P.2.4 Container Closure System - Device Design and Development
Validation Data		X	
<ul style="list-style-type: none"> • Human factors • Clinical data 		X	
Traceability Documentation	X		3.2.P.2.4 Container Closure System - Device Design and Development

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Design Verification Review

Design Input Requirement	Device Requirement Specification	Rationale	Meets Criteria
Device Component Requirements			
Syringe Barrel Dimensions	Dimensions of the barrel shall be in accordance with ISO 11040-4:2015, for a 1 mL long syringe barrel: <ul style="list-style-type: none"> • Nominal body height = 54 mm ± 0.5 mm • Diameter of the syringe at the flange end (widest diameter of flange) = 13.8 mm ± 0.4 mm • Diameter of the syringe at the flange end (narrowest diameter of flange) = 11 mm ± 0.4 mm • Inner barrel diameter = 6.35 mm ± 0.1 mm • Outer barrel diameter = 8.15 mm ± 0.1 mm 	As specified in ISO 11040-4:2015	Yes
Container Material	The material of the container shall be colorless or amber glass of hydrolytic resistance grain class HGA 1 in accordance with ISO 720:1985 and USP <660>.	As specified in ISO 11040-4:2015	Yes
Hydrolytic Resistance	When tested in accordance with ISO 4802-1 or ISO 4802-2, the hydrolytic resistance of the internal surface of the glass barrel shall comply with the requirements of hydrolytic resistance container class ISO 4802-HC 1.	As specified in ISO 11040-4:2015	Yes
Annealing Quality	The maximum residual stress shall not produce an optical retardation	As specified in ISO 11040-4:2015	Yes

6.1.1. Functional Temperature Testing

Table 3.2.P.2.4/ 9: DVT – Functional Temperature Range (40°C ± 2°C/50% ± 10% RH)

Test Requirement	Specification	Sample Size	MYL-1401H must function and maintain dose accuracy following storage for at least 4 hours at the following environmental conditions: 5°C (ambient RH), 23°C/50% RH and 40°C/50% RH				Met Requirement
			Min	Max	Mean	SD	
Dose Accuracy (mL)	MYL-1401H shall deliver 0.6 mL of solution (b) (4) mL with a target of (b) (4) mL.	60	0.63 mL	0.64 mL	0.64 mL	<0.01 mL	Yes
Rigid Needle Shield Removal Force (N)	The rigid needle shield pull-off force shall be suitable for the intended use. The rigid needle shield should be sufficient to maintain sterility of the needle. Removal of the rigid needle shield shall be with reasonable force, defined by the manufacturer as minimum, (b) (4) maximum with an individual force of no more than (b) (4)	60	6 N	7 N	6 N	<1 N	Yes
Break Loose Force (N)	No more than (b) (4) as per manufacturing in-process checks	60	3 N	5 N	4 N	<1 N	Yes
Glide Force (N)	No more than (b) (4) as per manufacturing in-process checks	60	<1 N	2 N	1 N	<1 N	Yes

The functional temperature range results demonstrate that MYL-1401H meets all design verification requirements for dose accuracy and device functionality.

6.1.2. Dry Heat/Cold Storage

Table 3.2.P.2.4/ 11: DVT – Dry Heat/Cold Storage (2°C ± 2°C/uncontrolled RH)

Test Requirement	Specification	Sample Size	MYL-1401H must function and maintain dose accuracy following storage for 96 hours at the following environmental conditions: 2°C/ambient RH and 8°C/ambient RH				Met Requirement
			Min	Max	Mean	SD	
Dose Accuracy (mL)	MYL-1401H shall deliver 0.6 mL of solution (b) (4) mL to (b) (4) mL with a target of (b) (4) mL.	60	0.60 mL	0.61 mL	0.61 mL	<0.01 mL	Yes
Rigid Needle Shield Removal Force (N)	The rigid needle shield pull-off force shall be suitable for the intended use. The needle shield should be sufficient to maintain sterility of the needle. Removal of the rigid needle shield shall be with reasonable force, defined by the manufacturer as (b) (4) minimum, (b) (4) maximum with an individual force of no more than (b) (4)	60	6 N	12 N	10 N	2 N	Yes
Break Loose Force (N)	No more than (b) (4) as per manufacturing in-process checks	60	3 N	6 N	4 N	1 N	Yes
Glide Force (N)	No more than (b) (4) as per manufacturing in-process checks	60	<1 N	3 N	2 N	<1 N	Yes

The dry heat/cold storage results demonstrate that MYL-1401H meets all design verification requirements for dose accuracy and device functionality.

6.1.3. Vibration (Transport)

Table 3.2.P.2.4/ 12: DVT – Vibration (Transport)

Test Requirement	Specification	Sample Size	MYL-1401H must function and maintain dose accuracy following subjection to vibration conditions at 3 axes as specified in IEC 60068-2-6:2007.				Met Requirement
			Min	Max	Mean	SD	
Dose Accuracy (mL)	MYL-1401H shall deliver 0.6 mL of solution (b) (4) mL to (b) (4) mL with a target of (b) (4) mL.	20	0.61 mL	0.61 mL	0.61 mL	<0.01 mL	Yes
Rigid Needle Shield Removal Force (N)	The rigid needle shield pull-off force shall be suitable for the intended use. The needle shield should be sufficient to maintain sterility of the needle. Removal of the rigid needle shield shall be with reasonable force, defined by the manufacturer as (b) (4) minimum, (b) (4) maximum with an individual force of no more than (b) (4)	20	6 N	11 N	9 N	1 N	Yes
Break Loose Force (N)	No more than (b) (4) as per manufacturing in-process checks	20	3 N	6 N	4 N	1 N	Yes
Glide Force (N)	No more than (b) (4) as per manufacturing in-process checks	20	<1 N	3 N	2 N	<1 N	Yes

The vibration (transport) results demonstrate that MYL-1401H meets all design verification requirements for dose accuracy and device functionality.

6.1.4. Stability Testing

The following information was taken from Document “Stability Data,” found under eCTD 3.2.P.8.3:

Table 3.2.P.8.1/ 3: Drug Product Specifications

Test	Method of Analysis/reference to pharmacopeia	Acceptance Criteria
Pre-filled syringe functionality testing		
Glide Force	ISO 11608/3 2012	NMT (b) (4) Newton
Break Loose Force	ISO 11608/3 2012	NMT (b) (4) Newton
Functional stability testing of Pre-filled along with Device		
Extractable Volume	Ph. Eur. 2.9.17/USP-NF General Chapter <1> Injections	(b) (4) mL
Actuation of Needle Guard	Activation of needle guard by simulated drug delivery	The device should be actuated and should cover the needle after completely dispensing the contents of the syringe

Table 3.2.P.8.1/ 6: Stability Protocol for PV batches – Long-Term Storage Condition (5 ± 3°C)

Test	Acceptance criteria	Testing frequency (in months)							
		Initial	3	6	9	12	18	24	36
Glide Force	NMT (b) (4) Newton	✓	✓	✓	✓	✓	✓	✓	✓
Break Loose Force	NMT (b) (4) Newton	✓	✓	✓	✓	✓	✓	✓	✓

Table 3.2.P.8.1/ 7: Stability Protocol for PV Batches – Accelerated Storage Condition (25 ± 2°C, 60% ± 5% RH)

Test	Testing frequency (in months)				
	Initial	1	2	3	6
Glide Force	✓	✓	✓	✓	✓
Break Loose Force	✓	✓	✓	✓	✓

Table 3.2.P.8.1/ 8: Functional Stability Study Protocol – Long-Term Conditions (5 ± 3°C)

Test	Testing frequency (in months)							
	Initial	3	6	9	12	18	24	36
Extractable Volume	✓	✓	✓	✓	✓	✓	✓	✓
Actuation of Needle Guard	✓	✓	✓	✓	✓	✓	✓	✓

Table 3.2.P.8.1/ 9: Functional Stability Study Protocol – Accelerated Conditions (25°C ± 2°C/60% ± 5% RH)

Test	Testing frequency (in months)			
	Initial	1	3	6
Extractable Volume	✓	✓	✓	✓
Actuation of Needle Guard	✓	✓	✓	✓

Reviewer Comment:

The functional and stability data provided confirm acceptable performance of the device for its intended use.

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

7.2. Summary of Risk Analysis

The following information was taken from Section 3.2.P.2.4.2.7 (Device Risk Management), Document “Container Closure System - Device Design and Development,” under 3.2.P.2.4 of the eCTD:

Risk assessments were undertaken by Mylan to identify and evaluate risks in consideration of the intended use and foreseeable misuse of the MYL-1401H device by the intended user population.

Table 3.2.P.2.4/ 23: Clinical Hazards Associated with the Use of MYL-1401H

Hazard	Potential Harm to User	Severity Rating
Missed dose – patient unaware (single MYL-1401H device malfunctions)	Neutropenia, febrile neutropenia, potential hospitalization, use of antibiotics	S3
Injection taken <24 hours after chemotherapy	Lack of efficacy resulting in neutropenia, potential hospitalization, and/or use of antibiotics	S3
Single missed dose – patient aware (0% of dose delivered)	Inconvenience	S1
Patient overdoses – takes multiple doses	Leukocytosis	S2
Partial dose	Longer neutropenia and increases risk of a febrile neutropenia.	S3
Intravenous injection	Lack of efficacy resulting in neutropenia, febrile neutropenia, potential hospitalization, and/or use of antibiotics	S3
Intramuscular injection	Lack of efficacy resulting in neutropenia, febrile neutropenia, potential hospitalization, and/or use of antibiotics	S3
User interaction with MYL-1401H device	Needle stick injury prior to injection – minor discomfort	S2
	Needle stick injury post injection to user or another person leading to potential infection by blood-borne virus	S3
	Skin laceration/scratches	S2
	Injection site bruising	S2
	Injection site swelling	S2
	Injection site pain	S2
User injects straight from refrigerator	Patient minor discomfort	S1

Risk control measures for each potential failure mode, regardless of the severity and occurrence scores applied, were considered. Three risks were identified with Severity Level 3 and Occurrence Level 3. On review of the potential failure modes it was determined that these risks are not unique to MYL-1401H, but common to both MYL-1401H and the reference product and that no additional product specific risk control could be applied to reduce the risk further. In addition, there is no reported evidence of these 3 failure modes being reported in relation to safety complaints related to the reference product. One potential risk observed in the reference product, accidental needle stick injury post injection, has been mitigated in MYL-1401H through the use of the (b) (4) UltraSafe Plus Passive Needle Guard. The potential failure modes and control measures associated with the use of MYL-1401H are presented in below:

(b) (4)

IFU Step	Individual User Interaction	Potential Failure Mode	Current Control
Storage	Store the MYL-1401H between 36°F to 46°F (2°C to 8°C)	User dose not store MYL-1401H per instructions	Instructions for Use and labelling give clear guidance on storage (illustrations are proposed): (b) (4)
	Store in Carton	User removes MYL-1401H from carton and stores in daylight	
Gather Supplies	Remove from refrigerator	User has multiple prescriptions in refrigerator and cannot differentiate correct PFS	Distinctive labelling to enable product differentiation (illustration is proposed as provided in Module 1). (b) (4)

Table 3.2.P.2.4/ 26: Residual Risk Evaluation Matrix

		Severity				
		1	2	3	4	5
Occurrence	1	14	8	6	0	0
	2	2	9	13	0	0
	3	0	0	3	0	0
	4	0	0	0	0	0
	5	0	0	0	0	0

Green = Tolerable Risk, Red = Not Tolerable Risk, requiring acceptance through Risk Benefit Analysis.

The residual risk assessment was conducted with consideration of the output from the risk management program, reference product complaints and user interface assessments. Risk acceptance applied to risks in MYL-1401H is also applicable to the reference product or is generally applicable to PFS use with a needle safety guard demonstrating that the MYL-1401H device is acceptable for the intended user population as confirmed by the MYL-1401H device Risk Benefit Analysis.

Reviewer Comment:

The risk management activities are acceptable give the similarities between the Neulasta PFS and MYL-140H.

8. HUMAN FACTORS JUSTIFICATION

The sponsor states the following with regards to their human factors assessment (pg. 70 of “3.2.P.2.4 Container Closure System - Device Design and Development”):

The MYL-1401H Human Factors Assessment took into consideration all aspects of user requirements, the user interface and the user-related risk assessment (discussed in Section 3.2.P.2.4.2.7) as well as existing knowledge on the device and the reference product. The syringe and needle guard are composed of components which are commercially available from (b) (4) and which have been demonstrated to be safe and effective for use through successful usability assessment. The intended use, user profiles, and intended use environment for MYL-1401H Intended Users (adults weighing 45 kg or greater) are the same as those of Neulasta. Therefore, there were no additional risks from new users with different demographics or characteristics, or from a different environment with different conditions.

The intended use and individual user interactions are fundamentally the same as Neulasta with the exception of the perceptual inputs, cognitive processes, and actions relating to the activation of the needle guard. For MYL-1401H, the required inputs, processes, and resulting actions are less; therefore, minimizing the risk of no activation of the safety mechanism resulting in an unshielded needle and potential needle stick injury opportunity. Although the MYL-1401H device user interface differs from the Neulasta device in 2 features (passive needle guard and plunger with larger head), these differences provide enhanced usability to the user. In addition, research undertaken during this assessment found no recalls or adverse events attributed to use errors relating to Neulasta or the (b) (4) UltraSafe Plus Passive Needle Guard.

Based on a review of information available on the UltraSafe Plus Passive Needle Guard and Neulasta, Mylan concluded that no additional information was required to support the Human Factors Assessment of the safe and effective use of the MYL-1401H device in consideration of its intended use, users, and use environment.

Reviewer Comment:

This rationale is acceptable.

9. INTERACTIVE REVIEW

Agency Information Request #1 (sent on 06/01/2017) - ADEQUATE

In the document 3.2.P.2.4 Container Closure System – Device Design and Development, you have provided summary level design verification results demonstrating that the design and functional inputs are met. However, it did not appear that the full test reports for these verification tests were included in the submission. Provide all full test reports for the design/functional verification testing contained in Document 3.2.P.2.4, or alternatively, point to where in the submission these reports can be found.

Sponsor Response (received on 06/16/2017)

A full report for the design and functional testing contained in Section 3.2.P.2.4 is provided in the document named, *Device Functionality Data Obtained During DVT of the MYL 1401H Device*. All individual data for the shipping simulation performed as part of DVT is included in Section 3.2.P.2.4.

Reviewer Comments:

The response is acceptable. The attached documents were reviewed.

Agency Information Request #2 (sent on 06/01/2017)- ADEQUATE

In the document 3.2.P.8.3 Stability Data, you have provided summary level stability data for glide force, break loose force, extractable volume, and actuation of needle guard. Full test reports for the stability testing of these four attributes is necessary to complete the review of the drug-device combination product. Provide full test reports for the long-term and accelerated stability testing of the glide force, break loose force, extractable volume, and actuation of needle guard, or alternatively, point to where in the submission these reports can be found.

Sponsor Response (received on 06/16/2017)

As per the Agency's recommendation, full test reports for glide force, break loose force at the long-term and accelerated stability testing is provided in the Glide Force & Break Loose Force Stability Report. Full test reports for extractable volume, and actuation of needle guard at the long-term and accelerated stability testing is provided in the Functional Stability Reports. The DP batch numbering system followed during manufacturing, packaging and stability testing is detailed below in Table 1.

Table 1: Batch Numbering System Followed During Manufacturing, Packaging and Stability Testing

Manufacturing batch number as per SAP numbering	Packing batch number as per SAP numbering	Corresponding stability batch number in the report
BS15007576	BF16003840	BM15002813
BS15007635	BF16003841	BM15002814
BS15007637	BF16003842	BM15002815

Reviewer Comments;

The response is acceptable. The attached documents were reviewed.

10.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable.

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

/s/

WONME K CHON

10/05/2017

electronically signed by Katie Chon, PharmD, RPh for Pete Basile

MEMORANDUM

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

DATE: August 24, 2017

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

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

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

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDBE, OSIS

SUBJECT: Routine inspection of PRA Group B.V., Groningen, The Netherlands

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of studies **MYL-1401H-1001** and **MYL-1401H-1002 (BLA 761075)** conducted at PRA Group B.V., Groningen, The Netherlands.

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

After reviewing the inspectional findings, I found the clinical data from the audited studies reliable. Thus, I recommend that the data from studies MYL-1401H-1001 and MYL-1401H-1002 and

other studies of similar design conducted at the site be accepted for further Agency review.

Inspected Studies:

BLA 761075

Study Number: MYL-1401H-1001

Study Title: "Single center, randomized, double-blind, three-period, three-treatments, three-way crossover pharmacokinetics (PK)/pharmacodynamics (PD) trial to assess PK, PD, safety and tolerability of MYL-1401H after single subcutaneous injection at one dose level (2 mg) comparing to an European Union (EU) and United States (US) marketed drug product (Neulasta®) in healthy volunteers."

Dates of study

conduct: August 26, 2014-June 30, 2015

Study Number: MYL-1401H-1002

Study Title: "Single center, randomized, open-label, parallel trial to compare immunogenicity, safety, and tolerability of MYL-1401H and US-licensed pegfilgrastim (Neulasta®) after two subcutaneous (sc) injections at one dose level (6 mg) in healthy subjects."

Dates of Study

conduct: July 29-October 24, 2015

ORA investigator Stephen Hansen (OBIMO/DBIMOII) audited the clinical portion of studies MYL-1401H-1001 and MYL-1401H-1002 conducted at PRA Group B.V., Groningen, The Netherlands from April 18-21, 2017.

The inspection included a thorough examination of compliance with the protocol, protocol amendments, protocol deviations, study records, inclusion/exclusion criteria, informed consent forms, SOPs, IRB approvals, screening, enrollment, randomization, treatment visits, test article control and accountability, medication compliance, primary efficacy data, case report forms, data security, record custody and retention,

adverse events, serious adverse events, and interviews/discussions with the firm's staff and management. In addition, investigator Hansen randomly selected and audited the study records for absolute neutrophil counts (ANC) from both studies. The ANC assessments were originally conducted at PRA Health Sciences-Early Development Services (PRA-EDS), Stationsweg 163, 9471 GP Zuidlaren, The Netherlands; however, when this clinical site closed, the ANC records were transferred to PRA Group B.V., Groningen, The Netherlands where the inspection took place.

The inspection revealed no issues with the ANC assessments. The neutrophil counts were generated using a validated hematology method. A calibrated Advia 212i Hematology analyzer was used to generate neutrophil counts and staff was trained to operate the analyzer. A standard operating procedure (SOP) was used for operation of the Hematology analyzer. There were no repeat analyses for ANC.

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

Conclusion:

After reviewing the inspectional findings, I found the data from the audited studies to be reliable. Therefore, I recommend that the data from audited studies MYL-1401H-1001 and MYL-1401H-1002 (BLA 761075) be accepted for further Agency review.

In addition, studies of similar design conducted by the site before the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Clinical Site:

NAI: PRA Group B.V., Groningen, The Netherlands
FEI#: 3005991010

cc:

OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/CDER-OSIS-
BEQ@fda.hhs.gov

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

OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

ORA/OBIMO/DBIMOII/Hansen

Draft: GM 08/21/2017

Edits: RCA 08/22/2017; CB 08/24/2017

ECMS:

[PRA-EDS University Medical Center, Groningen, The Netherlands-
BLA 761075-Pegfilgrastim](#)

OSIS File #: BE 7374

FACTS: 11719252

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

/s/

GAJENDIRAN MAHADEVAN
08/24/2017

RUBEN C AYALA
08/24/2017

CHARLES R BONAPACE
08/24/2017

Clinical Inspection Summary

Date	7/31/2017
From	Navid Homayouni, M.D., Medical Officer Janice Pohlman, M.D., Team Leader Kassa Ayalew, M.D., M.P.H.; Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Katie Chon, PharmD., Regulatory Project Manager Rachel Ershler, M.D., Clinical Reviewer Nicole Gormley, M.D., Cross Discipline Team Leader Division of Hematology Products
BLA #	761075 (BsUFA)
Applicant	Mylan
Drug	MYL-1401H (a proposed biosimilar to pegfilgrastim)
NME (Yes/No)	No
Therapeutic Classification	Colony Stimulating Factors
Proposed Indication(s)	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.
Consultation Request Date	January 19, 2017
Summary Goal Date	July 31, 2017
Action Goal Date	October 6, 2017
PDUFA Date	October 6, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study MYL-1401H-3001 was submitted to FDA in support of BLA 761075. Three clinical sites, Dr. Dzagnidze Giorgi, M.D. (Site 9901), Dr. Gia Nemsadze, M.D. (Site 9903), Dr. Zakaria Zautashvili, Ph.D. (Site 9906) and the Contract Research Organization, (CRO), [REDACTED] (b)(4) were selected for audit.

The data for Study MYL-1401H-3001 submitted by the Sponsor to the Agency in support of BLA 761075 appear reliable based on available information from the inspections of three clinical sites and the CRO. There were no significant inspectional observations for clinical investigators, Dr. Dzagnidze Giorgi, M.D., Dr. Gia Nemsadze, M.D, Dr. Zakaria Zautashvili, Ph.D. and the CRO, [REDACTED] (b)(4). The final classification for the inspections of Drs. Giorgi and Zautashvili and preliminary classification for the inspection of Dr. Nemsadze

and [REDACTED] ^{(b) (4)} is No Action Indicated (NAI).

A Clinical Inspections Summary Addendum will be provided if the final classifications of the inspections of Dr. Nemsadze and [REDACTED] ^{(b) (4)} are significantly different following receipt and review of the Establishment Inspection Report (EIR).

II. BACKGROUND

Mylan GmbH seeks approval of MYL-1401H, a proposed biosimilar to pegfilgrastim, for the prophylactic treatment of chemotherapy-induced neutropenia. Study MYL-1401H-3001 forms the basis for the clinical evaluation of the proposed biosimilar to Neulasta (pegfilgrastim) for the determination of safety and efficacy.

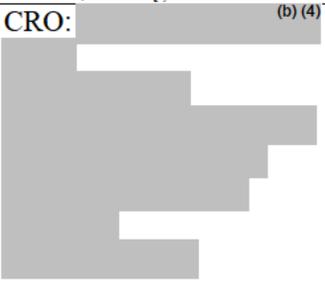
This was a two-arm study, comparing Mylan's biosimilar, MYL-1401H, to the innovator pegfilgrastim (Neulasta). The primary efficacy endpoint was duration of severe neutropenia (DSN) in cycle 1 defined as days with ANC < 0.5 x 10⁹/L.

The study was conducted from March 25, 2015 to February 9, 2016. There were 194 subjects randomized to treatment (127 to MYL-1401H, 67 to EU-Neulasta). There were 25 sites in 4 countries where subjects were enrolled (Bulgaria [5], Georgia [7], Hungary [4], and Ukraine [9]).

As reported by the Sponsor, MYL-1401 demonstrated equivalent efficacy to EU-Neulasta in prophylactic treatment of chemotherapy induced febrile neutropenia in patients with breast cancer.

Only foreign data were submitted to support the application. GCP inspection was conducted at a CRO site and at three clinical investigator (CI) sites. The CI sites for inspection were chosen because of high enrollment.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non- U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Classification
Giorgi Dzagnidze, M.D., PhD Site Number: 9901 S. Khechinashvili University Hospital 33 Chavchavadze Ave, Tbilisi, Georgia 0179	Protocol: MYL-1401H- 3001 Number of Subjects Enrolled: 13	April 24-28, 2017	NAI
Gia Nemsadze, M.D. Site Number: 9903 LTD Mammological Center 5 Lubliana Street Tbilisi, Georgia 0159	Protocol: MYL-1401H- 3001 Number of Subjects Enrolled: 13	May 1-5, 2017	Pending: Preliminary NAI
Zakaria Zautashvili, PhD Site Number: 9906 Research Institute of Clinical Medicine 13 Tevdore Mgvdeli Street Tbilisi, Georgia 0112	Protocol: MYL-1401H- 3001 Number of Subjects Enrolled: 17	May 1-5, 2017	NAI
CRO:  (b) (4)	Protocol: MYL-1401H- 3001	July 10-14, 2017	Pending: Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

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

1. Giorgi Dzagnidze, M.D., PhD (Site 9901)

The clinical site screened 13 subjects and 13 were enrolled and randomized. All randomized subjects completed the study. An audit of all subject's records was conducted.

The inspection evaluated all subject informed consent forms, financial disclosures, subject eligibility, test article accountability, blinding/randomization procedures, source documents, subject bone pain inventory diaries, primary and secondary endpoints, and adverse events to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued. The primary efficacy endpoint was verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice.

2. Gia Nemsadze, M.D. (Site 9903)

The site screened 15 subjects and 13 subjects were enrolled and randomized. All randomized subjects completed the study. An audit of 9 subject's records was conducted.

The inspection evaluated subject informed consent forms, screening and enrollment logs, source records, subject diaries, drug accountability logs, sponsor monitoring files and correspondence. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued. The primary efficacy endpoint was verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice.

3. Zakaria Zautashvili, PhD (Site 9906)

The site screened 19 subjects and 17 were enrolled and randomized. All randomized subjects completed the study. An audit of all screened and enrolled subject's records was conducted.

The inspection evaluated all subject informed consent forms, financial disclosures, subject eligibility, test article accountability, blinding/randomization procedures, source documents, subject bone pain inventory diaries, IxRS confirmation sheets, primary and secondary endpoints, and adverse events. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued. The primary efficacy endpoint was verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice.

4. CRO ([REDACTED] (b) (4))

The inspection focused on drug shipping and accountability records, monitoring reports, financial disclosures, training records, data transfer and management of biostatistics.

The inspection found no major regulatory violations or deficiencies. At the conclusion of the inspection, a form FDA 483 was not issued. However, two observations were discussed at the close-out meeting: (1) The return of the used syringes following investigational product administration was not documented on the accountability records for all 35 sites involved in the study; and (2) There was no documentation of the time the drug was taken from the refrigerator and the time of the administration of drug until October 2015 when the additional worksheet was made by the CRO/Sponsor to ensure that the study drug was not kept outside the refrigerator for more than 6 hours.

OSI Reviewer Comment:

Verbal Discussion Item #1 appears to be a minor issue related to lack of documentation of return of the used syringes to the pharmacy. The investigational product and comparator are single dose products administered by subcutaneous injection. Empty syringes were to be returned to the unblinded pharmacist who was to remove the drug label that was then to be maintained with each subject's drug records. Based upon follow-up communication with the investigator who conducted the inspection at CRO, it appears that after administration of the drug, the clinical research associates (CRAs) attached the peel-off drug label to the randomization print-out in each subject's record. Unlabeled used syringes were returned to the pharmacist who adequately documented local destruction of these syringes, however did not include this information on the drug accountability log returned to the sponsor.

Verbal Discussion Item #2 appears to be an issue related to documentation of time noted during inspection of the CRO rather than study process based upon follow-up communication with the field investigators who conducted the inspections at the three CI sites. The instructions related to drug storage and handling are clearly stated in the protocol. The protocol states that prior to injection, the drug may be allowed to reach room temperature for a maximum of 6 hours. Any syringe left at room temperature for more than 6 hours must be discarded and documented. Study documents did not require the unblinded pharmacist to document time of removal of the syringe from the refrigerator until October 2015, therefore elapsed time prior to administration was not recorded for the majority of subjects. Based upon follow-up discussion with the field investigators who conducted the three CI inspections, the unblinded pharmacist handed the syringe directly to the study personnel responsible for administering the investigational product.

Therefore, the lack of documentation of elapsed time from removal of investigational product from the refrigerator to time of administration is unlikely to have had significantly impact efficacy or safety.

{See appended electronic signature page}

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

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/Ann Farrell
Review Division /Medical Team Leader/Nicole Gormley
Review Division /Project Manager/Katie Chon
Review Division/MO/Rachel Ershler
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman
OSI/DCCE/GCP Reviewer/Navid Homayouni
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

NAVID N HOMAYOUNI
08/02/2017

JANICE K POHLMAN
08/02/2017

KASSA AYALEW
08/02/2017

MEMORANDUM

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

DATE: July 27, 2017

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

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

Amy Rosenberg, M.D.
Director
Division of Biotechnology Review and Research III
Office of Biotechnology Products
Office of Pharmaceutical Quality

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

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

SUBJECT: Amended EIR review for the surveillance inspection of

(b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies (b) (4) MYL-1401H-1001 (BLA 761075), and MYL-1401H-1002 (BLA 761075) conducted at

(b) (4)

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

(b) (4)

The evaluation of inspectional findings was provided in the review dated June 23, 2017. This review is being amended to include (b) (4) response to Form FDA 483 received on (b) (4) .

After evaluating (b) (4) response to Form FDA 483, my conclusion regarding data acceptability remains the same as provided in the initial review dated 6/23/2017.

Inspected Studies:

(b) (4)

BLA 761075

Study Number: MYL-1401H-1001

Study Title: "Analysis of normal human serum samples using a cell based assay for the detection of neutralizing antibodies against MYL-1401H and Neulasta[®] (US and/or EU) to support phase I clinical study MYL1401H-1001."

Dates of conduct: April 5-September 14, 2016

Study Number: MYL-1401H-1002

Study Title: "Analysis of normal human serum samples using a cell based assay for the detection of neutralizing antibodies against MYL-1401H and Neulasta[®] US to support phase I clinical study MYL1401H-1002."

Dates of conduct: April 6-September 23, 2016

(b) (4)

OSIS Pharmacologist Gajendiran Mahadevan, Ph.D. audited the analytical portion of the above studies at (b) (4)

from (b) (4) .

I thoroughly audited the study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff. As a part of surveillance approach, several key study components that best represent the firm's bioanalytical operations were selected and audited across multiple studies conducted at (b) (4) .

At the conclusion of the inspection, I observed objectionable findings and issued Form FDA 483 to (b) (4)

(Attachment-1). The firm responded to Form FDA 483 on (b) (4)

(Attachment-2). The Form FDA 483, the firm's response to Form FDA 483, and my evaluation follow.

Observation 1

(b) (4)

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(b) (4)

(b) (4)

Conclusion:

After reviewing the inspectional findings, there was evidence that significant deficiencies impacted the reliability of a portion of data from studies MYL-1401H-1001 and MYL-1401H-1002 (BLA 761075). The finding (b) (4) appears to be isolated in nature because it did not impact the reliability of study (b) (4) and other studies of similar analytical methodology conducted at (b) (4).

I recommend that the (b) (4) stability assessments from method validation study (b) (4) associated with studies MYL-1401H-1001 and MYL-1401H-1002 not be accepted for Agency review until the firm demonstrates the stability of MYL-1401H in pre-dose NC matrix. The firm conveyed plans to repeat the stability assessments and report results (b) (4). The review division should evaluate the stability results prior to accepting the analytical data for further review.

(b) (4)

(b) (4)

(b) (4)

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Analytical Site:

VAI: (b) (4)

FEI#: (b) (4)

CC:

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

OPQ/OBP/DBRRIII/Rosenberg/Verthelyi/Bowen

Draft: GM 07/21/2017; 07/27/2017

Edits: RCA 07/24/2017, 07/25/2017; AD 7/25/2017

ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881051c61>

OSIS File #: (b) (4)

FACTS: (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
07/31/2017

RUBEN C AYALA
07/31/2017

ARINDAM DASGUPTA
07/31/2017

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

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

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

Date of This Review:	July 28, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761075
Product Name and Strength:	Fulphila (pegfilgrastim-jmdb) Injection 6 mg/0.6 mL
Total Product Strength:	6 mg/ 0.6 mL
Product Type:	Drug-Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan GmbH
Panorama #:	2017-1123
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
OMEPRM Deputy Director (Acting):	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761075.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Mylan's Fulphila product is necessary to distinguish this proposed product from the Neulasta (pegfilgrastim). As explained in FDA's Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name for Fulphila include a distinguishing suffix that will facilitate safe use and optimal pharmacovigilance.

Mylan was notified of the Agency's intention to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an advice letter^a.

1. pegfilgrastim-jmdb

FDA generated a four-letter suffix, -jmdb. This suffix was evaluated against the criteria described in the guidance^b.

We determined that the FDA-generated suffix -jmdb, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, and does not make any misrepresentations with respect to safety or efficacy of this product.

These findings were shared with the TBBS, ORP, OCC and OPDP. In email correspondence dated July 26, 2017, the workgroup concurred with DMEPA's assessment and conclusion.

5. CONCLUSIONS

We find the suffix -jmdb acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to pegfilgrastim-jmdb.

6. COMMENTS TO THE APPLICANT

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

^a Merchant, L. Advice letter for BLA 761075. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 March 23.

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

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/s/

NICOLE B GARRISON
07/28/2017

LUBNA A MERCHANT
07/28/2017

MEMORANDUM

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

DATE: July 27, 2017

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

AND

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

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

THROUGH: Seongeun (Julia) Cho
Director
Division of Generic/New Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Analytical inspection at [REDACTED] (b) (4)
[REDACTED] covering BLA 761075

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of studies 8308-902, 8308-482, 8331-647 and 8329-463 (BLA 761075) conducted at [REDACTED] (b) (4)
[REDACTED].

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

Based upon the results of this inspection, I recommend that bioanalytical data from all inspected studies be accepted for Agency review, but with several considerations. Details are included in the Recommendation section below.

Inspected Studies:

BLA 761075

Study Number: MYL-1401H-1001

([REDACTED] (b) (4) **Studies 8308-902 and 8308-482)**

Study Title: "Single center, randomized, double-blind, 3-period, 3-treatments, 3-way crossover pharmacokinetics (PK)/pharmacodynamics (PD) trial to assess PK, PD, safety and tolerability of MYL-1401H after single subcutaneous injection at one dose level (2 mg) comparing to an European Union (EU) and United States (US) marketed drug product (Neulasta®) in healthy volunteers"

Dates of conduct: 02/09/15-03/01/16

Study Number: MYL-1401H-1002

([REDACTED] (b) (4) **Studies 8331-647 and 8329-463)**

Study Title: "Single center, randomized, open-label, parallel trial to compare immunogenicity, safety, and tolerability of MYL-1401H and US-licensed pegfilgrastim (Neulasta®) after two subcutaneous (sc) injections at one dose level (6 mg) in healthy subjects"

Dates of conduct: 10/09/15-12/22/15

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

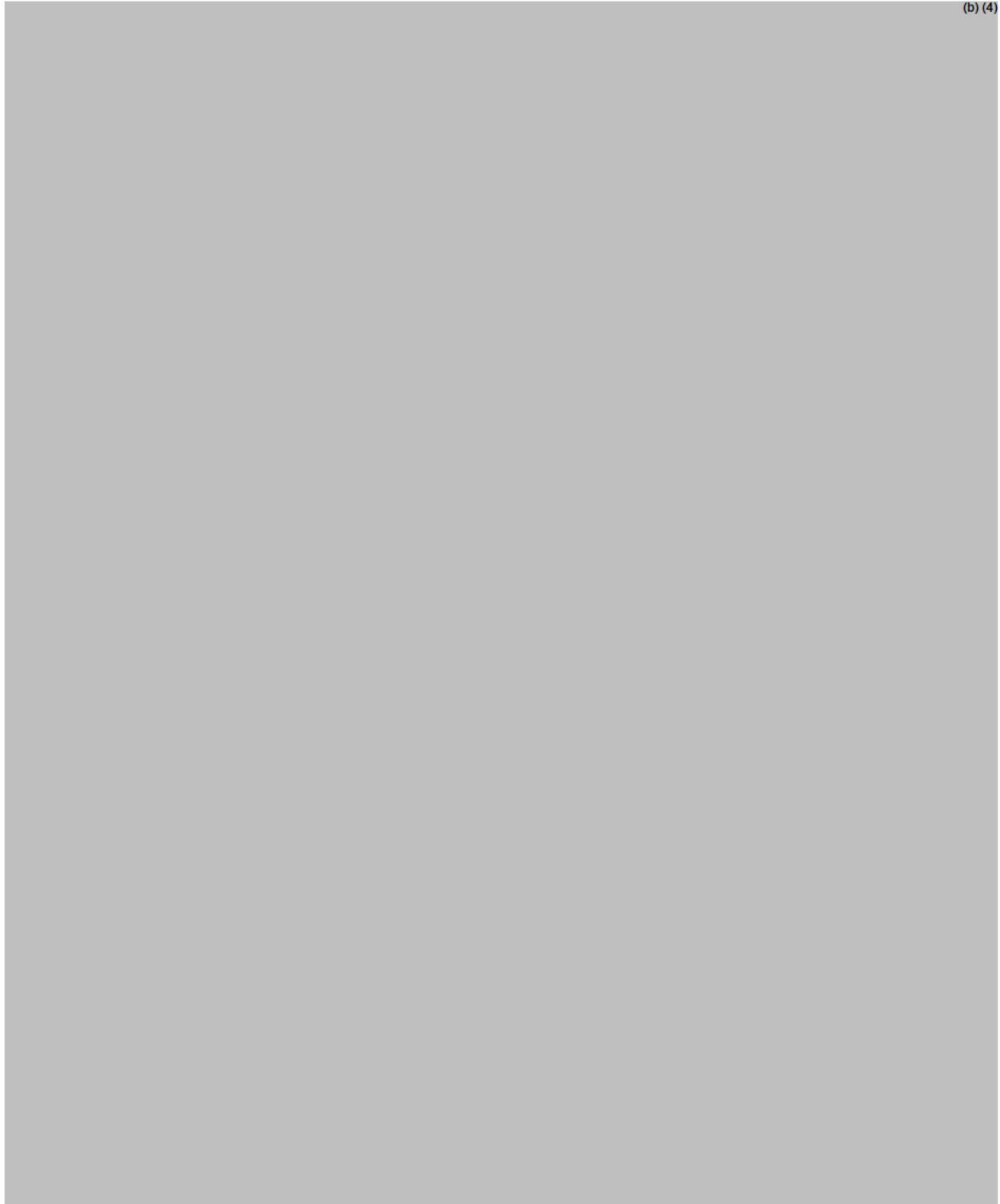
I, OSIS scientist, Xiaohan Cai, Ph.D., audited the analytical portions (PK and ADA) of the above studies at [REDACTED] (b) (4) [REDACTED] (b) (4) from [REDACTED] (b) (4) and from [REDACTED] (b) (4).

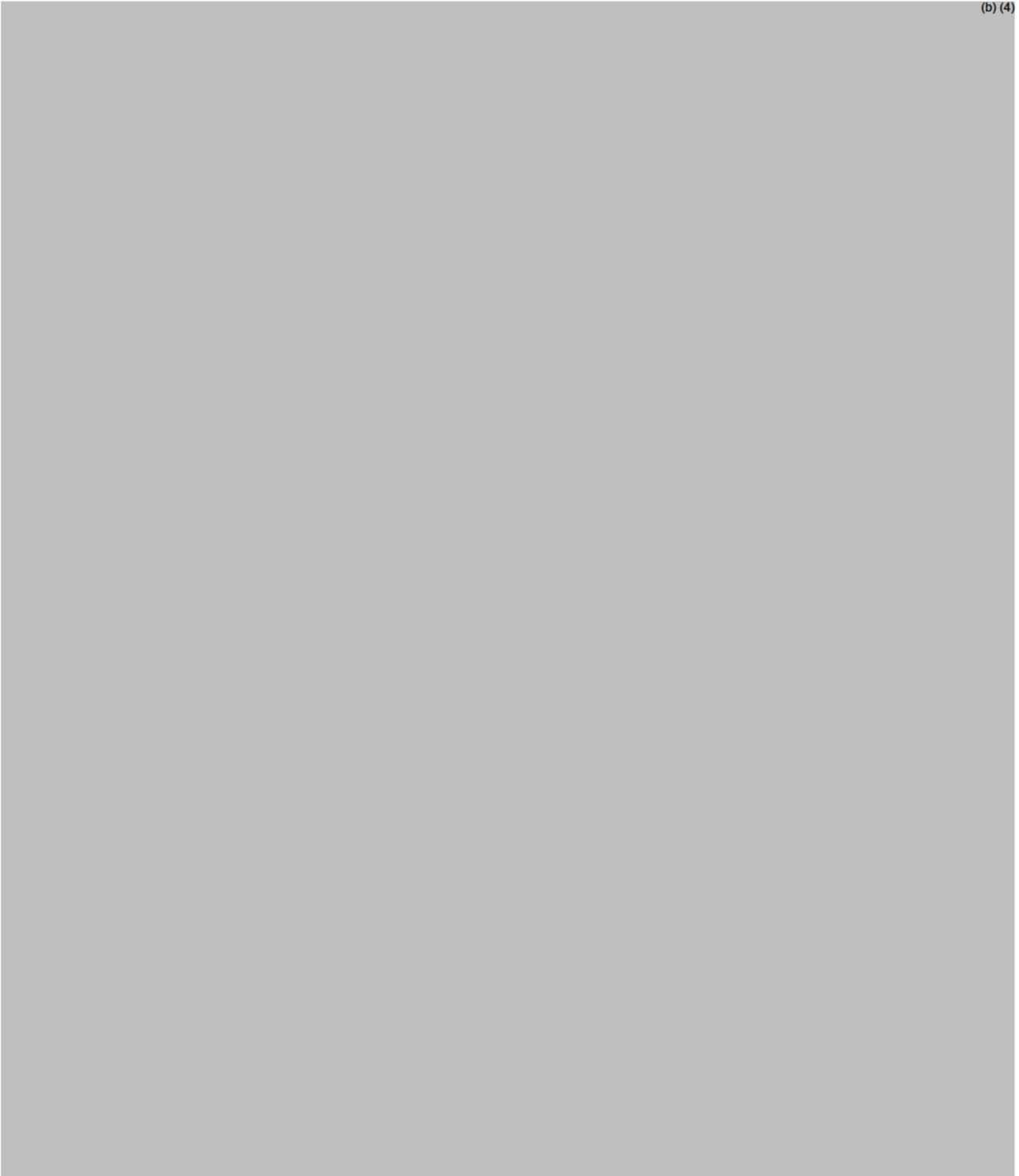
The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the conclusion of the inspection, I observed an objectionable finding and Form FDA 483 was issued to the analytical site. I also discussed additional items during the inspection and at the closing meeting. The Form FDA 483 observation (**Attachment 1**),

discussion items, the firm's response dated [REDACTED] (b) (4)
(Attachment 2), and my evaluation are presented below.

OBSERVATION 1:





Conclusion:

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

After reviewing the inspectional findings and the firm's response to Form FDA 483, I recommend accepting the PK and ADA data from the audited studies for further review. However, the review division should consider the following:

- For study 8308-902, the review division should consider the updated data in the amendment, which is to be submitted by July 31, 2017.
- When re-assessing the confirmatory assay results with 1% false positive rate, additional 12 and 10 samples for studies 8308-902 and 8331-647, respectively, were confirmed positive. The characterization or neutralizing activities of these samples were not further assessed.

Xiaohan Cai, Ph.D.
Visiting Associate

Final Classification:

VAI- [REDACTED] (b) (4)
FEI#: [REDACTED] (b) (4)

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

Draft: XHC 07/13/2017, 07/24/2017
Edit: YMC 7/19/2017, JC 7/20/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/[REDACTED] (b) (4)
[REDACTED] /BLA 761075_MYL-1401H Biosimilar to Neulasta

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

FACTS: [REDACTED] (b) (4)

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/s/

XIAOHAN CAI
07/27/2017

YOUNG M CHOI
07/27/2017

SEONGEUN CHO
07/27/2017

MEMORANDUM

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

DATE: June 23, 2017

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

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

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

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

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies [REDACTED] (b) (4) MYL-1401H-1001 (BLA 761075), and MYL-1401H-1002 (BLA 761075) conducted at [REDACTED] (b) (4).

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

Significant objectionable findings were observed during this inspection that impacted the reliability of a portion of the audited studies. Specifically, [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

1401H-1001 and MYL-1401H-1002. Thus, I recommend that analytical data from these studies not be accepted for Agency review. The Agency should request that these stability assessments be repeated [REDACTED].

(b) (4)

(b) (4)

Inspected Studies:

(b) (4)

BLA 761075

Study Number: MYL-1401H-1001

Study Title: "Analysis of normal human serum samples using a cell based assay for the detection of neutralizing antibodies against MYL-1401H and Neulasta[®] (US and/or EU) to support phase I clinical study MYL1401H-1001."

Dates of conduct: April 5-September 14, 2016

Study Number: MYL-1401H-1002

Study Title: "Analysis of normal human serum samples using a cell based assay for the detection of neutralizing antibodies against MYL-1401H and Neulasta® US to support phase I clinical study MYL1401H-1002."

Dates of conduct: April 6-September 23, 2016

OSIS Pharmacologist Gajendiran Mahadevan, Ph.D. audited the analytical portion of the above studies at [REDACTED] (b) (4)

[REDACTED] from [REDACTED] (b) (4) .

I thoroughly audited the study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff. As a part of surveillance approach, several key study components that best represent the firm's bioanalytical operations were selected and audited across multiple studies conducted at [REDACTED] (b) (4) .

At the conclusion of the inspection, I observed objectionable findings and issued Form FDA 483 to [REDACTED] (b) (4) (**Attachment-1**). The firm's response to Form FDA 483 is pending. This review will be amended after we receive and evaluate the firm's response to Form FDA 483.

The Form FDA 483 observations and my evaluation follows.

Observation 1

[REDACTED] (b) (4)

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[REDACTED]

(b) (4)

Conclusion:

After reviewing the inspectional findings, there was evidence that significant deficiencies impacted the reliability of a portion of data from studies MYL-1401H-1001 and MYL-1401H-1002 (BLA 761075). [REDACTED]

(b) (4)

I recommend that the [REDACTED] stability assessments from method validation study [REDACTED] associated with studies MYL-1401H-1001 and MYL-1401H-1002 not be accepted for Agency review. The Agency should request that these stability assessments be repeated [REDACTED]

(b) (4)

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Analytical Site:

VAI: [REDACTED] (b) (4)

FEI#: [REDACTED] (b) (4)

cc:

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

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ARINDAM DASGUPTA
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