CROSS-DISCIPLINE TEAM LEADER REVIEW

Application Number	**BLA 761080**
Application Type	Original 351(k) BLA
Applicant	Hospira, Inc., a Pfizer Company
Date of Receipt	9/21/2017
BSUFA Goal Date	7/21/2018
Division/Office	DHP/OHOP
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD
Proposed Proprietary Name	Nivestym*
Proposed Proper Name	filgrastim-aafi*
Dosage form / Strength(s)	Injection Vial (300 mcg/1.0 mL, 480 mcg/1.6 mL) Prefilled syringe (300 mcg/0.5 mL, 480 mcg/0.8 mL)
Applicant's Proposed Indication(s)/Population(s)	• To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. • For reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation. • For the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. • To reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
Recommendation on Regulatory Action	Approval

* For purposes of this review, the proposed product is referred to by either the proprietary name, the proper (nonproprietary) name, or the Sponsor's descriptor PF-06681893. The proposed proprietary name, Nivestym, and the proposed proper name, filgrastim-aafi, are only conditionally accepted until the application is approved.

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ADDITIONAL MATERIAL REVIEWED/CONSULTED

Review Document	Reviewer(s)
Product Quality Assessment	
Integrated Quality Review (6/18/2018)	Howard Anderson, PhD; Xianghong Jing, PhD
ADA Assay Review (6/6/2018)	Scott Lute, PhD; Harold Dickensheets, PhD
Drug Product Review (6/6/2018)	Scott Lute, PhD; Howard Anderson, PhD
Drug Substance and Analytical Similarity (6/6/2018)	Malini Wileman, PhD; Howard Anderson, PhD
CMC Statistical Review (6/7/2018)	Tianhua Wang, PhD; Meiyu Shen, PhD
Device Quality System Review (6/8/2018)	Crystal Lewis; Nazia Rahman
Device Performance Review (6/11/2018)	Kenya Brothers, PhD / John McMichael
DP Microbiology Review (6/11/2018)	Aimee L. Cunningham, PhD; Reyes Candau-Chacon, PhD
DS Microbiology Review (6/12/2018, 6/20/2018)	Maxwell Van Tassell, PhD; Reyes Candau-Chacon, PhD
Facilities Review (6/20/2018)	Marion Michaelis; Zhihao Qiu, PhD
Nonclinical Review (6/12/2018)	Pedro L. Del Valle, PhD; Christopher Sheth, PhD
Office of Clinical Pharmacology Review (6/12/2018)	Theingi Thway, PhD; Olanrewaju Okusanya, PharmD, MS
Clinical Review (6/12/2018)	Lea Cunningham, MD
Biostatistical Review (6/1/2018)	Lola Luo, PhD; Yuan-Li Shen, DrPH; Thomas Gwise, PhD
Office of Scientific Integrity and Surveillance Reviews	
(11/3/2017)	Shila S. Nkah
(1/22/2018)	Xiaohan Cai, PhD; Kara Scheibner, PhD
(4/2/2018)	Melkamu Getie-Kebtie, PhD; Amanda Lewin, PhD
(4/12/2018; 4/20/2018)	Gajendiran Mahadevan, PhD
Labeling Reviews	
Proprietary Name Review (12/14/2017)	Nicole Garrison, PharmD, BCPS
PLR Format Review (12/18/2017)	Wanda Nguyen, PharmD
Labeling Review (6/7/2018)	Robert Nguyen, PharmD
Use-Related Risk Analysis (6/8/2018)	Nicole Garrison, PharmD, BCPS
Proprietary Name Review (6/14/2018)	Nicole Garrison, PharmD, BCPS
Patient Labeling Review (6/18/2018)	Sharon R. Mills, BSN, RN, CCRP; Robert Nguyen, PharmD

1. Introduction

On September 21, 2017, Hospira, Inc., a Pfizer Company (Applicant) submitted BLA 761080 for PF-06881893 as a proposed biosimilar product to US-licensed Neupogen (Amgen Inc.). The Applicant seeks licensure of PF-06881893 under section 351(k) of the Public Health Service Act.

2. Background

2.1 Product Information

Proposed Proper Name:	filgrastim-aafi
Code Name:	PF-06881893
Proposed Trade Name:	Nivestym
Dosage Forms:	Injection, vial (300 mcg/1.0 mL, 480 mcg/1.6 mL) Injection, prefilled syringe (300 mcg/0.5 mL, 480 mcg/0.8 mL)
Therapeutic Class:	Leukocyte Growth Factor
Chemical Class:	Recombinant Protein
Mechanism of Action:	PF-06881893 acts on hematopoietic cells by binding to specific cell surface receptors. Signaling through the receptor affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation, including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens.

2.2 Reference Product

The applicant identified US-licensed Neupogen as the reference product. Neupogen (filgrastim) was approved in the United States initially in 1991, and five additional indications were approved subsequently based on supplements to the BLA. The indications are:

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (Approved 2/20/1991)
- To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (Approved 4/2/1998)

- To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (Approved 6/15/1994)
- To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (Approved 12/28/1995)
- To reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (Approved 12/19/1994)
- To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Approved 3/30/2015)

In this BLA submission, the Applicant proposed licensure of PF-06881893 for the same indications as approved for US-licensed Neupogen except the indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation. The acute radiation syndrome indication was not sought by the Applicant as US-licensed Neupogen has unexpired orphan drug exclusivity for this indication.[1]

2.3 Regulatory Background

A pre-IND meeting was held on March 11, 2011, and a Biosimilar Product Development (BPD) Type 2 meeting was held on February 25, 2015, to obtain advice on the US development program for PF-06881893. IND 109991 was submitted for PF-06881893 on September 4, 2015; the supporting clinical studies for this BLA were conducted in the US under IND 109991. A BPD Type 3 meeting was held on August 30, 2016, to discuss the preliminary analytical similarity data. A BPD Type 4 meeting was held on February 8, 2017, to discuss the overall content and format of the planned 351(k) BLA for PF-06881893. The initial Pediatric Study Plan (iPSP) was agreed on July 11, 2017.

3. Product Quality

(Excerpted in part from Dr. Anderson's review)

3.1 Drug Product

PF-06881893 is a 175-amino acid (18,799 Da), single-chain, nonglycosylated, recombinant human N-methionyl granulocyte colony-stimulating factor (G-CSF) protein manufactured in

[1] Neupogen's indication for increased survival in patients acutely exposed to myelosuppressive doses of radiation is protected by orphan drug exclusivity expiring on March 30, 2022. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not license PF-06881893 for this indication until the orphan drug exclusivity expires.

Escherichia coli. The primary structure of PF-06881893 is identical to endogenous G-CSF, except for an additional methionine residue at the N-terminus.

Nivestym injection drug product is a clear, colorless, preservative-free liquid presented in single-dose vials (SDV) (300 mcg/1.0 mL and 480 mcg/1.6 mL) and as prefilled syringes (PFS) (300 mcg/0.5mL and 480 mcg/0.8 mL) with a BD UltraSafe Plus™ Passive Needle Guard. It is formulated in (b) (4) acetate (b) (4), 50 mg/mL sorbitol, 0.04 mg/mL polysorbate 80, and water for injection, and it is intended for subcutaneous or intravenous use. All excipients are compendial grade. The single-dose vial drug products have an expiry of up to 18 months when stored at 2-8°C, and the prefilled syringe drug products have an expiry of up to 30 months when stored at 2-8°C. Natural rubber latex is not used in the syringe plunger stopper and needle cover.

The only issue remaining after review of the manufacturing process was the lack of routine monitoring for bioburden/endotoxin (b) (4). A postmarketing commitment was recommended by the Product Quality review team to resolve this issue. The facilities inspected were considered acceptable. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(c).

3.2 Analytical Similarity Assessment

The tests for the analytical similarity assessment and the lots used in each assay were defined prospectively by the applicant. The entire assessment included 26 PF-06881893 drug product lots (16 PFS and 10 SDV) manufactured from 14 drug substance lots, and 50 US-licensed Neupogen drug product lots. The results are summarized in Table 1.

Table 1: Summary of Analytical Similarity Testing

Assay	**Assay Parameter**	**Demonstration of similarity (Number of lots- Nivestym/ US-Licensed Neupogen)**
Tier 1-Equivalence Testing		
Potency	Cell Based Proliferation Assay	Yes (14 / 15)
Tier 2 Statistical Quality Range (3 standard Deviations)		
UV-Vis spectroscopy	Protein Concentration/Strength	***Yes (13/14 lots Nivestym / 24 lots Neupogen)***
ELISA based Competitive Receptor Binding Assay	Receptor Binding Assay	Yes (11 / 18)
Surface Plasmon Resonance	Receptor Binding Affinity (K_D)	Yes (11 / 17)
RP-HPLC	Total Product Related Substance and Oxidized Met 122, Met 138, reduced)	Yes (12 / 24)
RP-HPLC	Met 127 Oxidation	***Yes (11/12 Nivestym / 27 US licensed Neupogen)***

RP-HPLC	Deamidated	Yes (22 / 27)
Cation Exchange Chromatography (CEX)	Total Product Charge Variants	Yes (11 / 18)
Differential Scanning Calorimetry (DSC)	Tertiary Structure	Yes (11 / 18)
Tier 3 Visual Assessment of graphical displays		
Surface Plasmon Resonance	Receptor Binding Kinetics (K_{on}, K_{off}, K_D)	Yes (11 / 17)
CEX	Total Charge Variants (Acidic Variants peaks 1 and 2)	Yes (14 / 38)
CEX	Deamidated Peaks 1 and 2	Yes (22 / 27)
Glu-C Peptide Mapping	Site-specific deamidation of Gln12, Gln21, Gln68, Gln71, Gln91, Gln108, Gln120, Gln132, Gln159, and Gln174	Yes (11 / 11)
RP-UPLC-MS	Intact Molecular Weight	Yes (2 / 2)
Glu-C Peptide Mapping	Isomerization	Yes (11 / 12)
Glu-C Peptide Mapping/RP-UPLC-MS	Amino acid Sequence Confirmation	Yes (11 / 11)
Ellman's Test	Free Thiol	Yes (7 / 7)
Far-UV Circular Dichroism	Secondary Structure	Yes (16 / 23)
Intrinsic fluorescence	Tertiary Structure	Yes (16 / 23)
Hydrogen Deuterium exchange	Secondary and Tertiary Structure	Yes (3 / 4)
SV-AUC	Tertiary Structure, High Molecular Weigh Product Related Aggregates	Yes (16 / 32)
Nuclear Magnetic Resonance	Tertiary Structure	Yes (2 / 2)
X-ray crystallography	Tertiary Structure	Yes
SEC	High Molecular Weight Substances	Yes (26 / 38)
SDS-PAGE	Product Variants	Yes (16 / 18)
CE-SDS	Product Variants	Yes (12 / 10)
Glu-C Peptide Mapping	Met 1, 127, 138, Trp 59, 119 oxidations, Deamidation Gln 21, 71, 91, 108, 132, Aspartate Isomerization, N-terminal truncations, fMet1, Asp110 and related substances	Yes (11 / 11)
RP-HPLC	Succinimide, reduced species	Yes (22 Nivestym/ 23/27 US Licensed Neupogen)
RP-HPLC	Cys-37-Cys43 and Cys 65-Cys 75	Yes (22 / 27)
No Tier Assignment (18 Lots Nivestym and 5 lots US-licensed Neupogen)		
HCP, HCD, Osmolarity, Polysorbate 80, Appearance, Color Clarity, Visible Particles, Sub Visible Particles		

Source: Adapted from Dr. Anderson's Table 1.

Findings of the review team included:

- For the Tier 1 potency test, the 90% CIs of the mean difference (-0.76, 5.37) were within the prespecified equivalence limits (-8.77, 8.77).
- For the Tier 2 tests, the lots met the acceptance criterion that 90% were within mean ± three standard deviations with two minor differences:
  - For normalized protein concentration, 1 lot fell slightly outside the quality range, but the deliverable content was acceptable.
  - For Met 127 oxidation, 1 lot was slightly above the quality range, but in a related Tier 3 method using Glu-C peptide mapping there was no difference in Met 127 content.
  - The uncertainty raised by these differences was mitigated by the results of the functional potency assay.
- All Nivestym parameters met Tier 3 graphical visual assessment.

The Product Quality review team found that manufacturing is validated and well-controlled, and that it produces a product that is pure and potent. The issue regarding endotoxin testing (b) (4) will be addressed in a postmarketing commitment. On the basis of analytical testing, the reviewers concluded that Nivestym is highly similar to US-licensed Neupogen notwithstanding minor differences in clinically active components. The Office of Pharmaceutical Quality recommended approval of the BLA.

4. Nonclinical Pharmacology/Toxicology

(Excerpted in part from Dr. Del Valle's review)

The applicant conducted a comparative nonclinical 4-week toxicology study of PF-06881893 vs US-licensed Neupogen in Sprague-Dawley rats. The assessment included a comparison of the clinical and laboratory toxicities, local tolerance, absolute neutrophil count as PD biomarker, toxicokinetics and immunogenicity. The reviewer observed that, in this toxicology study, PF-06881893 and US-licensed Neupogen produced similar toxicity profiles, pharmacodynamic responses, systemic exposures, and anti-drug antibody responses.

The Nonclinical Pharmacology/Toxicology review team identified no residual uncertainties regarding the similarity of PF-06881893 to US-licensed Neupogen and concluded that the application was approvable.

5. Clinical Pharmacology

(Excerpted in part from Dr. Thway's review)

The applicant submitted three clinical studies in healthy subjects to support a demonstration of no clinically meaningful differences between PF-06881893 and US-licensed Neupogen (Table 2).

Table 2: Clinical Studies in BLA 761080

Protocol	Title	Subjects	Objectives	Dose/ Route/Duration
PK/PD Similarity Study				
ZIN-FIL-1502	A randomized open-label, single-dose, cross-over study evaluating the pharmacokinetics and pharmacodynamics of PF-06881893 to US-licensed Neupogen® following subcutaneous administration to healthy subjects	Healthy (N=24)	PK, PD (ANC), & safety	5 mcg/kg/day single SC dose of PF-06881893 versus US-licensed Neupogen with at least 28 days between treatments
ZIN-FIL-1501	A randomized open-label, multiple-dose, cross-over study evaluating the pharmacokinetics and pharmacodynamics of PF-06881893 to US-licensed Neupogen® following subcutaneous administration to healthy subjects	Healthy (N=60)	PD (CD34+), PK, & safety,	5 mcg/kg/day for 5 consecutive daily SC doses of PF-06881893 versus US-licensed Neupogen with at least 28 days between treatments
Immunogenicity Study				
C1121012	A randomized open-label, 2-period, parallel arm study to assess the immunogenicity of multiple subcutaneous (SC) doses of "Filgrastim Hospira" or US-licensed Neupogen® reference product in healthy subjects	Healthy (N=256)	Immunogenicity & safety	5 mcg/kg/day for 5 consecutive daily SC doses in period 1 followed by a single SC dose in period 2 of PF-06881893 versus US-licensed Neupogen with at least 26 days between the periods

Source: Adapted from Dr. Thway's Table 3

The reviewer found that the studies ZIN-FIL-1501 and ZIN-FIL-1502 had an appropriate size and design to assess for equivalence of the PK and PD endpoints. Data from only the single-dose study, ZIN-FIL-1502, were used to assess equivalence of PK. The findings of the reviewer are shown in Table 3.

Table 3: Geometric Mean Ratios (95% Confidence Interval) for PK and PD Endpoints

Product comparison	PK Endpoints[a]		PD Endpoints[a]			
	Study ZIN-FIL 1502		Study ZIN-FIL 1502		Study ZIN-FIL 1501	
	Cmax	$AUC_{0\text{-}inf}$	ANC_{max}	ANC $AUEC_{last}$	$CD34+_{max}$	$AUECCD34+_{last}$
PF-06881893 / US-licensed Neupogen	1.11	1.13	1.02	1.01	1.05	1.06
	(1.02 -1.21)	(1.05 -1.23)	(0.97 -1.07)	(0.97 -1.05)	(0.95 -1.17)	(0.99 -1.15)

Source: Adapted from Dr. Thway's Table 2

The reviewer noted the following:

- PK similarity was demonstrated between PF-06881893 and US-licensed Neupogen. The 90% CIs of the geometric mean ratio (GMR) for the primary PK endpoints of C_{max} and $AUC_{0\text{-}inf}$ were within the pre-specified limits of 0.8-1.25.

- PD similarity was demonstrated between PF-06881893 and US-licensed Neupogen in single- and multiple-dose studies. The 90% CIs of the GMR for the primary PD endpoints of

$AUEC_{ANC}$ and ANC_{max} in the single-dose study and $AUEC_{CD34+}$ and $CD34_{+max}$ with multiple doses were within the prespecified limits of 0.8-1.25.

The Office of Clinical Pharmacology recommended approval of PF-06881893 based on a demonstration of PK and PD similarity and no increase in immunogenicity risk between PF-06881893 and US-licensed Neupogen, which support a conclusion that there were no clinically meaningful differences.

6. Clinical

6.1 Efficacy

Given the lack of residual uncertainty at the conclusion of the review of the comparative analytical, nonclinical and clinical pharmacology data to assess similarity, no comparative clinical studies of PF-06681893 in the intended population were necessary to address residual uncertainty regarding the demonstration of no clinically meaningful differences and biosimilarity. The healthy subject population in studies ZIN-FIL-1502, ZIN-FIL-1501, and C1121012 is an acceptable, homogenous, and sensitive population to evaluate for no clinically meaningful differences between PF-06881893 and US-licensed Neupogen. The mechanism of action of filgrastim products for the PD endpoints in healthy subjects is the same as the mechanism of action for filgrastim products in the conditions of use (i.e., indications) for which the applicant is seeking licensure. Furthermore, the PK and PD endpoints in ZIN-FIL-1502 (C_{max}, AUC_{0-inf}, and ANC) and the PD endpoint in ZIN-FIL-1501 (CD34+ cells) are sufficiently sensitive and well-correlated with the intended clinical outcome. For these reasons, the study population and primary PK and PD endpoints used in studies ZIN-FIL-1502 and ZIN-FIL-1501 are acceptable to support assessment of PF-06881893 for the indications for which US-licensed Neupogen has been previously approved.

6.2 Immunogenicity

Study C1121012, the immunogenicity study (see Table 1 above), was an open-label, 2-period, parallel-arm study in healthy volunteers. The anti-drug antibody (ADA) and neutralizing antibody (NAb) assays were reviewed by Dr. Lute, who found them analytically valid for detection of antibodies against both PF-06881893 and US-licensed Neupogen.

(Excerpted in part from Dr. Luo's review)

The primary objective of Study C1121012 was to assess noninferiority of PF-06881893 to US-licensed Neupogen with regard to immunogenicity. The planned sample size (250 subjects) provided > 95% power to demonstrate noninferiority with a margin of 10%. The primary endpoint is the proportion of subjects with a negative ADA at baseline and a confirmed positive

ADA test result at any time after the first dose. There were 256 subjects randomized and 244 were in the full analysis set (FAS population). The findings of the reviewer included:

- ADA were detected in 7.4% of subjects on PF-06881893 and 4.9% of subjects on US-licensed Neupogen for a risk difference of 2.6% (90% CI: -2,72, 8.36).

- The upper limit of the risk difference remained below 10% in multiple sensitivity analyses using various calculation methods, in an analysis of the ITT population, and using as the endpoint subjects with new treatment-emergent ADA or with an increase in ADA titer for those whose baseline was positive.

- There were no NAb detected in either study arm.

The statistical reviewer concluded that the incidence of ADA was similar with PF-06881893 and US-licensed Neupogen, and that the data support a demonstration of no clinically meaningful differences between PF-06881893 and US-licensed Neupogen.

6.3 Clinical Safety

(Excerpted in part from Dr. Cunningham's review)

Comparative clinical safety analyses were conducted using data from the three clinical studies listed in Table 2. Results were assessed descriptively; there was no hypothesis testing. There were 255 subjects randomized and treated in C1121012, 57 subjects treated with at least one dose of PF-06881893 and one dose of US-licensed Neupogen in ZIN-FIL-1501, and 23 subjects treated with one dose of each biologic in ZIN-FIL-1502. Table 4 shows comparisons of the number and percentage of subjects with adverse events of special interest (AESI) in each study.

Table 4: Adverse Events of Special Interest in the Clinical Studies

	C1121012		ZIN-FIL-1501		ZIN-FIL-1502	
AESI	**PF-06881893**	**Neupogen**	**PF-06881893**	**Neupogen**	**PF-06881893**	**Neupogen**
Allergic reactions	1 (0.78)	0 (0)	0 (0)	1 (2)	1 (8)	0 (0)
Musculoskeletal events	44 (34.38)	45 (35.43)	7 (12)	9 (15)	0 (0)	0 (0)
Injection site reaction	2 (1.56)	13 (10.24)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Adapted from Dr. Cunningham's Table 6

The incidence of AESI did not differ substantially between treatment groups except for the injection site reactions in C1121012. On more detailed analysis, the difference in injection site reactions was due largely to a higher number of injection site hemorrhages in the US-licensed Neupogen arm (8 vs 1). Since the discrepancy in the incidence of AESI was not confirmed in

ZIN-FIL-1501, the observation was attributed to procedural issues rather than being an adverse reaction to the study products.

Other findings of the reviewer included:

- There were no substantial differences in adverse events by System Organ Class or Preferred Term in all 3 studies.
- There were no substantial differences in laboratory abnormalities in all 3 studies.
- There were no substantial differences in changes in vital signs or in treatment-emergent ECG changes in all 3 studies.

The clinical reviewer identified no clinically meaningful differences in safety outcomes between PF-06881893 and US-licensed Neupogen, which supports a demonstration of no clinically meaningful differences between PF-06881893 and US-licensed Neupogen.

7. Advisory Committee Meeting

This application was not discussed by an Advisory Committee.

8. Pediatrics

There are no studies of PF-06681893 in children. The labeling for the US-licensed Neupogen contains adequate pediatric information with respect to the indications for which the applicant is seeking licensure of PF-06681893. The proposed presentations of PF-06681893 allow for dosing across the applicable age ranges for these indications. Therefore, based on our determination that totality of the evidence establishes the biosimilarity of PF-06881893 to US-licensed Neupogen, the applicant has fulfilled its requirements under the Pediatric Research Equity Act by extrapolating the pediatric information from the reference product.

9. Other Relevant Regulatory Issues

None.

10. Labeling

10.1 Proprietary and Proper Name

The proposed proper name filgrastim-aafi was determined as conditionally acceptable on 4/23/2018. The proposed proprietary name Nivestym was determined as conditionally acceptable on 6/14/2018.

10.2 Prescribing Information

Based on established biosimilarity, the applicant's proposal that labeling for Nivestym incorporate relevant data and information from the reference product labeling, with appropriate modifications specific to Nivestym, is acceptable. However, the labeling will need to include the updated safety information added to the prescribing information for US-licensed Neupogen since submission of this BLA. Final labeling was still under negotiation at the time of completion of this review.

11. Recommendations

11.1 Recommended Regulatory Action

Approval

11.2 Basis for the Regulatory Recommendation

The Product Quality review noted that the analytical similarity data submitted by the applicant supported a determination that PF-06881893 is highly similar to US-licensed Neupogen notwithstanding minor differences in clinically active components, the Clinical Pharmacology review concluded that the results of Studies ZIN-FIL-1501 and ZIN-FIL-1502 supported a determination of PK and PD similarity, and the Nonclinical Pharmacology/Toxicology review identified no residual uncertainties regarding the similarity of PF-06881893 to US-licensed Neupogen. The results of Study C1121012 showed similar rates of ADA with PF-06881893 and US-licensed Neupogen, and the review of data from the comparative studies in humans showed no substantial differences in clinical safety.

Overall, the totality of the evidence supports the demonstration of no clinically meaningful differences between PF-06881893 and US-licensed Neupogen, and it provides an adequate basis for licensure of PF-06881893 as a biosimilar to US-licensed Neupogen for the indications requested.

11.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

11.4 Recommendation for Postmarketing Requirements and Commitments

One postmarketing commitment was recommended by the Product Quality review team:

To qualify an (b) (4) endotoxin test method with an increased method sensitivity to allow for the establishment of (b) (4) action limits. The (b) (4) after manufacture of 30 drug substance batches. The readjusted (b) (4) endotoxin limits will be reported per 21 CFR 601.12.

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/

DONNA PRZEPIORKA
06/29/2018