

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761111Orig1s000

OTHER REVIEW(S)



**DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES**

Date	4/6/2020		
To:	MICHAEL GWATHMEY		
Requesting Center/Office	CDER/OND	Clinical Review Division	NA
From	Gang Peng OPEQ/OHT3/DHT3C		
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR: ICCR-Prod-53450 ICC: ICC1901082 Submission: BLA761111 Sponsor: Hospira Inc., A Pfizer Company Drug/Biologic: Pegfilgrastim(drug)/NYVEPRIA(trade), proposed biosimilar to Neulasta® (pegfilgrastim) Indications for Use: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia		
Recommendation	<p>Final Recommendation:</p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable.</p> <p><input checked="" type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments,</p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies</p> <p>Comments to Review Team:</p> <p>Approvable with firm’s post market commitment of including lot release testing for safety activation force.</p> <p>PMC/PMR or CR Deficiencies:</p> <p>You provided a response to IR 3 in the document titled resp-to-fda-ir-13-feb-2020-qqr3. The existing control strategy in the response is inadequate because it does not contain lot release testing for the needle safety activation force specification. Without an adequate control strategy, you cannot ensure that produced lots will conform to the specification for needle safety activation force. Without conformance to the needle safety activation force specification, users may experience issues deploying the safety feature. Include lot release testing for needle safety activation force as part of you Post Market Commitment.</p>		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)
Gang Peng -S Digitally signed by Gang Peng -S Date: 2020.04.06 16:19:16 -04'00'	Rumi Young -S Rumi Young -S c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rumi Young -S, 0.9.2342.19200300.100.1.1=2002467918 2020.04.07 11:52:54 -04'00'	

1. PURPOSE

This review provides an assessment of the syringe device constituent part of the prefilled syringe product. Note that this review is for biosimilar to Neulasta.

This review will cover the following review areas:

- Device performance
- Stability – device performance on stability
- Essential Performance Requirements (EPR) Control strategy

CDRH Quality Systems Assessment / Facilities consult not required

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential¹) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

2.1. Picture of Final Device Presentation

From pharmaceutical dev container closure

The PF-06881894 prefilled syringe (PFS) is a 0.6ml single-dose, ready-to-use syringe for the administration of the medication to a patient. It is supplied in one dose strength containing 0.6 mg/0.6 mL.

The container closure system that is in direct contact with PF-06881894 drug product (DP) solution for the duration of the shelf life consists of the following components:

- The (b) (4) syringe assembly comprised of (b) (4) glass 1 mL long syringe with 27-gauge ½ inch staked stainless steel needle and a (b) (4) Rigid Needle Shield (RNS). The RNS is (b) (4) assembled to an elastomer needle shield (b) (4)
- The (b) (4) 1 mL Long (b) (4) plunger stopper (b) (4) and supplied by (b) (4). The (b) (4) plunger stopper is a (b) (4) elastomeric stopper (b) (4)

All of the syringe components and device constituents of the PF-06881894 PFS are off-the-shelf, ready-to-use (RTU) on-market commodities (b) (4) syringes and plunger stoppers are provided sterile, clean, and ready-to-use from the supplier, and no additional component preparation activities are required prior to the DP filling process.

¹ Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

2.2. Design Requirements

Syringe Description

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Professional use, contraindications include: allergic reaction to pegfilgrastim/filgrastim
Injection Site	Upper arm, stomach, buttocks, thigh
Injection tissue and depth of injection	Subcutaneous
Needle connection (e.g. luer, slip tip, staked)	staked
Syringe Volume	1mL
Delivered Dose Volume	0.6mL(0.6mg)

Additional Devices

Requirement	Describe
Hypodermic Needle: (length, gauge)	27-gauge ½ inch
Safety Features (e.g. Needle safety component/device)	Rigid need shield, spring activated to retract needle after activation

From “2.3.R.2 Device” document:

Table 2.3.R.2-1. Comparison of Neulasta and PF-06881894 PFS Components

Syringe Components	Neulasta PFS	PF-06881894 PFS
Prefillable Syringe	1mL Long glass syringe with a staked needle	
Needle Gauge	27-gauge	
Needle Length	½ inch	
Needle Cover (Cap)	Needle Cap – is made with dry natural rubber (derivative of latex)	Needle Cover – is not made with dry natural rubber
Plunger Stopper	Unknown	1 mL long Formulation ^{(b) (4)}
Dosage Strength and Volume	6 mg / 0.6 mL	
Needle Guard Type	Active Needle Guard - must be proactively and manually activated by the user.	BD UltraSafe Passive PLUS Needle Guard - gets automatically activated once the full contents of the PFS have been ejected.
Needle Guard Color	Blue	Clear
Plunger Rod Type	Small thumb button	Large thumb button
Plunger Rod Color	Blue	White
Syringe Label	The syringe label does not bear any graduation marks.	
Syringe Carton	Syringe tray (blister pack) containing 1 prefilled syringe	Syringe (inner) carton containing 1 prefilled syringe
Packaging Configuration	1-pack carton containing: a syringe tray (blister pack) with a prefilled syringe a package insert with Prescribing Information and Instructions for Use (IFU)	1-pack shelf (outer) carton containing: an inner syringe carton with a prefilled syringe a package insert with Prescribing Information and Instructions for Use (IFU)

Reviewer Comments

Both Neulasta and PF-06881894 PFS configurations include a 1 mL Long glass syringe with a 27-gauge ½ inch staked needle and a needle cover, and are assembled with a plunger rod and a needle guard (safety device). Both syringes are designed to deliver the entire contents(0.6mL) of the syringe and have identical needle length.

3. DEVICE PERFORMANCE REVIEW

Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Stability Module 3.2.P.8 (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	^{(b) (4)}	Y	Y	Y	Y
Break loose		Y	Y	Y	Y
Glide Force/Extrusion Force		Y	Y	Y	Y
Cap Removal Force		Y	Y	Y	Y

Needle Safety Device Performance	(b) (4)	Y	Y	Y	Y
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Table 3.2.R.2.3-3. Design Verification Testing Plan at Real-Time and Accelerated Time Points

Test	Real-Time		Accelerated Aging	
	T=0	T=3 (36 months)	T=1 (169 days equivalent to 18 months RT)	T=2 (337 days equivalent to 36 months RT)
Pre-Test Inspection	X	X	X	X
Break Loose Force	X	X	X	X
Extrusion Force	X	X	X	X
System Breach	X	X	X	X
Air Leakage	X	X	X	X
Plunger Rod Separation	X	X	X	X
Plunger Movement under Gravity	X	X	X	X
Axial Overload	X ^a	X ^a	X ^a	X
Label Adhesion	X	X	X	X
Printing Robustness	X	X	X	X
Needle Extraction Force	X	X	X	X
Needle Cover Removal Force	X ^a	X ^a	X ^a	X
Safety Device Override Force	X ^a	X ^a	X ^a	X
Safety Device Trigger Force	X ^a	X ^a	X ^a	X
Safety Device Activation Force	X ^a	X ^a	X ^a	X
Deliverable Volume ^b	X	X	X	X
Deadspace Volume ^b	X	X	X	X
Needle Corrosion ^c	X	NP	NP	NP
Foil Penetration Force ^e	X	NP	NP	NP
Syringe Removal Force	X ^a	X ^a	X ^a	X
Packaging Integrity Inspection ^d	X	X	NP	X

Table 3.2.R.2.3-4. Design Verification Sample Size Summary

Test	Type	Severity of Harm	Confidence %	Reliability %	Sample Size	
					Real-Time Aging	Accelerated Aging
Pre-Test Inspection	Attribute	5	90	99.6	575	60
Break Loose Force	Variable	3	90	99	50	50
Extrusion Force	Variable	3	90	99	50	50
System Breach	Attribute	5	90	99.6	575	60
Air Leakage	Attribute	5	90	99.6	575	60
Plunger Rod Separation	Attribute	3	90	99	230	60
Plunger Movement under Gravity	Attribute	5	90	99.6	575	60
Axial Overload	Attribute	3	90	99	230	60
Label Adhesion	Attribute	5	90	99.6	575	60
Printing Robustness	Attribute	5	90	99.6	575	60
Needle Extraction Force	Variable	3	90	99	50	50
Needle Cover Removal Force	Variable	5	90	99.6	50	50
Safety Device Override Force	Variable	5	90	99.6	50	50
Safety Device Trigger Force	Variable	3	90	99	50	50
Safety Device Activation Force	Variable	3	90	99	50	50
Deliverable Volume	Variable	2	90	97.5	50	50
Deadspace Volume	Variable	3	90	99	50	50
Needle Corrosion	Variable	5	90	99.6	3 ^a	NA
Foil Penetration Force	Variable	3	90	99	50	NA
Syringe Removal Force	Variable	2	90	97.5	50	50
Packaging Integrity Inspection	Variable	NA ^b	NA ^b	NA ^b	193 ^b	60

Reviewer Comments

The firm has provided device performance and validation. Note that the values specified for extrusion/glide force and cap removal forces are higher than those we typically recommend. For reference, recommended values for PFS: break loose force 25N, glide force 20N and cap removal force 35N. IR 1

In addition, the firm cites a confidence level of 90% for the sample size in design verification. Per ISO 11608-1, the appropriate confidence level for assessment is 95%. I will ask for justification for the confidence level based on the indication of the device. IR 2

Firm Response

IR1

The needle cover removal force upper specification limit of (b) (4) was established based on the supplier (b) (4) quality specification for (b) (4) 1 mL long syringes. The firm provided the following support:

- A study is provided on pinch strength of left handed older females showing healthy female adults in the 65-69 age range have a left-handed tip pinch strength of 46.7 N (Mathiowetz, 1985).
- A Government Consumer Safety Research for Strength Data survey (2000) measured that a left-handed chuck pinch and pulp pinch pull force on a 2 mm strip for females in the age range of 61-70 years is 44.88 N and 44.93 N, respectively.
- the needle cover removal force upper specification limit of (b) (4) has been established for a commercialized biosimilar prefilled syringe product Nivestym™ (filgrastim-aafi, BLA 761080), (b) (4). The Nivestym PFS was launched in the US market in September 2018. Analysis of the US complaint data (from September 2018 through 14 February 2020) for the Nivestym PFS shows there were zero (0) complaints related to a syringe needle cover that was difficult to remove. Since launch, there have been (b) (4) Nivestym PFS syringes shipped from the Hospira Zagreb, Croatia manufacturing site to the US market.

IR2

Tables 3.2.R.2.3-4 and 3.2.R.2.3-5 of Section 3.2.R.2.3 Device – Design Verification were updated to reflect the re-analysis of the testing data for break loose/glide force, dose accuracy, syringe removal force, safety override force, safety activation force, safety trigger force, needle extraction force, and needle cover removal force with a 95% confidence limit. The re-analyzed data met the pre-determined acceptance criteria.

Table 3.2.R.2.3-4. Design Verification Sample Size Summary

Test	Type	Severity of Harm	Confidence %	Reliability %	Sample Size	
					Real-Time Aging	Accelerated Aging
Pre-Test Inspection	Attribute	5	90	99.6	575	60
Break Loose Force	Variable	3	95 ^a	99	50	50
Extrusion Force	Variable	3	95 ^a	99	50	50
System Breach	Attribute	5	90	99.6	575	60
Air Leakage	Attribute	5	90	99.6	575	60
Plunger Rod Separation	Attribute	2	90	97.5	230	60
Plunger Movement under Gravity	Attribute	5	90	99.6	575	60
Axial Overload	Attribute	2	90	99	230	60
Label Adhesion	Attribute	5	90	99.6	575	60
Printing Robustness	Attribute	5	90	99.6	575	60
Needle Extraction Force	Variable	2	95 ^a	97.5	50	50
Needle Cover Removal Force	Variable	5	95 ^a	99.6	50	50
Safety Device Override Force	Variable	5	95 ^a	99.6	50	50
Safety Device Trigger Force	Variable	5	95 ^a	99.6	50	50
Safety Device Activation Force	Variable	2	95 ^a	97.5	50	50
Deliverable Volume	Variable	3	95 ^a	99	50	50
Deadspace Volume	Variable	3	95 ^a	99	50	50
Needle Corrosion	Variable	5	90	99.6	3 ^b	NA
Foil Penetration Force	Variable	2	90	97.5	50	NA
Syringe Removal Force	Variable	2	95 ^a	97.5	50	50
Packaging Integrity Inspection	Variable	NA ^c	NA ^c	NA ^c	193 ^c	60

Reviewer Comment

IR1

IR1 has been resolved internally. While the justification provided by the firm is inadequate, it was decided that the specification is acceptable as there is end user is not a physically impaired group which would have issues with the (b) (4)

specification. Furthermore, the specification has a high level of validation. Based on the above, CDRH has resolved that the (b) (4) specification, while not ideal, is acceptable.

IR2

The firm has updated the evaluation on the requested PFS characteristics with a 95% confidence interval. The reanalyzed data still meets the acceptance criteria.

4. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or <u>release testing activities</u> :	Acceptable (Y/N/NA)
Dose Accuracy	(b) (4)	Y
Break loose Force		Y
Glide Force		Y
Needle safety activation force		N

Reviewer Comments

The control strategy is inadequate, the firm will perform release testing and stability testing to ensure that the EPRs of the product are within specifications. However, needle safety activation force is missing from the control strategy. IR3

Firm Response 2/28/2020

IR 3

Please note that “needle safety activation force” corresponds to the “safety device trigger force” (DI-PFS-91) throughout the Sponsor’s documentation. The safety device trigger force evaluation demonstrates that the syringe system meets the acceptable levels of the axial force to trigger the safety device activation, in accordance with ISO 23908:2011 (E), Clause 4.2.

Table 1. Control Strategy Summary for Safety Device of PF-06881894 PFS

Control Description	Reference
<i>Routine Controls</i>	
<div style="background-color: #cccccc; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>	3.2.P.7 Container Closure System 3.2.P.7 Safety Device Certificate of Conformance
	As per site procedures
	3.2.R.2.3 Device – Design Verification ^a Safety Device Trigger Force: DHF-PFS-12-001-0199 ^a (T=0 and T=1) INX100328163 ^a (T=2) Pre-Test Inspection INX100322043 VR02048/2

a. The referenced 3.2.R.2.3 Device – Design Verification section and safety device trigger reports were updated to reflect the 95% confidence limit, per the Agency’s Request for Information dated 13 Feb 2020 (Question #2).

Reviewer Comment

IR 3

The firm clarified that safety activation force and safety device trigger force are used interchangeably. However, the firm did not provide an adequate control strategy. The provided control strategy includes the following:

(b) (4)

The firm has not provided a control strategy which demonstrates that devices produced will meet the specification for safety activation force.

Firm Response 3/16/2020

IR3

The firm provides additional data to support why the existing control strategy for needle safety activation force is adequate, including:

T0 Analysis

The firm evaluated the specification across multiple lots at T0 as part of design verification. They state that the use of multiple lots in this analysis accounts for lot to lot variability.

Design verification analysis

The firm evaluated the specification on multiple lots at real time and accelerated aging.

Process capability analysis

The firm leverages the package qualification test results from Nivestym PFS. The firm states that the Nivestym has the same properties as the subject drug and is packaged by the same manufacturer (b) (4). The firm states that the process capability index (cpk) of the process is (b) (4) thus indicating that there is a high degree of assurance of producing conforming product.

Reviewer Comment

IR 3

The firm has not revised the control strategy. The additional information provided does not demonstrate that future product lots manufactured will meet the specification for safety activation force. The firm is recommended to include the specification in the lot release test.

Firm Response 4/2/2020 LCM

The firm stated during the LCM that they will add lot release testing for the safety activation force specification. However, due to the timeline, they will be including this as part of the post market commitment (PMC).

Reviewer Comment

The response is adequate. The firm has committed to including lot release testing for safety activation force.

IR

1. You have provided device performance specification of (b) (4) for cap removal force. The values specified appear to be too high. If the cap removal force is too high, then a user would not be capable of removing the cap. Provide anthropometric data validating the cap removal force specification.
2. In Table 3.2.R.2.3-4 Design Verification Sample Size Summary, you have provided the confidence and reliability level for testing performed, citing a 90% confidence. A 90% confidence level is not appropriate for verification of the pre-filled syringe performance and is inconsistent with applicable standards (ISO 11608-1 Needle-based injection systems for medical use – Requirements and test methods Part 1: Needle-based injection systems) and guidances (Medical Devices with Sharps Injury Prevention Features) that recommend a 95% confidence limit. Re-analyze your data for break loose/glide force, dose accuracy, syringe removal force, safety override force, safety activation force, safety trigger force, needle extraction force, and needle cover removal force assuming a 95% confidence limit and provide updated reports.
3. You have provided control strategy for deliverable volume, break loose and glide force in the 3.2.P.2.3 Manufacturing Process Development Control Strategy document. You have not included a description of the control strategy for needle safety activation force. A control strategy should be provided for needle safety activation force in order to demonstrate that the feature of the device will perform as intended and that the patient will not experience incomplete injections. Note that needle safety activation force should be assessed on the final finished device. Provide a control strategy for the needle safety activation force of the device.

Follow up IR 3

In the document titled “resp-to-fda-ir-13-feb-2020-qqr3”, you provided a response describing the control strategy for the needle safety activation force. The control strategy includes (b) (4). The provided control strategy is inadequate. The control strategy proposed is not sufficient to ensure that the manufactured product meets the specification for needle safety activation force, which is influenced by interactions between the device constituents (plunger rod and safety device) and syringe (i.e., gliding forces). Update your lot release testing to include needle safety activation force testing.

<<END OF REVIEW>>

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

/s/

MICHAEL V GWATHMEY
06/25/2020 05:14:32 PM

351(k) BLA IMMUNOGENICITY ASSAYS ASSESSMENT

Application Type	BLA
Application Number	761111 STN 0001
Submit Date	June 10, 2019
Received Date	June 10, 2019
BsUFA Goal Date	June 10, 2020
Division/Office	DBRR3/OBP
Assessment Completion/Revision Date	4/16/2020
Product Code Name	PF-06881894 (pefilgrastim, company code)
Proposed Nonproprietary Name¹	Pegfilgrastim
Proposed Proprietary Name¹	Nyvepria
Pharmacologic Class	Colony stimulating factor
Applicant	Pfizer
Applicant Proposed Indication(s)	Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Recommended Regulatory Action	Approval

Immunogenicity Assessors

Primary Assessor(s)	Xu Di, Ph. D. and Susan Kirshner Ph.D.
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¹ The proposed nonproprietary and proprietary names are conditionally accepted until such time that the application is approved.

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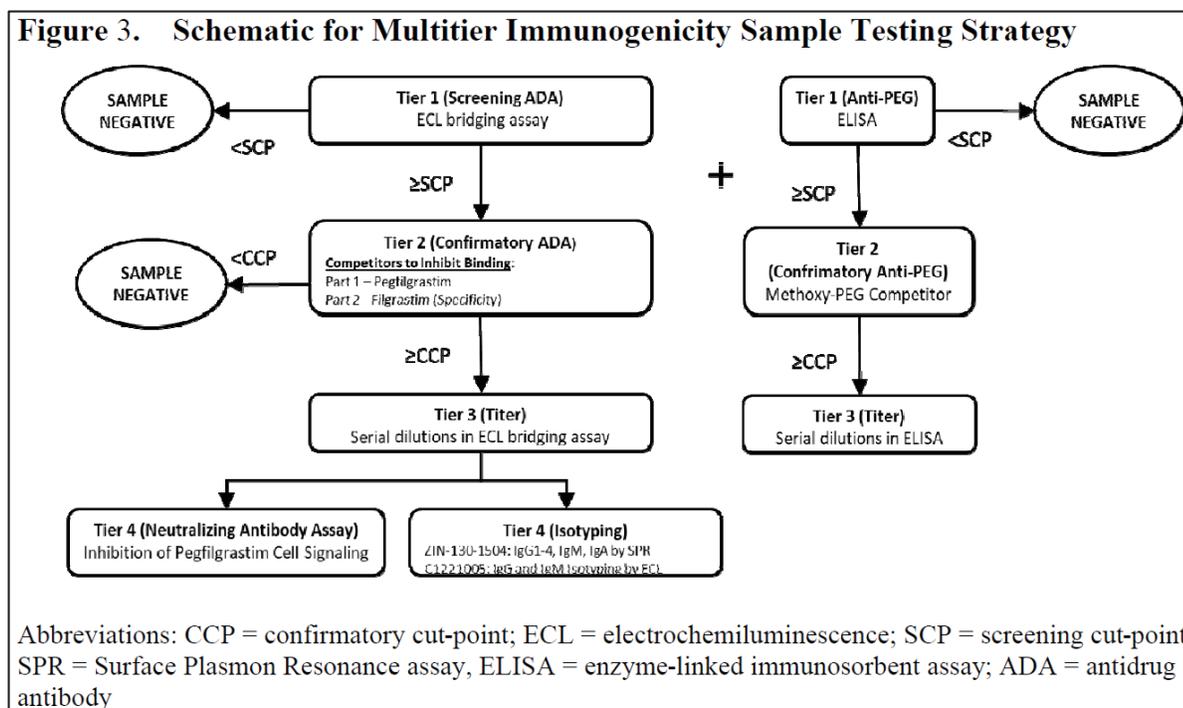
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1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary and Recommendation

The Applicant developed assays to detect anti-drug antibodies (ADA) that recognize pegfilgrastim and PEG, neutralize pegfilgrastim activity in a cell-based potency assay, and characterize ADA isotype. A standard tier-based testing strategy was used as depicted below in the Applicant's Figure 3. Assay validations were initially performed with serum from healthy subjects. For Study C1221002 (ZIN-130-1504), which was performed in patients with breast cancer, the initial assay validation was supplemented with studies using purchased serum from patients with breast cancer and in-study pre-dose samples from patients with breast cancer. The tiered testing strategy and assay development and validation are consistent with recommendations in FDA Guidance for Industry FDA Guidance for Industry Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection (2019). All the assays are acceptable.

The testing strategy of the immunogenicity assays is provided in the Applicant's Figure 3 below.



Immunogenicity Assay Summary Table

Assessor Table 1: Summary of immunogenicity assays used in supportive clinical studies.

Clinical Study	C1221001 (ZIN-130-1505): an open-label, randomized, single-dose, three-way crossover comparative PK/PD in health subjects. PF-06881894: 6mg US-licensed Neulasta: 6 mg EU-approved Neulasta: 6 mg	C1221005: an open-label, randomized, parallel design no-inferiority, comparative immunogenicity study in healthy volunteers. PF-06881894: 6mg x 2 doses US-licensed Neulasta: 6mg x 2 doses	C1221002 (ZIN-130-1504): an open-label, single/multi-dose, open label, non-comparative Phase1/2 PK/PD and safety (including immunogenicity) studies in breast cancer patients (non-integral to biosimilarity). PF-06881894: 3 or 6 single-dose, or 3 and 6 mg for multi-doses
ADA assay ECL based ELISA pegfilgrastim/ sulfa Tag- pegfilgrastim In house PC: human anti-PF- 0688194 polyclonal Ab	<p>Screening Sensitivity: 9.1 ng/mL Drug tolerance: 100 ng/ml tolerates up to 100 ug/mL drug</p> <p>Confirmatory Sensitivity: same Drug tolerance: same</p> <p>Titer Sensitivity: same Drug tolerance: same</p> <p>Validation performed with serum from healthy subjects. Antigenic equivalence is acceptable. Performance of all the assays is acceptable.</p> <p>.</p>	<p>Screening Sensitivity: 2.8 ng/mL Drug tolerance: 14.4 ng/ml tolerates up to 1 ug/mL drug</p> <p>Confirmatory Sensitivity: 8.9 ng/mL Drug tolerance: 14.4 ng/mL</p> <p>Titer Sensitivity: same Drug tolerance: same</p> <p>Aspects of assay performance were evaluated with commercial serum samples from patients with cancer and in-study pre-dose serum samples.* Antigenic equivalence is acceptable. Performance of all the assays is acceptable.</p>	
ADA assay (anti-PEG): Colorometric based sandwich ELISA. PC: Commercially sourced human serum PC pool Commercially sourced monoclonal anti-mPEG	<p>Screening Sensitivity: 41.9 ng/mL Drug tolerance: LPC pool 1:4 tolerates up to 100 ug/mL mPEG 200 ng/ml Mab tolerates up to 100 ug/mL PF-06881894</p> <p>Confirmatory Sensitivity: same Drug tolerance: same</p> <p>Titer Sensitivity: same</p>	<p>Screening Sensitivity: 1:17.8 dilution Drug tolerance: LPC pool tolerates up to 100 ug/mL mPEG</p> <p>Confirmatory Sensitivity: 1:6.88 dilution Drug tolerance: same</p> <p>Titer Sensitivity: same</p>	

	<p>Drug tolerance same</p> <p>Validation performed with serum from healthy subjects. Antigenic equivalence is acceptable. Performance of all the assays is acceptable.</p>	<p>Drug tolerance: same</p> <p>Aspects of assay performance were evaluated with in-study pre-dose serum samples. Antigenic equivalence is acceptable. Performance of all the assays is acceptable.</p>
<p>NAb assay Cell-based luciferase reporter ELISA assay In house PC: human anti-anti-PF-06881894 polyclonal Ab</p>	<p>Screening Sensitivity: 4.2 ug/ml Drug tolerance: 4 ug/mL tolerates up to 10 ng/mL PF-06881894 or Neulasta</p> <p>Validation performed with serum from healthy subjects. Antigenic equivalence is acceptable. Performance of all the assays is acceptable.</p>	<p>Screening** Sensitivity: 2.64 ug/mL when stimulated with PF-06881894 3.3 ug/mL when stimulated with Neulasta Drug tolerance: 3.34 ng/mL tolerates up to 6.2 ng/mL pf-06881894 or 18.5 ng/mL Neulasta</p> <p>Aspects of assay performance were evaluated with in-study pre-dose serum samples. Antigenic equivalence is acceptable. Performance of all the assays is acceptable.</p>

* Only results from studies with in-study samples are provided in this table. Results from all studies are summarized in the tables below.

** Sensitivity and drug tolerance are evaluated using 2-fold titration curves. Differences less than a 4-fold dilution are considered to be within the error of the assay and are not significant.

PC: positive control

1.2 Deficiencies and Other Recommended Comments to Applicant

None.

Assessment

Document Reviewed Report number	Report Issued Date	Title	Method number
181683	4/23/2015	The Detection of Anti-HSP-130 Antibodies in Human Serum by Electrochemiluminescent Assay (ECLA)	Mo8.anti-HSP-130.huse.1
181685	11/12/2015	The Detection of Anti-PEG Antibodies in Human Serum by Enzyme Linked Immunosorbent Assay (ELISA)	M08.anti-PEG.huse.1
183265	2/24/2016	The Detection of Anti-HSP-130 Antibodies in Human Serum by Electrochemiluminescent Assay (ECLA)	M08.anti-HSP-130.huse.1
184335	7/20/2016	The Detection of Anti-HSP-130 Antibodies in Human Serum by Electrochemiluminescent Assay (ECLA)	M08.anti-HSP-130.huse.1
186288	3/28/2018	The Detection of Anti-HSP-130 Antibodies in Human Serum by Electrochemiluminescent Assay (ECLA)	M08.anti-HSP-130.huse.1
186410 (Pfizer C1227001)	12/11/2018	Addendum 2 to the Report Entitled: "Validation Report for the Detection of Anti-HSP-130 Antibodies in Human Serum by a Bridging Electrochemiluminescent Assay (ECLA), (b) (4) Job Number 181683."	M08.anti-HSP-130.huse.1, Rev. 11
186408 (Pfizer C1227002)	1/14/2019	Addendum 1 to the Report Entitled: "Validation Report for the Detection of Anti-Peg Antibodies in Human Serum by a Direct Binding Immunoassay Using an Enzyme Linked Immunosorbent Assay (ELISA) (b) (4) Job Number 181685." A Partial Validation of an ELISA Method for the determination of anti-PEG in Human Serum	M08.anti-PEG.huse.1, Rev. 13
C1227003	6/2/2019	Partial Validation of a NAb Assay for Determination of Neutralizing anti-PF-06881894 (anti-Pegfilgrastim) Antibodies in Human Serum	(b) (4) -HS-2015-01
186958 (Pfizer C1227004)	2/1/2019	Qualification Report for the Detection of Anti-PF-06881894 (Anti-HSP-130) IgG and IgM Antibody Isotypes in Human Serum by a Bridging Electrochemiluminescent Assay (ECLA), (b) (4) Job Number 186958	M08.anti-HSP-130.huse.2, Rev. New
(b) (4) 16-074-021-REP	8/7/2017	Partial Validation of a Cellular Assay for the Detection of Neutralizing Antibodies against Filgrastim in Human Serum	(b) (4) HS-2015-01
(b) (4) -HS-2015-B-06-11	9/22/2015	Validation of a cellular assay for the detection of neutralizing antibodies against HSP-130 in human serum	(b) (4) HS-2015-01
(b) (4) -HS-2015-06	5/20/2015	Validation Report ADA immunoglobulin isotypes	

2.1 Background Immunogenicity Information

PF-06881894 is a covalent conjugate of G-CSF (filgrastim) and a 20kDa mono-methoxy-polyethylene glycol propionaldehyde (mPEG-p). Filgrastim is expressed in *E. coli* and has no post-translational modifications. It is indicated to decrease the incidence of infection, as manifested by febrile

neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia.

PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU are administered by subcutaneous injection. Subcutaneous routes of administration could result in ADA of the IgM and IgG isotype, with IgG isotype ADA dominating a persistent response.

2.2 Validation of Anti-Drug Antibody Assay

The Applicant used a tiered approach for ADA assay development including screening, confirmatory, titrating, and neutralizing assays. To detect the ADA in serum samples, the Sponsor contracted the development of a MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA to [REDACTED] (b) (4). The Applicant used a single-assay approach using the proposed biosimilar for capture and detection. The single assay was demonstrated during development to have similar antigenic equivalence for PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU through cold competition experiments. The NAb assay is discussed in section 2.3 below.

***Assessor comment:** The tiered approach to ADA assessment is consistent with FDA recommendations in FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products-Developing and Validating Assays for Anti-Drug Antibody Detection (2019) and is acceptable. The use of a single assay that uses the proposed biosimilar for capture and detection is consistent with FDA recommendations in FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015) and is acceptable.*

2.2.1 Validation Exercises

Screening Assay

Method Principle:

Serum samples are first subjected to an acid treatment with 0.8% acetic acid to dissociate the pre-formed ADA-drug complexes. Samples are then incubated Ruthenylated (sulfo-tagged) pegfilgrastim and biotinylated pegfilgrastim, and the resulting complexes are added to a streptavidin-coated MesoScale Discovery (MSD) plate. The chemiluminescent signal readout is obtained from an electrochemiluminescent (ECL) reaction (ruthenium/ tripropylamine) and measured by an MSD plate reader. The signal is proportional to the amount of anti-PF-06881894 antibody present.

***Assessor comment:** The Applicant used a bridging assay format for the screening and confirmatory assays for anti-pegfilgrastim antibodies. Bridging assays can detect all antibody isotypes therefore, this is an acceptable approach.*

The validation results for ADA screening, confirmatory, and titer assays used in each clinical study and a reviewer assessment are provided in Summary Table 2.2.1 below. Raw validation data are not provided unless necessary to discuss identified validation issues.

**Table 2.2.1: Validation Results and Assessor Assessment for ADA assays
Anti-Pegfilgrastim ADA ECL Method**

Validation Parameter	Val Reports for anti-HSP-130:181683/183265/184335/186288/C1227001	Assessor Comment
Contract Research Org	(b) (4) Validation performed by at least 2 analysts over at least 3 separated days	Bioanalytical inspection was performed by OSIS. There were no objectionable findings and a Form FDA 483 was not issued (see memo dated 1/24/2020 from YiYue Zhang in DARRTS)
Assay principle	<ul style="list-style-type: none"> MSD (ECL) based Single Bridging ELISA with Biotinylated pegfilgrastim + Sulfo-tagged pegfilgrastim onto streptavidin coated MSD assay plates. The ELC signal (Relative Light Units) is proportional to the amount of anti-PF-06881894 antibody. Blocking is performed with Diluent Buffer (Wash Buffer with 1% BSA). 	Applicant used single assay approach based on the proposed biosimilar, consistent with 2015 FDA Guidance Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry
Sample Pretreatment (Acid dissociation)	Samples are diluted 1:5 in 1x PBS-T/1% BSA and acidified by adding an equal volume of 0.8% acetic acid followed by a 1:1 dilution in Trizma neutralization buffer, including equal concentration of sulfo-tagged pegfilgrastim (100ng/mL) and biotinylated pegfilgrastim (100ng/mL). Final serum concentration=5%	Acid dissociation is a common approach to reduce drug interference. A single round of acid dissociation was performed. Results were acceptable.
Positive control (PC)	Purified rabbit anti-PEG-GCSF polyclonal antibody Lot# 21887C supplied by Hospira, stored at -70°C.	PC used in validation of ADA and NAb assays, including LPC and HPC preparation. The Sponsor demonstrated antigenic equivalence in that the PC antibody bound similarly to PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU. The Rabbit anti-PEG-GCSF polyclonal antibody is suitable as the PC.
PC Dose Curve and Hook Effect	No hook effect was observed up to 60 µg/mL of PC	This is acceptable.
LPC	6.5ng/ml LPC calculated to fail ~1%	This is consistent with FDA guidance ¹ and is acceptable.

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	100 ng/mL in 100% human serum	
HPC	5,000 ng/ml in 100% human serum	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
Matrix and NC	Normal Human Serum pool	<i>The signals of blank samples must be below SCP. The use of healthy human serum pool as the matrix control is consistent with FDA guidance¹ and is acceptable.</i>
MRD	1:20 (1:5 dilution in JX PBS-Til% BSA followed by acid dissociation and neutralization)	<i>Correctly includes acid dissociation and buffer neutralization steps to determine MRD.</i>
NC system suitability range	The upper limit ≤ 117 RLU (Relative light unit)	<i>The range is based on mean normalized signal – (t0.01,df x SD), t0.01df =2.845</i>
LPC system suitability range	The lower limit ≥ 4.05 (normalized signal)	
HPC system suitability range	The lower limit ≥ 172 (normalized signal)	
Antigenic Equivalence testing (Competitive DOE)	HPC and LPC signals were similarly inhibited by addition of unlabeled PF-06881894, pegfilgrastim-US, or pegfilgrastim-EU.	<i>Assay performance was assessed through side-by-side comparisons of results from LPC and HPC samples spiked with 0.00, 0.50, 1.00, 5.00, 10.0, 25.0, 50.0, 100 and 500 $\mu\text{g/mL}$ PF-06881894, pegfilgrastim-US, or pegfilgrastim-EU. This approach is acceptable.</i>
Screening cut- point (SCP) Floating CP= Mean PNC of plate x CP factor	ZIN-130-1505 (C1221001) and C1221005: SCP factor 1.08 using 95% CI ZIN-130-1504 (C1221002): SCP factor 1.13 using 95% CI commercial samples SCP factor 1.02 using 95% CI in-study samples	ZIN-130-1505 (C1221001) and C1221005: <i>The SCP was determined using 51 individual commercial NHS lots analyzed in duplicate on three separate days by two analysts. Floating SCP were calculated using a S/N ratio and both parametric and non-parametric approaches. Outliers were assessed by ANOVA and data skewness by the Shapiro-Wilk test. The SCP was the same using both approaches. The false positive rate was above 1% with 99.9% CI; therefore, the CP is acceptable</i> ZIN-130-1504 (C1221002): <i>The SCP was determined using 34 individual commercially obtained lots from patients with breast cancer analyzed in duplicate on four days by two analysts. Statistical analysis was performed as described above.</i>

		<p><i>The SCP was determined using 50 pre-dose in-study serum samples analyzed in duplicate over 6 days. Day 1 false positive rate for all pre-dose samples was 2.9% with 99.9% CI.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
Confirmatory cut-point (CCP) Fixed	<p>ZIN-130-1505 (C1221001) and C1221005: 21.5% based on 99.9% CI; 0.1% FP rate</p> <p>ZIN-130-1504 (C1221002): 19.2% based on 99%CI; 1% FP rate, commercial samples</p> <p>15.4% based on 99.9% CI; 0.1% FP rate, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221002: <i>The CCP was determined using 51 commercially obtained NHS lots analyzed in duplicate on two separate days by two analysts. Samples were evaluated with and without a spike of 50.0 µg/mL pegfilgrastim DS. The Sponsor assessed the cut point using 1% and 0.1% FP rates with a parametric approach and 1% with a non-parametric approach. Outliers were assessed by ANOVA and data skewness by the Shapiro-Wilk test. The cut points were 21.5%, 16.2% and 17.3%. Because these cut points are all statistically valid, similar, and low and because ADA to pegfilgrastim are low risk it is acceptable to use the 21.5% cut point.</i></p> <p>ZIN-130-1504 (C1221002): <i>The CCP was determined using 34 individual lots from patients with breast cancer analyzed in duplicated on four days by two analysts.</i></p> <p><i>The CCP was determined using 50 individual pre-dose samples analyzed in duplicate on 6 separate days. Samples were evaluated with and without a spike of 50.0 µg/mL pegfilgrastim DS.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
Titer Cut Point (TCP)	<p>ZIN-130-1505 (C1221001) and C1221005: TCP 1.20 based on 99.9% CI; 0.1% FP rate</p> <p>ZIN-130-1504 (C1221002): TCP 1.22 based on 99.9%CI; 0.1% FP rate, commercial samples</p>	<p><i>The TCP was determined similarly to the SCP using a parametric approach and 0.1% FP rate.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>

Assay Drug Tolerance	<p>ZIN-130-1505 (C1221001) and C1221005: LPC (100 ng/mL) tolerates up to 100 ug/mL drug HPC (500 ng/mL) tolerates up to 100 ug/mL drug</p> <p>ZIN-130-1504 (C1221002): LPC (100 ng/mL) tolerates up to 100 ug/mL, drug commercial samples HPC (500 ng/mL) tolerates up to 100 ug/mL drug, commercial samples</p> <p>LPC 14.4 ng/mL tolerates drug at 1 ug/mL, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and ZIN-130-1504 (C1221005) <i>The impact of pegfilgrastim DS or Neulasta at different concentrations (0.00, 0.50, 1.00, 5.00, 10.0, 25.0, 50.0, and 100 µg/mL) on PC at 100 ng/mL and 5000 ng/mL was assessed. Addition of DS did not result in a signal below the cut point for any of the samples.</i></p> <p>ZIN-130-1504 (C1221002): <i>LPC at 11.2 ng/mL and 14.4 ng/mL spiked with 0 – 50 ug/mL pegfilgrastim. 11.2 ng/mL tolerated up to 10ug/mL pegfilgrastim. 14.4 ng/mL tolerated up to 1 ug/mL.</i></p> <p><i>The Clinical Pharmacology assessor, Xiling Jiang, confirmed that day 0 and day 13 serum drug concentrations are 0 and 200 pg/mL respectively. Clinical samples for ADA assessment are obtained pre-dose, day 14, and day 30. Therefore, serum drug concentrations at time of sampling should allow for sensitive ADA detection.</i></p> <p><i>The drug tolerance of the assay is acceptable.</i></p>
Sensitivity	<p>ZIN-130-1505 (C1221001) and C1221005: 9.09 ng/mL in pooled NHS</p> <p>ZIN-130-1504 (C1221002): Screening 2.8 ng/mL in-study samples Confirmatory 8.92 ng/mL in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Sensitivity was determined by analyzing PC titer curves prepared in pooled NHS on 3 plates and calculated using using 4-parameter logistic curve fit.</i></p> <p>ZIN-130-1504 (C1221002): <i>Sensitivity was determined from 6 runs in both the screening and confirmatory formats with a 95% CI.</i></p> <p><i>Sensitivity is consistent with current FDA guidance¹ of ≤100ng/ml and is acceptable.</i></p>
Repeatability/Intra-assay variability	<p>ZIN-130-1505 (C1221001) and ZIN-130-1504 (C1221002): Mean PNC % CV: 5.87% Mean LPC %CV: 1.37% Mean HPC %CV: 3.81%</p> <p>ZIN-130-1504 (C1221005): Mean LPC at 14.4ng/mL %CV: ≤2.1, in study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Intra-assay precision was assessed using data from 21 runs performed over four days by two analysts.</i></p> <p>ZIN-130-1504 (C1221002): <i>LPC at 11.2 ng/mL and 14.4 ng/mL were analyzed in duplicate six times.</i></p>

		<i>It is acceptable that the supplemental study was less robust than the initial validation because it is confirmatory. This is consistent with FDA guidance¹ and is acceptable.</i>
Intermediate Precision (IP)/inter-assay variability	ZIN-130-1505 (C1221001) and C1221005: Mean PNC % CV: 10.8 % Mean LPC %CV: 5.43% Mean HPC %CV: 10.7% ZIN-130-1504 (C1221002): Mean LPC at 14.4 ng/mL %CV: 2.54%, in-study samples	ZIN-130-1505 (C1221001) and C1221005: <i>Precision was assessed using data from 21 runs performed over four days by two analysts.</i> C1221005: <i>LPC at 11.2 ng/mL and 14.4 ng/mL were analyzed in duplicate over multiple days.</i> <i>Intermediate precision was less than 15%CV which is acceptable for this assay format.</i>
Selectivity	ZIN-130-1505 (C1221001) and C1221005: 10 of 10 sera from healthy subjects passed ZIN-130-1504 (C1221002): 10 of 10 sera from patients with breast cancer passed, commercial samples 10 of 10 sera from healthy subjects passed using the in-study cut point	ZIN-130-1505 (C1221001) and C1221005: <i>LPC at 100ng/mL were spiked into ten individual lots of serum from healthy subjects, patients with breast cancer, negative control, hemolytic, and lipemic serum. Recovery was calculated as the %Difference in values between the individual samples and the negative control. Acceptance criteria were <25% difference in values.</i> ZIN-130-1504 (C1221002): <i>LPC at 11.2 ng/mL and 14.4 ng/mL were compared to the plate cut-point. LPC at 11.2 ng/mL passed 4 of 10 time where LPC at 14.4 ng/mL passed 10 of 10 times.</i> <i>This is consistent with FDA guidance¹ and is acceptable.</i>
Specificity	ZIN-130-1505 (C1221001) and C1221005: 23.9% based on 99.9% CI; 0.1% FP rate ZIN-130-1504 (C1221002): 15.3 % based on 99% CI; 1% FP rate, commercial samples 18.0% (based on 90% CI; 1% FP rate), in-study samples	ZIN-130-1505 (C1221001) and C1221005: <i>51 individual lots of NHS were evaluated in duplicate in 3 independent assays with and without a spike of 50.0 µg/mL filgrastim intermediate.</i> ZIN-130-1504 (C1221002): <i>34 individual lots of serum from breast cancer patients were evaluated in duplicate on two separate days in by two analysts.</i> <i>50 pre-dose serum samples were evaluated with and without a spike of 50 ug/mL filgrastim in duplicate over 6 days.</i>

Stability	ZIN-130-1505 (C1221001), and ZIN-130-1504 (C1221002): LPC and HPC are stable at RT for 4.5 hours prior to processing and after 3 freeze thaw cycles.	<i>Stability of the PC was assessed under conditions representative of assay performance. Results show that PC remain stable for up to 16 freeze thaw cycles at -20 °C or -70 °C, and up to 4.5 hrs at RT.</i>
ADA Assay Assessment		<i>This is acceptable.</i> <i>The screening, confirmatory, and titer assay validation exercises for anti-drug antibodies were acceptable. Critical assay parameters, including establishment of cut points, were assessed using serum from healthy subjects, commercially obtained serum from patients with breast cancer and in-study pre-dose samples from patients with breast cancer. The Applicant established that assay performance is similar for PF-06881894, pegfilgrastim-U.S., and pegfilgrastim E.U. The assay validation studies are acceptable and no further action is indicated.</i>

¹FDA Guidance for Industry – Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection.

Anti-PEG antibody assay

Method Principle:

Anti-PEG antibodies are measured using an enzyme-linked immunosorbent assay (ELISA) method. Ninety-six (96) well plates are coated with mono pegylated BSA, incubated, washed, and blocked using diluent. Samples are diluted 1:50 and added to the plate. After a 1 h incubation the plates are washed and a secondary antibody, Rabbit anti-human IgG/A/M conjugated to horseradish peroxidase (HRP) is added to the plate. After a 1hour incubation plates are washed and a tetramethylbenzidine (TMB) peroxidase substrate solution is added. Color develops in proportion to the amount of anti-PEG antibodies present. The reaction is stopped with phosphoric acid and the plates are read at 450 nm for detection and 620 nm for background.

Assessor comment: *The Applicant used a sandwich assay format for the screening and confirmatory assays for anti-PEG antibodies. The detecting reagent allows for the detection of IgG/A/M isotype antibodies. The subcutaneous route of drug administration would generate IgM and IgG antibodies. Therefore, this approach is acceptable. The validation results for ADA screening, confirmatory, and titer assays used in each clinical study and a reviewer assessment are provided in Summary Table 2.2.2 below. Raw validation data are not provided unless necessary to discuss identified validation issues.*

**Table 2.2: Validation Results and Assessor Assessment for ADA assays
Anti-Pegfilgrastim ADA ECL Method**

Validation Parameter	Val Reports for Anti-PEG: 181685/	Assessor Comment
Contract Research Org	(b) (4). Validation performed by at least 2 analysts over at least 3 separated days	<i>Bioanalytical inspection was performed by OSIS. There were no objectionable findings and a Form FDA 483 was not issued (see memo dated 1/24/2020 from YiYue Zhang in DARRTS)</i>
Assay principle	<ul style="list-style-type: none"> ELISA based colorimetric method. Plates coated with monopegylated BSA the reaction is detected using a Rabbit anti-human IgG/A/M conjugated to HRP. Color (OD450) is proportional to the amount of anti-PEG antibody. 	
Positive control (PC)	<p>ZIN-130-1505 (C1221001) and C1221005:</p> <p>Human serum positive control pool prepared at (b) (4) (reference 11998-38-44) diluted 1:1 for high positive control and 1:4 for low positive control</p> <p>Monoclonal anti-mPEG (clone 9B5-6-25-7) supplied by (b) (4)</p> <p>ZIN-130-1504 (C1221002):</p> <p>Human serum positive control pool prepared at (b) (4) (reference 11998-38-44) diluted 1:1 for high positive control, 1:10 for LPC screening assay, and 1:4 for low positive control confirmatory assay</p> <p>Monoclonal anti-mPEG (clone 9B5-6-25-7) supplied by (b) (4)</p>	<p><i>ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002):</i></p> <p><i>PC used in validation of screening and confirmatory, the Rabbit anti-PEG-GCSF polyclonal antibody is suitable as the PC.</i></p> <p><i>The anti-PEG mAb was used for evaluating drug tolerance.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
Matrix and NC	Pooled human serum	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
MRD	1:50	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
NC system suitability range	Ratio of HPC mean signal/NPC mean signal must be ≥ 10.4	<i>There is little guidance on system suitability acceptance criteria. This was established empirically and is acceptable.</i>
LPC system suitability range	<p>Screening:</p> <p>Mean raw signal of at least 2/3 of LPC mean response must be \geq assay cut point</p> <p>Confirmatory:</p>	<i>There is little guidance on system suitability acceptance criteria. This was established empirically and is acceptable.</i>

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	At least 1 of 2 sets of duplicates for each LPC must have a percent inhibition $\geq 72.1\%$	
HPC system suitability range	<p>Screening: Ratio of HPC mean signal/NPC mean signal must be ≥ 10.4</p> <p>Confirmatory: At least 1 of 2 sets of duplicates for each HPC must have a percent inhibition $\geq 72.1\%$</p>	
<p>Screening cut- point (SCP) Floating CP= Mean PNC of plate x CP factor</p>	<p>ZIN-130-1505 (C1221001) and C1221005: SCP factor 1.73 using a 5% false positive rate</p> <p>ZIN-130-1504 (C1221002): SCP factor 2.29 using a 5% false positive rate, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>SCP was evaluated using 96 individual lots of serum from healthy donors. Lots were analyzed in duplicate replicates on 8 days by 2 analysts. Outliers were assessed and removed. Due to lack of data normality a non-parametric SCP was determined. This is a suitable statistical approach.</i></p> <p>ZIN-130-1504 (C1221002): <i>SCP was evaluated using 50 randomly selected pre-dose serum samples. Lots were analyzed in duplicate replicates on 6 days by 2 analysts. Outliers were assessed and removed. Due to lack of data normality a non-parametric SCP was determined. This is a suitable statistical approach.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
Confirmatory cut-point (CCP) Fixed	<p>ZIN-130-1505 (C1221001) and C1221005: CCP:72.1% samples from healthy subjects</p> <p>ZIN-130-1504 (C1221002): 74% in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>CCP was evaluated using 96 individual lots of serum from healthy donors analyzed with and without spikes of 100 ug/mL methoxy PEG. Lots were analyzed in duplicate replicates on 8 days by 2 analysts. Outliers were assessed and removed. A parametric approach was used to determine the CCP. This is acceptable because skewness was -0.04 and parametric approaches are generally acceptable when skewness is between -1 and 1.</i></p> <p>ZIN-130-1504 (C1221002): <i>CCP was evaluated using 50 randomly selected pre-dose serum samples analyzed with and without spikes of 100 ug/mL methoxy PEG. Lots were analyzed in duplicate replicates on 8 days by 2 analysts. Outliers were assessed and removed. A parametric</i></p>

		<p><i>approach was used to determine the CCP. This is acceptable because the data were normally distributed.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
<p>Titer Cut Point (TCP) Floating cut point factor</p>	<p>ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): TCP factor 2.03 using 99.9% CI</p>	<p><i>TCP was evaluated using 96 individual lots of serum from healthy donors. Lots were analyzed in duplicate replicates on 8 days by 2 analysts. A parametric approach with a 0.1% false positive rate was used.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
<p>Assay Drug tolerance</p>	<p>Free PEG ZIN-130-1505 (C1221001) and C1221005: LPC pool: 1:4 dilution tolerates up to 100 ug/mL mPEG LPC (200 ng/mL) tolerates up to 100 ug/mL mPEG HCP (1000 ng/mL) tolerates up to 100 ug/mL mPET</p> <p>PF-06881894 LPC pool: 1:4 dilution tolerates up to 100 ug/mL PF-06881894 LPC (200 ng/mL) tolerates up to 100 ug/mL PF-06881894 HCP (1000 ng/mL) tolerates up to 100 ug/mL PF-06881894</p> <p>ZIN-130-1504 (C1221002): LPC 1:10 tolerates up to 5 ug/mL of mPEG in-study samples</p>	<p>ZIN-130-1505 (C1221001) and ZIN-130-1504 (C1221002): <i>Free PEG</i> <i>The impact of free-PEG at different concentrations (0.00, 0.50, 1.00, 5.00, 10.0, 25.0, 50.0, and 100 ug/mL) on LPC pool or on an anti-PEG mAb at 1000 ng/mL or 200 ng/mL was assessed.</i></p> <p><i>Addition of mPEG did not result in a signal below the cut point for the LPC or either concentration of the mAb PC.</i></p> <p>PF-06881894 <i>The impact of PF-06881894 at different concentrations (0.00, 0.50, 1.00, 5.00, 10.0, 25.0, 50.0, and 100 ug/mL) on LPC pool or on an anti-PEG mAb at 1000 ng/mL or 200 ng/mL was assessed.</i></p> <p><i>Addition of PF-06881894 did not result in a signal below the cut point for the LPC or either concentration of the mAb PC.</i></p> <p>ZIN-130-1504 (C1221002) <i>LPC at 1:10 dilution was spiked with 0 – 50 ug/mL free PEG.</i></p> <p><i>The Clinical Pharmacology assessor, Xiling Jiang, confirmed that day 0 and day 13 serum drug concentrations are 0 and 200 pg/mL respectively. Clinical samples for ADA assessment are obtained pre-dose, day 14, and day 30. Therefore, serum drug concentrations at time of sampling should allow for sensitive ADA detection. Free PEG is was not evaluated in serum samples, however free PEG in drug is maximally 6.6 ug/dose.</i></p>

		<i>Therefore, serum concentrations of free PEG should allow for sensitive ADA detection.</i>
Sensitivity	<p>ZIN-130-1505 (C1221001) and C1221005: Screening 41.9 ng/mL</p> <p>ZIN-130-1504 (C1221002): Screening 1:17.8 dilution, in-study samples Confirmatory 1:6.88 dilution, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Sensitivity was determined by analyzing PC titer curves prepared in pooled NHS. The results were calculated using titer cut point factor of 2.03 using 4-parameter logistic curve fit. The relative sensitivity was determined to be 41.9 ng/mL in pooled NHS</i></p> <p>ZIN-130-1504 (C1221002): <i>Sensitivity was determined by analyzing PC titer curves prepared in pooled NC by 2 analysts on 2 days. Sensitivity was determined by the concentration at which the PC produces a response equal to the cut point.</i></p> <p><i>Sensitivities for both studies are within current FDA recommended ≤ 100ng/ml</i></p>
Repeatability/Intra-assay variability	<p>ZIN-130-1505 (C1221001) and C1221005: Mean PNC % CV: $\leq 10\%$ Mean LPC %CV: $\leq 9\%$ Mean HPC %CV: $\leq 9\%$</p> <p>ZIN-130-1504 (C1221002): Mean LPC %CV: $\leq 7\%$, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Intra-assay precision was assessed using data from 51 runs performed over 13 days by two analysts. This is consistent with FDA guidance¹ and is acceptable. Normalized results are expressed as the mean response of HPC or LPC/mean response of PNC</i></p> <p><i>Intra-assay precision is $\leq 10\%$ which is acceptable for this type of assay.</i></p> <p>ZIN-130-1504 (C1221002): <i>Both LPC were tested in duplicate a total of 6 times.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
Intermediate Precision (IP)/inter-assay variability	<p>ZIN-130-1505 (C1221001) and C1221005: Mean PNC % CV: 18% Mean LPC %CV: $\leq 21\%$ Mean HPC %CV: $\leq 21\%$</p> <p>ZIN-130-1504 (C1221002): Mean LPC %CV: $\leq 8\%$, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Inter-assay precision was assessed using data from 51 runs performed over 13 days by two analysts. Normalized results are expressed as the mean response of HPC or LPC/mean response of PNC</i></p> <p>ZIN-130-1504 (C1221002): <i>Both LPC were tested in duplicate a total of multiple days.</i></p>

		<i>It is acceptable that the supplemental study was less robust than the initial validation because it is confirmatory. Inter-assay precision is $\leq 21\%$ which is acceptable for this type of assay.</i>
Selectivity	ZIN-130-1505 (C1221001) and ZIN-130-1504 (C1221002) and C1221005: 10 of 10 samples from healthy subjects passed for all conditions tested.	ZIN-130-1505 (C1221001) and ZIN-130-1504 (C1221002) and C1221005: <i>Results from LPC diluted 1:4 or 1:10 spiked into 10 individual drug naïve serum samples were compared to LPC spiked into the NC. Results passed if the values from the LPC spiked individual sera were within 25% of the values from LPC spiked NC serum sample.</i> <i>Ten of ten individual samples spiked with 200 ng/mL anti-PEG mAb all passed.</i> <i>This is a reasonable approach to evaluating matrix effects and is acceptable.</i>
Stability	ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): After 3 freeze and thaw, HPC and LPC have the percentage difference of -8 and -6%, respectively, compared to untreated ones. PC: stable at RT for 19 hours prior to processing.	ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): <i>Stability testing shows PC remain stable for up to 3 freeze thaw cycles when stored at ≤ -20 °C, and up to 4.5 hrs at RT. This is acceptable.</i>
ADA Assay Assessment		<i>The screening, confirmatory, and titer assay validation exercises for anti-PEG antibodies were acceptable. Critical assay parameters, including establishment of cut points, were assessed using serum from healthy subjects, commercially obtained serum from patients with breast cancer and in-study pre-dose samples from patients with breast cancer. The anti-PEG antibody assay detects both free PEG and pegfilgrastim. The assay validation studies are acceptable and no further action is indicated.</i>

¹FDA Guidance for Industry – Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection.

PNC – pooled negative control



APPEARS THIS WAY ON ORIGINAL

2.3 Validation of Neutralizing Antibody Assay

2.3.1 Method Principle

The ADA positive samples are confirmed for neutralizing antibody (Nab) activity using an engineered stable GloResponse™ SIE-Luc2P U937 leukemia cell line (Promega), which expresses humanized luciferase gene Luc2P for. Luciferase expression is controlled by the sis-inducible element (SIE) and a minimal-promoter (TAT-Box), which are activated after interaction of PF-06881894 with the G-CSF receptor. When Nab are present PF-06881894 mediated luciferase activity, as measured by luminescence, is decreased. Briefly, 5×10^4 U937 cells/well were prepared and human serum samples were heat-inactivated at 56°C for 30-45 mins prior to use. A pre-incubated mix (50µl) of final 1 ng/mL PF-06881894 and positive control anti-hG-CSF antibodies are added to 96-well microplate. Then the cells are added to and incubated for 6 hours in the presence of 5 % human serum.

The sample is reported as NAb positive when the inhibition -signal is equal to or greater than the assay cut-point.

Assessor's Comment:

The Sponsor provided a feasibility report ((b) (4)-2015-C-05-02), which is attached to the validation report (b) (4)-2015-B-06-11. The feasibility report provided comparative data of assay parameters for Nab detection from two cell lines, GloResponseTMSIE-luc2P U937 cells and NFS-60 cells. The U937 cells use a luciferase-based readout and NFS-60 cell is based on a proliferation readout system MTS. The U937 cell line was chosen as an appropriate assay system for detection of Nab because this cell line has increased assay robustness and throughput and decreased variability while retaining acceptable sensitivity.

2.3.2 Validation Exercises

The assay validation results for the NAb detection assays used in each clinical study along with the reviewer assessment are provided in Summary Table 2.2 below, which was compiled by the assessor. Raw validation data are not provided unless necessary to discuss identified validation issues. PF-06881894 lot 2459066 and Neulasta lot 1072004 were used in the validation study.

Table 2.3.1: Validation Results and Assessor Assessment for NAb Detection assays in original validation reports to HSP-130 (b) (4) report (b) (4)-2015-B-06-11) and to filgrastim (b) (4) report (b) (4)-16-074-021)

Validation Parameter	(b) (4)-2015-B-06-11	Assessor Comment (b) (4)
Contract Research Org	(b) (4) Validation performed by at least 2 analysts on at least 3 separated days	<i>Bioanalytical inspection waived by OSIS as (b) (4) had been recently inspected.</i>
Assay principle competitive ligand binding assay (CLBA)	Intensity of luminescence is proportional to the intensity of the G-CSF receptor signaling.	<i>Applicant used single assay approach based on the proposed biosimilar, consistent with 2015 FDA Guidance Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry, which is acceptable.</i>
Positive control (PC)	Goat polyclonal affinity purified antibody against human G-CSF from R&D system, Ca#: AF-214-NA. PC was prepared in heat inactivated 100% NHS pool.	<i>PC used in validation of ADA and NAb assays, including LPC and HPC preparation. The Sponsor demonstrated antigenic equivalence in that the PC antibody bound similarly to PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU. The Rabbit anti-PEG-GCSF polyclonal antibody is suitable as the PC.</i>
Negative control (NC)	Pooled serum from 10 healthy donors, heat inactivated	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
LPC	ZIN-130-1505 (C1221001) and C1221005: LPC1: 4 µg/mL LPC2: 8 µg/mL ZIN-130-1504 (C1221002): In-study LPCs For CP and sensitivity runs: LPC1 at 4.0 µg/ml LPC2 at 3.5 µg/ml LPC3 at 4.5 µg/ml For drug tolerance and precision: LPC1corr at 3.34 µg/ml LPC2 at 8.8 µg/ml (not for precision runs)	<i>For the initial CP calculation, an incorrect BLI value was used and led to an incorrect CP calculation, which was identified after preparation of a new set of LPCs, which were used for drug tolerance assessments. Followed a new CP calculation, the CP was corrected from 43.5% to 34.3% and a corrected LPC (LPC1corr with 3.34 µg/mL) was prepared and the drug tolerance was repeated for LPC1corr. Only the corrected values are provided here.</i>
HPC	ZIN-130-1505 (C1221001) and C1221005:	<i>Both HPC tested 100% positive for all tested conditions, as expected.</i>

	50 µg/mL ZIN-130-1504 (C1221002): 50 µg/mL	
Matrix and NC	Normal human serum pool samples from 10 normal humans with no detectable neutralizing anti-hG-CSF.	<i>The signals of blank samples must be below SCP. The use of healthy human serum pool as the matrix control is acceptable.</i>
MRD	5 % serum	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
Antigenic Equivalence testing		<i>Antigenic equivalence was established in the sensitivity and drug tolerance studies (see below).</i>
NAb assay cut- point (NACP) Normalized CP (% inhibition): Mean plus 2.33*SD	ZIN-130-1505 (C1221001) and C1221005: Fixed SCP: 41.5%: 99% CI, 1% FP ZIN-130-1504 (C1221002): In-study fixed SCP: 34.3%	ZIN-130-1505 (C1221001) and C1221005: <i>Used 51 healthy human serum samples assessed in two assay runs by one analyst. No outliers were statistically identified based on box-plot analysis CP Data determined to be normally distributed. Therefore, a parametric approach was used to calculate the cut point.</i> ZIN-130-1504 (C1221002): <i>Thirty pre-dose samples were assessed in 6 independent runs by 2 analysts. Outliers were removed which resulted in normal distribution of the data. Therefore, a parametric approach was used to calculate the cut-point.</i> <i>This is consistent with FDA guidance¹ and is acceptable.</i>
Assay Drug tolerance	ZIN-130-1505 (C1221001) and C1221005: LPC1 and LPC2 tolerate up to 10ng/mL PF-06881894 or Neulasta HPC tolerates up to 100ng/mL PF-06882894 ZIN-130-1504 (C1221002): HCP tolerated up to 166.7 ng/mL PF-06881894 or Neulasta, in-study samples LPC1 (3.34 µg/mL) tolerated up to 6.2 ng/mL PF-06881894 and 18.5 ng/mL Neulasta, in-study samples	ZIN-130-1505 (C1221001) and C1221005: <i>NC pool was spiked with HPC and up to 60 ug/mL PF-06881894, incubated and titrated onto cells.</i> ZIN-130-1504 (C1221002): <i>NC pool was spiked with HPC or LPC and incubated with PF-06881894 or Neulasta prior to titration onto cells.</i> <i>The Clinical Pharmacology assessor, Xiling Jiang, confirmed that day 0 and day 13 serum drug concentrations are 0 and 200 pg/mL respectively. Clinical samples for ADA assessment are obtained pre-dose, day 14, and day 30. Therefore, serum drug concentrations at time of sampling should allow for sensitive ADA detection.</i> <i>The drug tolerance of the assay is acceptable</i>

Sensitivity	<p>ZIN-130-1505 (C1221001) and C1221005: 4.3ug/mL</p> <p>ZIN-130-1504 (C1221002): 2.64 ug/mL cells stimulated with PF-06881894, in-study samples 3.3 ug/mL cells stimulated with Neulasta, in-study samples</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Assay sensitivity was assessed by evaluating titration curves of anti-GCSF antibodies ranging from 150 – 0.04 ug/mL in the presence of 1 ng/mL PF-06881894 in three assay runs by one analyst.</i></p> <p>ZIN-130-1504 (C1221002): <i>Sensitivity was assessed by evaluating titration curves from 6 independent runs by 2 analysts using PF-06881894 or Neulasta. 4.34 ug/mL based on back calculated concentrations at the cut point with 5 % false positive rate</i></p> <p><i>Assay sensitivity is poor, however neutralizing ADA were detected in-study. In-study NAb were specific for PEG. No further action indicated.</i></p>
Repeatability/Intra-assay variability	<p>ZIN-130-1505 (C1221001) and C1221005: NC \leq14.2% CV HPC: 2.5% CV, in-study samples LPC: 13.8% CV, in-study samples</p> <p>ZIN-130-1504 (C1221002): NC \leq5.4% CV</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Intra-assay precision was assessed by running the control sample in six duplicates by one analyst in one run. Repeatability for both studies are $<$15% and are acceptable.</i></p> <p>ZIN-130-1504 (C1221002): <i>Intra-assay precision was only evaluated for the new NC pool.</i></p> <p><i>Intra-assay precision is acceptable for this type of assay.</i></p>
Intermediate Precision/inter-assay variability	<p>ZIN-130-1505 (C1221001) and C1221005: NC \leq13.4% CV HPC: 5.3 %CV, in-study samples LPC1: 7.1 %CV, in-study samples</p> <p>ZIN-130-1504 (C1221002): NC \leq7.4% CV</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>IP was assessed for the control sample run in four assays by 2 analysts. IP for both studies are \leq20% and are acceptable.</i></p> <p>ZIN-130-1504 (C1221002): <i>IP was only assessed for the new NC pool.</i></p> <p><i>Interassay precision is acceptable for this type of assay.</i></p>
Selectivity Specificity/cross-reactivity	<p>ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): LPC1, LPC2, and HPC: tolerated up to 40 pg/mL GM-CSF</p>	<p>ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): <i>NC was spiked with PC and different amounts of GM-CSF ranging from 20 pg/mL to 0.16 pg/mL. GM-CSF concentration in human serum are usually $<$ 2 pg/mL.</i></p>

		<i>Selectivity is acceptable and should allow for sensitive detection of NAb.</i>
Stability	<p>ZIN-130-1505 (C1221001) and C1221005: LPC and HPC: pass 4 freeze/thaw cycles with 80-120% recovery LPC and HPC: stable at RT for 24 hours with 80 – 120% recovery</p> <p>ZIN-130-1504 (C1221002): LPC and HPC: 6 freeze/thaw cycles with 80-120% accuracy LPC and HPC: stable at RT for 24 hours with 80 – 120% Accuracy</p>	<p>ZIN-130-1505 (C1221001) and C1221005: <i>Freeze thaw stability was assessed in a single study of 4 freeze/thaw cycles of -20oC to ambient temperature for HPC, LPC1, and LPC2. PCs were frozen for at least 12 h. Bench top stability was assessed in a single experiment after overnight storage of HCP, LPC1, and LPC2 at ambient temperature.</i></p> <p>ZIN-130-1504 (C1221002): <i>Freeze thaw stability was assessed in a single study of 6 freeze/thaw cycles of -20°C to ambient temperature for HPC, LPC1, and LPC2. PCs were frozen for at least 12 h. Bench top stability was assessed in a single experiment after 24 h storage of HCP, LPC1, and LPC2 at ambient temperature.</i></p> <p><i>Freeze thaw stability is acceptable.</i></p>
Robustness	<p>ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): Assay time should be 5-6 hours with 4E4-6E4 cells/well with 80-120% recovery</p>	<p>ZIN-130-1505 (C1221001), C1221005, and ZIN-130-1504 (C1221002): <i>Robustness was assessed by evaluating incubation times between 5 – 7 h and starting cell numbers between 4E4 cells/well and 6E4 cells/well in a single assay.</i></p> <p><i>Robustness is acceptable.</i></p>
NAb Assay Assessment		<i>The neutralizing antibody assay validation were acceptable. Critical assay parameters, including establishment of cut points, were assessed using serum from healthy subjects, commercially obtained serum from patients with breast cancer and in-study pre-dose samples from patients with breast cancer. The Applicant established that assay performance is similar for PF-06881894, pegfilgrastim-U.S., and pegfilgrastim E.U. The assay validation studies are acceptable and no further action is indicated.</i>

¹*FDA Guidance for Industry – Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection.*

2.4 Isotyping assay Antibody Assay

2.4.1 Method Principle

Samples are either diluted 1:5 in diluent and added to polypropylene plates or are directly added to polypropylene plates. Samples are acidified and neutralized with a mix containing ruthenylated (sulfo-tagged) anti-human IgG, sulfo-tagged anti-human IgM, or sulfo-tagged pegfilgrastim, and pegylated biotinylated pegfilgrastim. Isotype specific anti-pegfilgrastim antibodies will bind both the sulfo-tagged detector and biotinylated pegfilgrastim. Samples are then transferred to streptavidin coated MSD plates, and after washing tripoylamin (TPA) containing read buffer is added. The chemiluminescent signal readout is obtained from an electro-chemiluminescent (ECL) reaction (ruthenium/ tripropylamine) and measured by an MSD plate reader. The signal is proportional to the amount of anti-PF-06881894 antibody present.

Assessor comment: *The Sponsor used a bridging assay format for the isotyping assay. The assay design should allow for determination of ADA isotypes. The qualification results are provided in Summary Table 2.4.1 below. Raw validation data are not provided unless necessary to discuss identified validation issues.*

Assessor comment: *This assay design should allow for the characterization of ADA isotypes.*

Validation Parameter	Val Reports for anti-HSP-130:181683/183265/184335/186288/C1227001	Assessor Comment
Contract Research Org	(b) (4)	<i>Bioanalytical inspection was performed by OSIS. There were no objectionable findings and a Form FDA 483 was not issued (see memo dated 1/24/2020 from YiYue Zhang in DARRTS)</i>
Assay principle	<ul style="list-style-type: none"> MSD (ECL) based Single Bridging ELISA with sulfotagged IgG or IgM + biotinylated pegfilgrastim onto streptavidin coated MSD assay plates. The ELC signal (Relative Light Units) is proportional to the amount of anti-pegfilgrastim IgG or IgM bound. 	
Sample Pretreatment	Samples are acidified by adding an equal volume of 0.8% acetic acid followed by a 1:1 dilution in Trizma neutralization buffer, including equal concentration of	<i>Acid dissociation is a common approach to reduce drug interference A single round of acid dissociation was performed.</i>

351(k) BLA 761111 (Nyvepria) Immunogenicity Assessment

(Acid dissociation)	sulfo-tagged IgG, IgM or pegfilgrastim and biotinylated pegfilgrastim. Final serum concentration=5%	<i>Results were acceptable.</i>
Positive control (PC)	Rabbit anti-PEG-GCSF polyclonal antibody	<i>PC used in validation of ADA and NAb assays, including LPC and HPC preparation. The Applicant demonstrated antigenic equivalence in that the PC antibody bound similarly to PF-06881894, pegfilgrastim-US, and pegfilgrastim-EU.</i> <i>The Rabbit anti-PEG-GCSF polyclonal antibody is suitable as the PC.</i>
LPC	14.4 ng/mL	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
HPC	5000 ng/mL	<i>This is consistent with FDA guidance¹ and is acceptable.</i>
IgG Isotype Control	Human IgG whole molecule biotin conjugated 100 ng/mL	
IgM Isotype Control	Human IgM (myeloma) whole molecule biotin conjugated 100 ng/mL	
Matrix and NC	Pooled human serum	<i>The signals of blank samples must be below SCP.</i> <i>The use of healthy human serum pool as the matrix control is consistent with FDA guidance¹ and is acceptable.</i>
MRD		<i>Correctly includes acid dissociation and buffer neutralization steps to determine MRD.</i>
NC system suitability range	Mean upper limit 117 RLU	<i>The range is based on mean normalized signal – (t0.01,df x SD), t0.01df =2.845</i>
System suitability	HCP: Lower limit 101 RLU LPC: Lower limit assay cut point IgG: Lower limit 17.5 RLU IgM: Lower limit 2.95 RLU	<i>The range is based on mean normalized signal + (t0.01,df x SD), t0.01df =2.845</i>
Antigenic Equivalence testing (Competitive DOE)		<i>Assay performance was assessed through side-by-side comparisons of results from LPC and HPC samples spiked with 0.00, 0.50, 1.00, 5.00, 10.0, 25.0, 50.0, 100 and 500 µg/mL PF-06881894, pegfilgrastim-US, or pegfilgrastim-EU. This approach is acceptable.</i>
Cut- point (CP)	CP factor plate acceptance: 1.08 CP factor Human IgG: 1.04	<i>IgG: The SCP was determined using 50 individual commercial NHS lots analyzed in duplicate on three separate days by two</i>

Floating CP= Mean PNC of plate x CP factor	CP factor Human IgM: 0.997	<p><i>analysts. No outliers were identified. The data were non-normally distributed. Therefore, a non-parametric statistical approach was used by calculating the 95th percentile of the data.</i></p> <p>IgM: <i>The SCP was determined using 50 individual commercial NHS lots analyzed in duplicate on three separate days by two analysts. No outliers were identified. Data were normally distributed. Therefore, a parametric statistical approach was used for calculating the cut point.</i></p> <p><i>This is consistent with FDA guidance¹ and is acceptable.</i></p>
Sensitivity	IgG: 0.379 ng/mL IgM: 1.77 ng/mL	<p><i>Sensitivity was determined as the concentration at which the IgG or IgM produced a signal equal to the SCP. Results from 3 independent sensitivity curves from 10 – 0.078 ng/mL of biotinylated IgG or 100 – 0.078 ng/mL IgM were used.</i></p> <p><i>Sensitivity is consistent with current FDA guidance¹ of ≤100ng/ml and is acceptable.</i></p>
Repeatability/Intra-assay variability	IgG: 7.11%CV IgM: 3.18%CV	<p><i>Intra-assay precision was assessed using data from the IgG and IgM controls on each plate.</i></p> <p><i>Isotyping is used as for further characterization of the ADA response and the approach is suitable for the intended purpose. Intra-assay precision is acceptable for this assay format.</i></p>
Intermediate Precision (IP)/inter-assay variability	IgG: 19%CV IgM: 19.6%CV	<p><i>IgG and IgM controls were analyzed on multiple days to assess IP.</i></p> <p><i>Isotyping is used as for further characterization of the ADA response and the approach is suitable for the intended purpose. Intermediate precision is acceptable for this assay format.</i></p>
Selectivity	IgG on IgM negative IgM on IgG negative	<p><i>Selectivity was assessed by determining the amount of reactivity each isotype specific detector reagent has to a non-specific antibody isotype. Sample signals were assessed using the SCP appropriate for the isotype, e.g. IgG coat with IgG isotype SCP</i></p>

		<p><i>with IgM samples. Cross-reactivity curves from 100 – 0.781 ng/mL were evaluated.</i></p> <p><i>This is approach is acceptable.</i></p>
ADA Assay Assessment		<p><i>The isotyping assay qualification studies were acceptable. Critical assay parameters, including establishment of cut points, sensitivity, and selectivity (cross-reactivity) were established. The assay is used for ADA characterization and is suitable for its intended purpose. No further action is indicated.</i></p>

2.5 Facility Inspection Summary

Bioanalytical inspection was performed by OSIS. There were no objectionable findings and a Form FDA 483 was not issued (see memo dated 1/24/2020 from YiYue Zhang in DARRTS).

2.6 Assessment of Assay Performance in Clinical Studies

See comments in the assay validation assessments.

2.7 Information Requests Sent During Assessment

None.



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Susan
Kirshner

Digitally signed by Susan Kirshner

Date: 4/16/2020 11:38:10PM

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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: March 20, 2020

Requesting Office or Division: Division of Hematology Products (DHP)

Application Type and Number: BLA 761111

Product Name, Dosage Form, and Strength: PF-06881894^a
Nyvepria (pegfilgrastim-apgf)
Injection
6 mg/0.6 mL

Applicant/Sponsor Name: Hospira Inc., a Pfizer Company (Hospira)

FDA Received Date: March 13, 2020

OSE RCM #: 2019-1274-1

DMEPA Safety Evaluator: Stephanie DeGraw, PharmD

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Hospira submitted revised carton and container labels for Nyvepria (pegfilgrastim-apgf) on March 13, 2020 (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review^b.

2 CONCLUSION

We note that all previous recommendations were accepted and implemented. DMEPA concludes the revised container label and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

^a PF-06881894 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name, Nyvepria, and nonproprietary name, pegfilgrastim-apgf, are conditionally approved only with the approval of "PF-06881894".

^b DeGraw, S. Label and Labeling Review for Nyvepria PF-06881894 (pegfilgrastim-xxxx) BLA 761111. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 16. RCM No.: 2019-1274.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON MARCH 13, 2020

Container Label – Syringe



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

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

/s/

STEPHANIE L DEGRAW
03/20/2020 11:43:59 AM

HINA S MEHTA
03/23/2020 03:26:19 PM

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: February 10, 2020

To: Michael Gwathmey, RN
Regulatory Health Project Manager
Division of Hematologic Malignancies 2 (DHM2)

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

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

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Emily Dvorsky, 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/nonproprietary name): NYVEPRIA (pegfilgrastim-apgf)¹ [PF-06881894]

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761111

Applicant: Hospira, Inc. a Pfizer Company

¹ PF-06881894 has been developed as a proposed biosimilar to US-licensed Neulasta. At the time of this review, the proposed proprietary name NYVEPRIA has been found conditionally acceptable by DMEPA on August 19, 2019. A four letter suffix for the proposed non-proprietary (proper) name has been determined to be conditionally acceptable on February 6, 2020.

1 INTRODUCTION

On June 10, 2019, Hospira, Inc., a Pfizer Company, submitted for the Agency's review an original Biologics License Application (BLA) 761111 for [PF-06881894] NYVPERIA (pegfilgrastim-apgf) injection, a proposed biosimilar to Neulasta (pegfilgrastim) injection (BLA 125031). The proposed indication for NYVPERIA (pegfilgrastim-apgf) injection is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. The Applicant's proposed proprietary name, NYVPERIA, was found conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on August 19, 2019.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 2 (DHM2) on August 5, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NYVEPRIA (pegfilgrastim-apgf) injection.

DMPP conferred with DMEPA and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft NYVEPRIA (pegfilgrastim-apgf) injection PPI received on June 10, 2019, and revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 16, 2019.
- Draft NYVEPRIA (pegfilgrastim-apgf) injection Prescribing Information (PI) and IFU received on June 10, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 16, 2019.
- Approved NEULASTA (pegfilgrastim) injection (BLA 125031) labeling dated April 16, 2019, June 18, 2018, and April 28, 2016.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved 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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SUSAN W REDWOOD
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EMILY M DVORSKY
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SHARON R MILLS
02/10/2020 01:58:23 PM

LASHAWN M GRIFFITHS
02/10/2020 02:08:38 PM

MEMORANDUM

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

DATE: Feb 4, 2020

TO: Angelo DeClaro, MD
Director (Acting)
Division of Hematologic Malignancies 1 (DHM1)
Office of Oncologic Diseases
Office of New Drugs

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

THROUGH: Seongeun Cho, Ph.D.
Director Director
DGDSI
OSIS

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

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) and the Office of Regulatory Affairs (ORA) inspected the analytical PK portion of Study ZIN-130-1505 (BLA 761111) conducted at [REDACTED] (b) (4)
[REDACTED]

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. However, we brought up several discussion items during the close-out meeting. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the discussion items and the firm's response to discussion items, I conclude that the PK data from study ZIN-130-150 may not be reliable until additional data from selectivity and hemolysis effect experiments are evaluated.

2. Inspected Studies

Study ZIN-130-1505 (BLA 761111)

"A Phase 1 Study Assessing the Pharmacodynamic and Pharmacokinetic Equivalence of HSP-130 With US-Approved Neulasta

(Registered) and EU-Approved Neulasta (Registered) Administered as a Single Subcutaneous Dose to Healthy Volunteers”

Sample Analysis Period: 03/09/2016 - 06/01/2016

3. Scope of Inspection

OSIS scientist Xiaohan Cai, Ph.D. and the ORA investigator Lina Yang audited the analytical portion of the above study at

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

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

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to [REDACTED] (b) (4). However, we discussed the following items with management during the inspection and at close-out. My evaluation of the discussion items, and the firm’s response dated 12/13/2019 (**Attachment 1**) are presented below.

4.1. Discussion items

We discussed following items with the firm’s management.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

OSIS Evaluation: The firm's corrective action is acceptable. The validity of the pegfilgrastim concentrations in the 153 hemolyzed samples (**Attachment 2**) from study ZIN-130-1505 will be determined based on the outcome of the firm's additional hemolysis effect data.

[REDACTED] (b) (4)

5. Conclusion

After review of the inspectional findings, I conclude that validity of the PK data from the audited study ZIN-130-1505 will be determined based on the firm's additional evaluation on selectivity and hemolysis effect. These experiments are expected to be completed in Jan 2020.

Studies using similar methods conducted between the previous inspection [REDACTED] (b) (4) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI-

[REDACTED] (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Cai
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: XHC 1/21/2020; 1/28/2020; 2/3/2020
Edit: YMC 1/28/2020; 1/30/2020, JC 1/29/2020

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ [REDACTED] (b) (4)

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

FACTS: [REDACTED] (b) (4)

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MEMORANDUM

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

DATE: January 24, 2020

TO: Angelo DeClaro, M.D.
Director (Acting)
Division of Hematologic Malignancies 1 (DHM1)
Office of Oncologic Diseases (OOD)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

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

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

Inspection Summary

OSIS and the Office of Regulatory Affairs (ORA) inspected the analytical portion of **Studies ZIN-130-1505** and **C1221005** (BLA 761111, Pegfilgrastim/HSP-130/PF-06881894) conducted at [REDACTED] (b) (4)

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI). One verbal item was discussed with the site's management regarding insufficient assessment of freeze-thaw stability for the immunogenicity assays during sample analysis. Specifically, some subject samples exceeded the established freeze-thaw stability during sample analysis. However, the sample signal responses were consistent throughout the analyses suggesting that the exceeded freeze-thaw cycles did not affect the stability of the anti-Pegfilgrastim antibodies (ADA) and anti-PEG antibodies. Therefore, this finding is unlikely to have impact on data integrity.

Recommendation

Based on my review of the inspectional findings and the site's response, I conclude the immunogenicity data from **Studies ZIN-130-1505** and **C1221005** are reliable to support a regulatory decision. The review division can request the method validation reports of further assessment on the additional freeze-thaw stability to verify if exceeded freeze-thaw cycles affected the stability of ADA and anti-PEG antibodies.

Inspected Studies

BLA 761111

Study #1: ZIN-130-1505

Study Title: "A Phase 1 Study Assessing the Pharmacodynamic and Pharmacokinetic equivalence of HSP-130 With US-Approved Neulasta (Registered) and EU-Approved Neulasta (Registered) Administered as a Single Subcutaneous Dose to Healthy Volunteers"

Bioanalytical Report #1: "Immunoassay Sample Analysis Report for the Detection of Anti-HSP-130 Antibodies in Human Serum by an Electrochemiluminescent Assay (ECLA)"
([REDACTED] (b) (4) #183332)

Sample Analysis Period: January - June 2016

Bioanalytical Report #2: "Immunoassay Sample Analysis Report for the Detection of Anti-PEG Antibodies in Human Serum by an Enzyme Linked Immunosorbent Assay (ELISA)" ([REDACTED] (b) (4) #183333)

Sample Analysis Period: January - July 2016

Study #2: C1221005

Study Title: "Phase 1, Randomized Open Label, Multiple Dose, Parallel Study to Assess the Immunogenicity of Multiple Subcutaneous (SC) Doses of the Proposed Pegfilgrastim Biosimilar (PF-06881894) and US-Approved Neulasta (Registered) in Healthy Volunteers"

Bioanalytical Report #1: "Immunoassay Sample Analysis Report for the Detection of Anti-HSP-130 Antibodies in Human Serum by an Electrochemiluminescent Assay (ECLA)"
([REDACTED] (b) (4) #186311)

Sample Analysis Period: June 2018 - January 2019

Bioanalytical Report #2: "Immunoassay Sample Analysis Report for the Detection of Anti-PEG Antibodies in Human Serum by an Enzyme Linked Immunosorbent Assay (ELISA)" ([REDACTED] (b) (4) #186309)

Sample Analysis Period: September 2018 - February 2019

Bioanalytical Report #3: "Immunoassay Sample Analysis Report for the Detection of Anti-HSP-130 Antibodies in Human Serum by an Electrochemiluminescent Assay (ECLA)" ([REDACTED] (b) (4) #187555)

Sample Analysis Period: November 2018 - February 2019

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

Scope of Inspection

OSIS scientists Yiyue Zhang, Ph.D., Gabriel Davila, DVM, and ORA Investigator Karen Kosar (OBIMO) conducted the analytical inspection of **Studies ZIN-130-1505** and **C1221005** at [REDACTED] (b) (4) from [REDACTED] (b) (4)

The previous BIMO analytical inspection was conducted from [REDACTED] (b) (4) and covered immunogenicity and pharmacokinetic (PK) studies submitted to BLA [REDACTED] (b) (4). A three-item Form FDA-483 was issued at the inspection close-out [REDACTED] (b) (4)

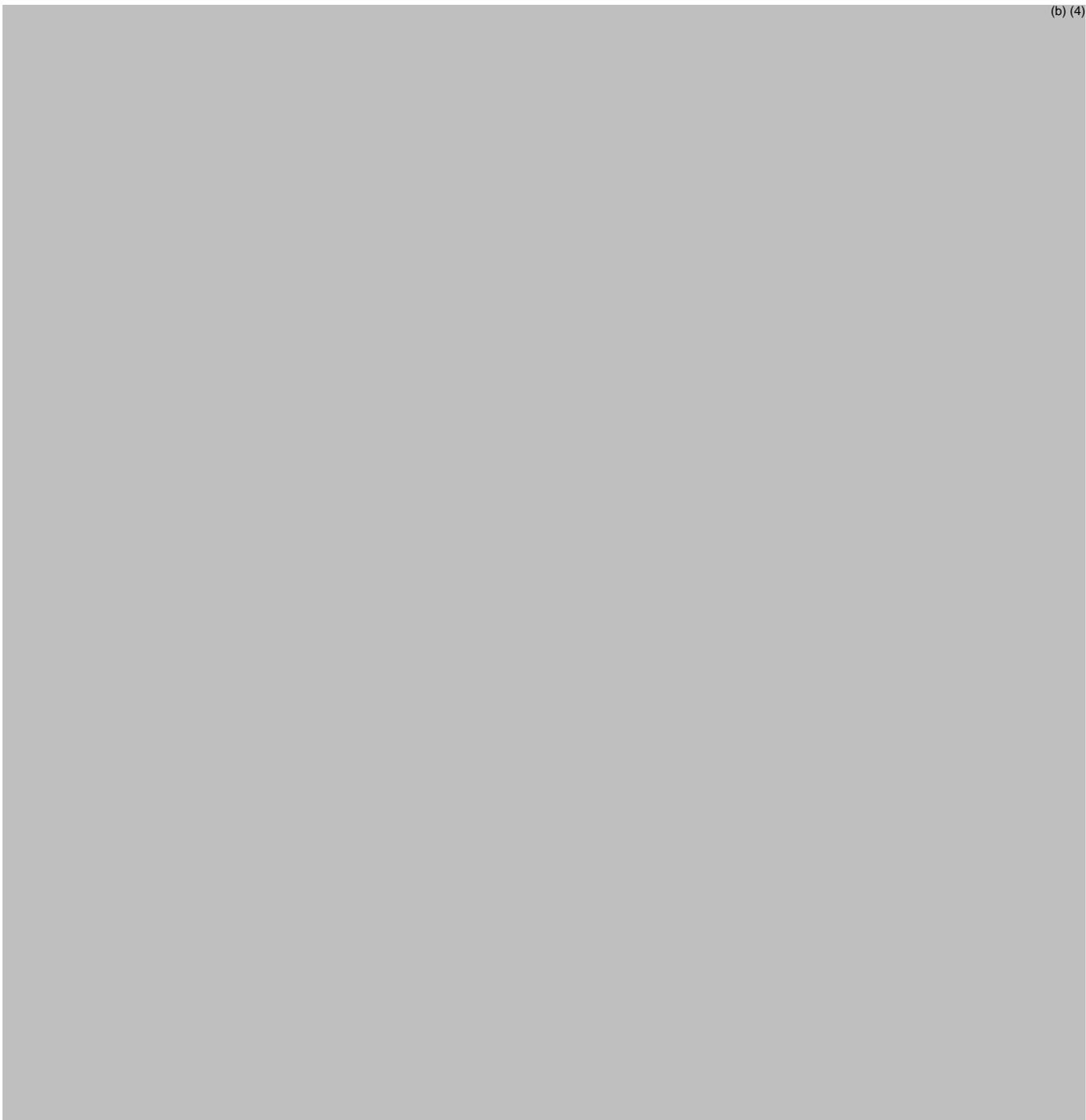
[REDACTED] During the current inspection, I verified that proposed corrective and preventive actions had been implemented. The site's management also provided a written response (**Attachment 1**) during the inspection to clarify the proposed revision of two SOPs are currently ongoing.

The current inspection included a thorough audit of available paper and electronic study records of method validation and sample analysis, and interviews with the site's management and staff.

Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions and did not issue a Form FDA 483. However, we discussed the following item with the site's management at the inspection close-out. The inspectional findings, my evaluations, and the site's response during the inspection (**Attachment 1**) are presented below.

(b) (4)



Conclusion

Based on my review of the inspectional findings and the site's responses, I conclude the immunogenicity data from **Studies ZIN-130-1505** and **C1221005** are reliable to support a regulatory decision. The review division can request the method validation reports for further assessment [REDACTED] (b) (4)

Additionally, immunogenicity studies conducted by [REDACTED] (b) (4) between the previous inspection [REDACTED] (b) (4) and the end of the current surveillance interval should be scrutinized on the issues of [REDACTED] (b) (4) identified in this review to determine data reliability prior to being used to support a regulatory decision.

Yiyue Zhang, Ph.D.
Senior Staff Fellow

Final Classification

Analytical Site

NAI - [REDACTED] (b) (4)

Attachments:

Attachment 1. Written responses provided by [REDACTED] (b) (4) during the inspection

Attachment 2. [REDACTED]

(b) (4)

cc:

OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza/Davila
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov/Kosar

Draft: YZ 01/10/2020, 01/22/2020

Edit: RCA 1/22/2020, 1/23/2020; AD 01/23/2020

ECMS: Cabinets/CDER OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/

(b) (4)

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

FACTS: [REDACTED] (b) (4)

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ARINDAM DASGUPTA
01/24/2020 10:58:20 AM

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:	January 16, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761111
Product Name, Dosage Form, and Strength:	Nyvepria [PF-06881894]* (pegfilgrastim-xxxx)** Injection 6 mg/0.6 mL
Product Type:	Single Ingredient Product, Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira Inc., a Pfizer Company (Hospira)
FDA Received Date:	June 10, 2019
OSE RCM #:	2019-1274
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

*PF-06881894 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name, Nyvepria, is conditionally approved only with the approval of "PF-06881894".

**The nonproprietary name suffix for this BLA has not yet been determined; therefore, the placeholder, pegfilgrastim-xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1. REASON FOR REVIEW

Hospira Inc., a Pfizer Company (Pfizer) submitted BLA 761111 on June 10, 2019. This review evaluates the proposed container label, carton labeling, Prescribing Information (PI), Patient Information, and Instructions for Use (IFU) for Nyvepria (pegfilgrastim-xxxx) for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT BACKGROUND

Hospira submitted 351(k) BLA 761111 seeking licensure for Nyvepria as a biosimilar to US-licensed Neulasta. US-licensed Neulasta (pegfilgrastim) was approved on January 31, 2002, under BLA 125031. Nyvepria is being proposed for the indication of decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Nyvepria is being proposed as a 6 mg/0.6 mL solution in a single-dose prefilled syringe with a passive needle guard. Like US-licensed Neulasta, Nyvepria's syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe for direct administration.

1.2 REGULATORY HISTORY

A BPD Type 2 meeting was held with Hospira on May 1, 2017. During this meeting the Agency recommended that Hospira perform a comprehensive use-related risk analysis of the proposed PF-06881894 prefilled syringe (PFS) to determine the necessity of a human factors (HF) validation study.^a

DMEPA evaluated the use-related risk analysis, physical comparison, and IFU comparison of PF-06881894 with US-licensed Neulasta submitted by Hospira under IND 124793 on November 21, 2017. The review concluded that the comparative analyses did not identify any new or unique risks for PF-06881894 when compared to US-licensed Neulasta. Therefore, it was determined that an HF validation study did not need to be submitted for Agency review for the proposed single-use prefilled syringe at that time.^b

2. MATERIALS 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

^a Memorandum of Meeting Minutes for HSP-130 (IND 124793). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2017 Jun 01.

^b Garrison, N. PF-06881894 (IND 124793) Use-Related Risk Analysis Review Memo. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 2. RCM No. 2018-425.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F
Pediatric Considerations	G

N/A=not applicable for this review

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

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, PI, and IFU for Nyvepria to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed Nyvepria PI did not identify unique areas of vulnerability that may lead to medication errors; however, our evaluation of the proposed Nyvepria IFU, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations below.

4. CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Nyvepria PI did not identify unique areas of vulnerability that may lead to medication errors. We have no recommendations for the PI at this time.

However, our evaluation of the proposed Nyvepria IFU, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations for the division in Section 4.1 and recommendations for Hospira in Section 4.2 below. We advise they be implemented prior to approval of BLA 761111.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Instructions for Use

1. **Guide to Parts:** As currently presented, the “Before Use” figure does not include a label for the needle guard spring. Therefore, we recommend labeling the spring in this image as “needle safety spring” or “needle safety guard unactivated”.
2. **Step 1 Prepare:** We recommend revising “inner syringe carton” to read “inner carton containing the syringe” to improve clarity.
3. **Step 4 Finish**
 - a. **Step I:** As currently presented, this step does not inform users to keep the plunger pressed down so that the needle guard is not activated until

the syringe is removed from the injection site. Therefore, we recommend revising these instructions to state “When the syringe is empty, keep the plunger fully pressed down while you carefully pull the needle straight out from the injection site and off your skin”.

- b. **Step J:** We recommend revising these instructions to improve clarity. Revise to read “Slowly release the plunger and allow the syringe needle guard to automatically cover the exposed needle.”
- c. **Step L:** As currently presented, this step which instructs users to examine the injection site for blood appears after the discard syringe step. We recommend relocating this step so that it appears immediately after step J.

4.2 RECOMMENDATIONS FOR HOSPIRA

A. Carton Labeling (Shelf and Unit Cartons)

1. As currently presented, the strength is located at the bottom of the principal display panel. We recommend relocating the strength so that it appears directly below the proper name to ensure it is not missed.
2. We recommend de-bolding the “Rx Only” statement as this information appears with equal prominence to critical information on the principal display panel.
3. Revise “Usual Dosage: see prescribing information for dosage and instructions for use” to read “Dosage: See Prescribing Information” to ensure consistency with all doses described in the prescribing information.
4. We recommend removing the trailing zeros that appear on the back panel (i.e., 4.0 and 30.0 mg) to avoid misinterpretation of the numbers (i.e., 4 versus 40 and 30 versus 300).

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Nyvepria that Hospira Inc., a Pfizer Company submitted on June 10, 2019, and US-licensed Neulasta.

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

^c Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Apr 2019. [cited 2019 NOV 13]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125031s198lbl.pdf.

	<p>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome:</p> <ul style="list-style-type: none"> • Give 6 mg subcutaneously for adult victims with body weight \geq 45 kg for two doses given one week apart; for pediatric patients weighing less than 45 kg, use weight-based dosing. <p>The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.</p> <p>Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg</p> <table border="1" data-bbox="537 1192 979 1528"> <thead> <tr> <th>Body weight</th> <th>Neulasta Dose</th> <th>Volume to administer</th> </tr> </thead> <tbody> <tr> <td>Less than 10kg*</td> <td>See below*</td> <td>See below*</td> </tr> <tr> <td>10-20 kg</td> <td>1.5 mg</td> <td>0.15 mL</td> </tr> <tr> <td>21-30 kg</td> <td>2.5 mg</td> <td>0.25 mL</td> </tr> <tr> <td>31-44 kg</td> <td>4 mg</td> <td>0.4 mL</td> </tr> </tbody> </table> <p>*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta</p>	Body weight	Neulasta Dose	Volume to administer	Less than 10kg*	See below*	See below*	10-20 kg	1.5 mg	0.15 mL	21-30 kg	2.5 mg	0.25 mL	31-44 kg	4 mg	0.4 mL	<p>The NYVEPRIA prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of NYVEPRIA less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.</p> <p>Table 1. Dosing of NYVEPRIA for Pediatric Patients Weighing Less than 45 kg</p> <table border="1" data-bbox="1008 1119 1451 1419"> <thead> <tr> <th>Body Weight</th> <th>NYVEPRIA 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 NYVEPRIA.</p>	Body Weight	NYVEPRIA 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
Body weight	Neulasta Dose	Volume to administer																														
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10-20 kg	1.5 mg	0.15 mL																														
21-30 kg	2.5 mg	0.25 mL																														
31-44 kg	4 mg	0.4 mL																														
<p>How Supplied</p>	<p>Neulasta is a clear, colorless, preservative-free solution available as single dose prefilled syringe with an UltraSafe® Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim as well as an OnPro kit</p>	<p>NYVEPRIA (pegfilgrastim-xxxx) injection is a sterile, clear, colorless, preservative-free solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-xxxx, supplied with a</p>																														

	which contains 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the on-body Injector for Neulasta.	27-gauge ½-inch needle and a BD UltraSafe Plus™ Passive Needle Guard.
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 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 15 days. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 14, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Nyvepria' and 'PF-06881894'. Our search identified two previous reviews^{d,e}, and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. Summary of Previous DMEPA Reviews for Nyvepria or PF-06881894		
OSE RCM #	Review Date	Summary of Recommendations
2019-32308118	2019 AUG 08	The proposed proprietary name, Nyvepria, is acceptable.
2018-425	2018 APR 02	The comparative analyses did not identify any new or unique risks when compared to US-licensed Neulasta; the intended user group, intended users, and use environments for Nyvepria aligns with US-licensed Neulasta for febrile neutropenia; therefore, an HF validation study does not need to be submitted for our review for the proposed single-use prefilled syringe.

^d Vee, S. Proprietary Name Review for Nyvepria (BLA 761111). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 08. RCM No.: 2019-32308118.

^e Garrison, N. Human Factors – Use-Related Risk Analysis Review Memo for PF-06881894 (IND 124793). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 02. RCM No.: 2018-425.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Nyvepria labels and labeling submitted by Hospira Inc., a Pfizer Company on June 10, 2019.

- Container label(s)
- Carton labeling
- Prescribing Information – includes Instructions for Use (image not shown)
Annotated: <\\cdsesub1\evsprod\bla761111\0001\m1\us\lab-1186-0-1-uspi-track-change.doc>
Clean: <\\cdsesub1\evsprod\bla761111\0001\m1\us\lab-1186-0-1-uspi-clean.doc>

F.2 Label and Labeling Images

Container label – Syringe



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

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APPENDIX G. Pediatric Considerations

As part of Hospira's submissions to BLA 761111, Hospira submitted a request for deferral for its pediatric assessments. We note the following:

- October 4, 2019, DMEPA memorandum (archived to BLA 125031). On October 4, 2019, DMEPA finalized a memorandum of a comprehensive review and analysis of medication errors associated with doses of pegfilgrastim products less than 0.6 mL (6 mg) in pediatric patients. PF-06881894 has the same strength, dosage form, and route of administration as US-licensed Neulasta, and, like US-licensed Neulasta, would only be available in a prefilled syringe without graduation marks. Additionally, the proposed labeling for PF-06881894, in relevant part, is substantially the same as US-licensed Neulasta's labeling, including with respect to pediatric use information and the statements that the prefilled syringe is not designed to allow for direct administration and cannot accurately measure doses less than 0.6 mL (6 mg). Therefore, if the requirements for biosimilarity are met, PF-06881894 would be expected to be associated with the same type of dosing error and potential consequences as US-licensed Neulasta. See also October 10, 2019, Memorandum on Requirements for Pediatric Assessments Pursuant to Section 505B(b)(1) of the FD&C Act.
- Order letter to sponsor of US-licensed Neulasta. On October 10, 2019, FDA issued an order letter pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to the sponsor of US-licensed Neulasta, requiring it to submit pediatric assessments as described in section 505B(a)(2)(A) of the FD&C Act. As described in the letter, the sponsor of U.S.-licensed Neulasta is subject to a postmarketing requirement referred to as submission of pediatric assessments for Neulasta (pegfilgrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta (pegfilgrastim) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. In the letter, FDA stated it expected that a pediatric presentation – such as a vial or a pediatric-sized pre-filled syringe (with an appropriate concentration of product) – that can be used to directly and accurately deliver doses of less than 0.6 mL (6 mg) of pegfilgrastim to pediatric patients could be an "appropriate formulation" as described in section 505B(a)(2)(A). (FDA issued similar letters to sponsors of the licensed pegfilgrastim biosimilars, Udenyca (BLA 761039) and Fulphila (BLA 761075). On November 4, 2019, FDA licensed Ziextenzo (BLA 761045), which is also subject to a similar postmarketing requirement.)

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/s/

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

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

Memorandum

Date: December 17, 2019

To: Michael Gwathmey, Regulatory Project Manager
Division of Hematology Malignancies 1 (DHM1)

From: Emily Dvorsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

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

BLA: 761111

In response to DHM1 consult request dated August 5, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU) for the original BLA submission for Nyvepria™(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 DHM1 (Michael Gwathmey) on August 13, 2019 and we do not have any comments.

PPI/IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4253 or Emily.Dvorsky@fda.hhs.gov.

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/s/

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