

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**125031Orig1s175**

*Trade Name:* NEULASTA

*Generic or Proper Name:* pegfilgrastim

*Sponsor:* Amgen Inc.

*Approval Date:* 12/23/2014

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

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 125031Orig1s175

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*APPLICATION NUMBER:*

**125031Orig1s175**

**APPROVAL LETTER**



BLA 125031/S-175

**SUPPLEMENT APPROVAL**

Amgen Inc.  
Attention: Ray Silkaitis, RPh, PhD  
Director, Regulatory Affairs, Global Regulatory Affairs and Safety  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320-1799

Dear Dr. Silkaitis:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 27, 2014, received June 27, 2014, submitted under section 351(a) of the Public Health Service Act for Neulasta<sup>®</sup> (pegfilgrastim).

We acknowledge receipt of your amendments dated August 12 and 14 (2); September 26; October 3, 22 (3), 23 (2), and 24; November 3, 14, and 24; and December 15, 17 and 22, 2014.

This “Prior Approval” supplemental biologics application provides for updates to the labeling for a combination product consisting of Neulasta in pre-filled syringe and co-packaged with a drug delivery device.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and text for the patient package insert and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)”.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125031/S-175.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

*{See appended electronic signature page}*

Edvardas Kaminskas, MD  
Deputy Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

### ENCLOSURES:

Content of Labeling  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EDVARDAS KAMINSKAS  
12/23/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125031Orig1s175**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Neulasta safely and effectively. See full prescribing information for Neulasta.

Neulasta® (pegfilgrastim) injection, for subcutaneous use  
Initial U.S. Approval: 2002

-----RECENT MAJOR CHANGES-----

- Dosage and Administration (2.3 and 2.4) 12/2014
- Warnings and Precautions (5.4) 12/2014

-----INDICATIONS AND USAGE-----

Neulasta is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (1)

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

-----DOSAGE AND ADMINISTRATION-----

- 6 mg administered subcutaneously once per chemotherapy cycle. (2)
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2)

-----DOSAGE FORMS AND STRENGTHS-----

- Injection: 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only. (3)
- Injection: 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta. (3)

-----CONTRAINDICATIONS-----

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim. (4)

-----WARNINGS AND PRECAUTIONS-----

- Fatal splenic rupture can occur. Evaluate for splenomegaly or splenic rupture in patients with left upper abdominal or shoulder pain. (5.1)

- Acute respiratory distress syndrome (ARDS) can occur. Evaluate for ARDS in patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Neulasta in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis, can occur. Permanently discontinue Neulasta in patients with serious allergic reactions. (5.3)
- The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction (5.4)
- Severe and sometimes fatal sickle cell crises can occur. (5.5)

-----ADVERSE REACTIONS-----

Most common adverse reactions (≥ 5% difference in incidence) in placebo controlled clinical trials are bone pain and pain in extremity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm. Physicians are encouraged to enroll pregnant patients in Amgen’s Pregnancy Surveillance Program by calling 1-800-772-6436 (1-800-77-AMGEN). (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)
- Pediatric Use: The safety and effectiveness of Neulasta have not been established. (8.4)
- Geriatric Use: No overall differences in safety or effectiveness were observed in patients age 65 and older. (8.5)
- Renal Impairment: No dose adjustment required. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2014

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Neulasta 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 a clinically significant incidence of febrile neutropenia [see *Clinical Studies (14)*].

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

#### 2.2 Administration

Neulasta is administered subcutaneously via a single prefilled syringe for manual use or for use with the On-body Injector for Neulasta which is co-packaged with a single prefilled syringe.

For manual use or On-body Injector for Neulasta use, visually inspect parenteral drug products (prefilled syringe) for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Neulasta if discoloration or particulates are observed.

The needle cap on the prefilled syringes contains dry natural rubber (derived from latex); persons with latex allergies should not administer these products.

#### 2.3 Special Healthcare Provider Instructions for the On-body Injector for Neulasta

A healthcare provider must fill the On-body Injector with Neulasta using the prefilled syringe and then apply the On-body Injector for Neulasta to the patient's skin (abdomen or back of arm). The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector for Neulasta. Approximately 27 hours after the On-body Injector for Neulasta is applied to the patient's skin, Neulasta will be delivered over approximately 45 minutes. A healthcare provider may initiate administration with the On-body Injector for Neulasta on the same day as the administration of cytotoxic chemotherapy, as long as the On-body Injector for Neulasta delivers Neulasta no less than 24 hours after administration of cytotoxic chemotherapy.

The prefilled syringe co-packaged in the Neulasta Delivery Kit must only be used with the On-body Injector for Neulasta. The prefilled syringe contains additional solution to compensate for liquid loss during delivery through the On-body Injector for Neulasta. If the prefilled syringe co-packaged in the Neulasta Delivery Kit is used for manual subcutaneous injection, the patient will receive an overdose. If the single use prefilled syringe for manual use is used with the On-body Injector for Neulasta, the patient may receive less than the recommended dose.

Do not use the On-body Injector for Neulasta to deliver any other drug product except the Neulasta prefilled syringe co-packaged with the On-body Injector for Neulasta.

The On-body Injector for Neulasta should be applied to intact, non-irritated skin on the arm or abdomen.

A missed dose could occur due to an On-body Injector for Neulasta failure or leakage. If the patient misses a dose, a new dose should be administered by single prefilled syringe for manual use, as soon as possible after detection.

Refer to the Healthcare Provider Instructions for Use for the On-body Injector for Neulasta for full administration information.

#### **2.4 Advice to Give to Patients Regarding Administration via the On-body Injector for Neulasta**

Advise patients to avoid activities such as traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute delivery period plus an hour post-delivery). Patients should have a caregiver nearby for the first use.

Refer the patient to the dose delivery information written on the Patient Instructions for Use. Provide training to patients to ensure they understand when the dose delivery of Neulasta will begin and how to monitor the On-body Injector for Neulasta for completed delivery. Ensure patients understand how to identify signs of malfunction of On-body Injector for Neulasta. [see *Warnings and Precautions (5.3) and Patient Counseling Information (17)*].

### **3 DOSAGE FORMS AND STRENGTHS**

- Injection: 6 mg/0.6 mL solution in a single use prefilled syringe for manual use only.
- Injection: 6 mg/0.6 mL solution in a single use prefilled syringe co-packaged with the On-body Injector for Neulasta (Neulasta Delivery Kit).

### **4 CONTRAINDICATIONS**

Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Splenic Rupture**

Splenic rupture, including fatal cases, can occur following the administration of Neulasta. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta.

#### **5.2 Acute Respiratory Distress Syndrome**

Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta, for ARDS. Discontinue Neulasta in patients with ARDS.

#### **5.3 Serious Allergic Reactions**

Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta in patients with serious allergic reactions. Do not administer Neulasta to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

#### **5.4 Allergies to Acrylics**

The On-body Injector for Neulasta uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction.

## 5.5 Use in Patients With Sickle Cell Disorders

Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

## 5.6 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte-colony stimulating factor (G-CSF) receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [See Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [See Warnings and Precautions (5.2)]
- Serious Allergic Reactions [See Warnings and Precautions (5.3)]
- Use in Patients with Sickle Cell Disorders [See Warnings and Precautions (5.5)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [See Warnings and Precautions (5.6)]

The most common adverse reactions occurring in  $\geq 5\%$  of patients and with a between-group difference of  $\geq 5\%$  higher in the pegfilgrastim arm in placebo controlled clinical trials are bone pain and pain in extremity.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 1 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m<sup>2</sup> every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and <1% Asian, Native American or other.

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Table 1. Adverse Reactions With  $\geq 5\%$  Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

System Organ Class Preferred Term	Placebo (N= 461)	Neulasta 6 mg SC on Day 2 (N= 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

### *Leukocytosis*

In clinical studies, leukocytosis (WBC counts > 100 x 10<sup>9</sup>/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving Neulasta. No complications attributable to leukocytosis were reported in clinical studies.

## **6.2 Immunogenicity**

As with all therapeutic proteins, there is a potential for immunogenicity. Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Neulasta with the incidence of antibodies to other products may be misleading.

## **6.3 Postmarketing Experience**

The following adverse reactions have been identified during post approval use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) reported frequency of the reaction, or (3) strength of causal relationship to Neulasta.

*Gastro-intestinal disorders:* Splenic rupture [see Warnings and Precautions (5.1)]

*Blood and lymphatic system disorder:* Sickle cell crisis [see Warnings and Precautions (5.5)]

*Hypersensitivity reactions:* Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema and flushing [see Warnings and Precautions (5.3)]

*Respiratory, thoracic, and mediastinal disorder:* ARDS [see Warnings and Precautions (5.2)]

*General disorders and administration site conditions:* Injection site reactions

*Skin and subcutaneous tissue disorders:* Sweet's syndrome, Cutaneous vasculitis

## 7 DRUG INTERACTIONS

No formal drug interaction studies between Neulasta and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim was embryotoxic and increased pregnancy loss in pregnant rabbits that received cumulative doses approximately 4 times the recommended human dose (based on body surface area). Signs of maternal toxicity occurred at these doses. Neulasta should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In animal reproduction studies, when pregnant rabbits received pegfilgrastim at cumulative doses approximately 4 times the recommended human dose (based on body surface area), increased embryoletality and spontaneous abortions occurred. Signs of maternal toxicity (reductions in body weight gain/food consumption) and decreased fetal weights occurred at maternal doses approximately equivalent to the recommended human dose (based on body surface area). There were no structural anomalies observed in rabbit offspring at any dose tested. No evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area) [*see Nonclinical Toxicology (13.3)*].

Women who become pregnant during Neulasta treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

### 8.3 Nursing Mothers

It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness of Neulasta in pediatric patients have not been established. The adverse reaction profile and pharmacokinetics of pegfilgrastim were studied in 37 pediatric patients with sarcoma. The mean ( $\pm$  standard deviation [SD]) systemic exposure ( $AUC_{0-\infty}$ ) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 22.0 ( $\pm$  13.1) mcg·hr/mL in the 6 to 11 years age group (n = 10), 29.3 ( $\pm$  23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13), and 47.9 ( $\pm$  22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11). The terminal elimination half-lives of the corresponding age groups were 20.2 ( $\pm$  11.3) hours, 21.2 ( $\pm$  16.0) hours, and 30.1 ( $\pm$  38.2) hours, respectively. The most common adverse reaction was bone pain.

### 8.5 Geriatric Use

Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were age 65 and over, and 18 (2%) were age 75 and over. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

## 8.6 Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. Therefore, pegfilgrastim dose adjustment in patients with renal dysfunction is not necessary [*Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

The maximum amount of Neulasta that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum absolute neutrophil count (ANC) of  $55 \times 10^9/L$ , with a corresponding mean maximum WBC of  $67 \times 10^9/L$ . The absolute maximum ANC observed was  $96 \times 10^9/L$  with a corresponding absolute maximum WBC observed of  $120 \times 10^9/L$ . The duration of leukocytosis ranged from 6 to 13 days. The effectiveness of leukapheresis in the management of symptomatic individuals with Neulasta-induced leukocytosis has not been studied.

## 11 DESCRIPTION

Neulasta (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of *E coli* transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

Neulasta comes in two presentations:

- Neulasta for manual subcutaneous injection is supplied in 0.6 mL prefilled syringes.
- On-body Injector for Neulasta is supplied with a prefilled syringe containing 0.64 mL of Neulasta in solution that delivers 0.6 mL of Neulasta in solution when used with the On-body Injector for Neulasta.

The delivered 0.6 mL dose from either the prefilled syringe for manual subcutaneous injection or the On-body Injector for Neulasta contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

### 12.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim were studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of Neulasta ranged from 15 to 80 hours after subcutaneous injection. In healthy volunteers, the pharmacokinetics of pegfilgrastim were

comparable when delivered subcutaneously via a manual prefilled syringe versus via the On-body Injector for Neulasta.

No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients ( $\geq 65$  years of age) compared with younger patients ( $< 65$  years of age) [see Use in Specific Populations (8.5)]. The pharmacokinetics of pegfilgrastim were studied in pediatric patients with sarcoma [see Use in Specific Populations (8.4)]. Renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim. [see Use in Specific Populations (8.6)]. The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

### 13.3 Reproductive and Developmental Toxicology

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

## 14 CLINICAL STUDIES

Neulasta was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin  $60 \text{ mg/m}^2$  and docetaxel  $75 \text{ mg/m}^2$  administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of Neulasta. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia ( $\text{ANC} < 0.5 \times 10^9/\text{L}$ ) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies, and the efficacy of Neulasta was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of Neulasta

(100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of Neulasta-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the Neulasta arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the Neulasta arm compared to 1.6 days in the Filgrastim arm [difference in means 0.1 (95% CI -0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m<sup>2</sup> administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature  $\geq 38.2^{\circ}\text{C}$  and ANC  $\leq 0.5 \times 10^9/\text{L}$ ) was lower for Neulasta-treated patients as compared to placebo-treated patients (1% versus 17%, respectively,  $p < 0.001$ ). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the Neulasta-treated patients compared to the placebo-treated patients.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 Neulasta single use prefilled syringe for manual use**

Neulasta is supplied in a prefilled single use syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe<sup>®</sup> Needle Guard.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Neulasta is provided in a dispensing pack containing one sterile 6mg/0.6 mL prefilled syringe (NDC 55513-190-01).

Store refrigerated between 36° to 46°F (2° to 8°C) 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.

### **16.2 Neulasta Delivery Kit**

The Neulasta Delivery Kit is provided in a carton containing one sterile prefilled syringe and one sterile On-body Injector for Neulasta (NDC 55513-192-01).

The single use prefilled syringe contains 0.64 mL of solution that delivers 6 mg/0.6 mL of pegfilgrastim when used with the On-body Injector for Neulasta. The prefilled syringe is supplied with a 27-gauge, 1/2-inch needle with an UltraSafe<sup>®</sup> Needle Guard.

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).

Store the Kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. Because the On-body Injector for Neulasta is at room temperature during the period of use, the Kit should not be held at room temperature longer than 12 hours prior to use. Discard the Kit if stored at room temperature for more than 12 hours.

Do not use the On-body Injector for Neulasta if its packaging has been previously opened.

## 17 PATIENT COUNSELING INFORMATION

Advise patients of the following risks for Neulasta:

- Splenic rupture
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis

Have patients immediately contact their healthcare provider and report:

- Left upper quadrant or shoulder pain
- Shortness of breath
- Signs or symptoms of sickle cell crisis
- Signs or symptoms of infection
- Flushing, dizziness, or rash

Advise patients on the use of the On-body Injector for Neulasta:

- Review the Patient Information and Patient Instructions for Use with the patient and provide the instructions to the patient.
- **Refer the patient to the dose delivery information written on the Patient Instructions for Use.**
- **Tell the patient when their dose delivery of Neulasta will begin and when their dose delivery should be completed.**
- **Advise the patient that serious allergic reactions can happen with Neulasta. Patients should have a caregiver nearby for the first use. Patients should plan to be in a place where they can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery. Advise the patient to avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta.**
- **If the On-body Injector for Neulasta is placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector for Neulasta.**
- If a patient calls the healthcare provider regarding any On-body Injector for Neulasta problems, the healthcare provider is advised to call Amgen at 1-800-772-6436.
- Advise the patient:
  - to call their healthcare provider immediately if the status light on the On-body Injector for Neulasta is flashing red (see the Patient Instructions for Use).
  - to inform their healthcare provider if the adhesive on the On-body Injector for Neulasta becomes saturated with fluid, or there is dripping, as this may be evidence of significant product leakage, resulting in inadequate or missed dose (see the Patient Instructions for Use).
  - to keep the On-body Injector for Neulasta dry for approximately the last 3 hours prior to the dose delivery start to better enable potential leak detection.
  - that the On-body Injector for Neulasta should only be exposed to temperatures between 41°F and 104°F (5°C-40°C)
  - to keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector for Neulasta at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

- that if the needle is exposed after On-body Injector for Neulasta removal, place the used On-body Injector for Neulasta in a sharps disposal container to avoid accidental needle stick and call their healthcare provider immediately.
- to remove the On-body Injector for Neulasta after the green light shines continuously and to place the used On-body Injector for Neulasta in a sharps disposal container (see the Patient Instructions for Use).
- Advise the patient:
  - **do not** reapply the On-body Injector for Neulasta if the On-body Injector for Neulasta comes off before full dose is delivered and instead call their healthcare provider immediately.
  - avoid bumping the On-body Injector for Neulasta or knocking the On-body Injector for Neulasta off the body.
  - **do not** expose the On-body Injector for Neulasta to medical imaging studies, e.g. X-ray scan, MRI, CT scan, ultrasound and oxygen rich environments such as hyperbaric chambers to avoid On-body Injector for Neulasta damage and patient injury.
- Advise the patient to avoid:
  - airport X-ray scans and request a manual pat down instead; remind patients who elect to request a manual pat down to exercise care to avoid having the On-body Injector for Neulasta dislodged during the pat down process.
  - sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta as this may affect On-body Injector for Neulasta performance.
  - getting body lotions, creams, oils and cleaning agents near the On-body Injector for Neulasta as these products may loosen the adhesive.
  - using hot tubs, whirlpools, or saunas and avoid exposing the On-body Injector for Neulasta to direct sunlight as these may affect the drug.
  - peeling off or disturbing the On-body Injector for Neulasta adhesive before delivery of full dose is complete.



Neulasta® (pegfilgrastim)

**Manufactured by:**

Amgen Inc.  
 One Amgen Center Drive  
 Thousand Oaks, California 91320-1799  
 US License No. 1080

Patent: <http://pat.amgen.com/neulasta/>

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[www.neulasta.com](http://www.neulasta.com)

1-800-77-AMGEN (1-800-772-6436)

12/2014

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**Patient Information**  
**Neulasta® (nu-las-tah)**  
**(pegfilgrastim)**  
**injection**  
**On-body Injector for Neulasta**

Read this Patient Information before you receive Neulasta and each time you receive Neulasta with the On-body Injector for Neulasta. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?**

- **See the Instructions for Use for the On-body Injector for Neulasta for detailed information about the On-body Injector for Neulasta and important information about your dose delivery that has been written by your healthcare provider.**
  - Know the time that delivery of your dose of Neulasta is expected to start.
  - Avoid traveling, driving, or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied. Avoid activities and places that may interfere with monitoring during the **45-minute** period that Neulasta is expected to be delivered by the On-body Injector for Neulasta, and for 1 hour after delivery.
- A caregiver should be with you the first time that you receive Neulasta with the On-body Injector for Neulasta.
- **If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.**
- **You should only receive a dose of Neulasta on the day your healthcare provider tells you.**
- **You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy.** The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- **Do not** expose the On-body Injector for Neulasta to the following because the On-body Injector for Neulasta may be damaged and you could be injured:
  - MRI
  - X-ray
  - CT-Scan
  - Ultrasound
  - Oxygen rich environments, such as hyperbaric chambers

- Avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector for Neulasta from being accidentally removed.
- **Keep the On-body Injector for Neulasta at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances.** If the On-body Injector for Neulasta is too close to electrical equipment, it may not work correctly and can lead to a missed or incomplete dose of Neulasta.
- **Call your healthcare provider right away if the:**
  - On-body Injector for Neulasta comes off before or during a dose delivery. **Do not re-apply it.**
  - On-body Injector for Neulasta is leaking.
  - adhesive on your On-body Injector for Neulasta becomes noticeably wet (saturated) with fluid, or there is dripping. This may mean that Neulasta is leaking out of your On-body Injector for Neulasta. If this happens you may only receive some of your dose of Neulasta, or you may not receive a dose at all.
  - On-body Injector for Neulasta status light is flashing red.

### **What is Neulasta?**

Neulasta is a prescription medicine used to help reduce the chance of infection due to a low white blood cell count, in people with certain types of cancer (non-myeloid), who receive anti-cancer medicines (chemotherapy) that can cause fever and low blood cell count.

It is not known if Neulasta is safe and effective in children.

### **Who should not take Neulasta?**

**Do not** take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta<sup>®</sup>) or to filgrastim (Neupogen<sup>®</sup>).

### **What should I tell my healthcare provider before receiving Neulasta?**

**Before you receive Neulasta, tell your healthcare provider if you:**

- have sickle cell trait or sickle cell disease
- have had severe skin reactions to acrylic adhesives
- are allergic to latex
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.

**Pregnancy Registry:** There is a pregnancy registry for women who become pregnant during treatment with Neulasta. The purpose of this registry is to collect information about the health of you and your baby. You are encouraged to enroll in this registry.

Your healthcare provider may enroll you, or you may enroll by calling 1-800-AMGEN (1-800-772-6436).

- are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

### **How will I receive Neulasta?**

**See the Instructions for Use for detailed information about how you will receive a dose of Neulasta with the On-body Injector for Neulasta, and how to remove and dispose of the On-body Injector for Neulasta.**

- **See the section “What is the most important information I need to know about receiving Neulasta with the On-body Injector for Neulasta?”**
- Neulasta is given as an injection under the skin (subcutaneous). The On-body Injector for Neulasta will be applied to the stomach area (abdomen) or back of your arm by your healthcare provider. If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the On-body Injector for Neulasta.
- Your healthcare provider should place the On-body Injector for Neulasta on an area of your skin that does not have swelling, redness, cuts, wounds, or abrasions. Tell your healthcare provider about any skin reactions that happen in the On-body Injector for Neulasta application area after it has been applied.
- The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector for Neulasta on your skin.
- The dose of Neulasta will be delivered over about 45 minutes. During dose delivery and for 1 hour after delivery, it is best to stay in a place where you or a caregiver can monitor the On-body Injector for Neulasta to make sure you receive your full dose of Neulasta and watch for symptoms of an allergic reaction.
- Keep the On-body Injector for Neulasta dry for about the last 3 hours before the dose delivery is expected to start. This will help you to better detect possible leaking from the On-body Injector for Neulasta.
- Only expose the On-body Injector for Neulasta to temperatures between 41°F to 104°F (5°C to 40°C).

### **What should I avoid while the On-body Injector for Neulasta is in place?**

**While the On-body Injector for Neulasta is in place you should avoid:**

- traveling, driving or operating heavy machinery during hour 26 through hour 29 after the On-body Injector for Neulasta is applied.
- sleeping on the On-body Injector for Neulasta or applying pressure on the On-body Injector for Neulasta. The On-body Injector for Neulasta may not work properly.
- bumping the On-body Injector for Neulasta or knocking it off your body.

- getting body lotion, creams, oils, and skin cleansing products near the On-body Injector for Neulasta. These products may loosen the adhesive that holds the On-body Injector for Neulasta onto your body.
- using hot tubs, whirlpools, or saunas, and direct sunlight. These may affect Neulasta.
- peeling off or disturbing the On-body Injector for Neulasta adhesive before you receive your full dose of Neulasta.

### **What are possible side effects of Neulasta?**

#### **Neulasta can cause serious side effects, including:**

- **Spleen rupture.** Your spleen may become enlarged or may rupture during treatment with Neulasta. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- **A serious lung problem called Acute Respiratory Distress Syndrome (ARDS).** Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of ARDS: fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** Get emergency medical help right away if you get any of these symptoms of a serious allergic reaction with Neulasta: shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, sweating, and hives.

**If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector for Neulasta by grabbing the edge of the adhesive pad and peeling off the On-body Injector for Neulasta. Get emergency medical help right away.**

- **Sickle cell crises.** Severe sickle cell crises, and sometimes death, can happen in people with sickle cell trait or disease who receive filgrastim, a medicine similar to Neulasta (pegfilgrastim).

The most common side effect of Neulasta is pain in the bones and in your arms and legs.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Neulasta. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **General information about the safe and effective use of Neulasta**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you would like more information about Neulasta, talk with your

healthcare provider or pharmacist. You can ask your pharmacist for information about Neulasta that is written for health professionals.

For more information, go to [www.neulasta.com](http://www.neulasta.com) or call 1-844-696-3852 (1-844-MYNEULASTA).

### **What are the ingredients in Neulasta?**

Active ingredient: pegfilgrastim

Inactive ingredients: acetate, polysorbate 20, and sodium, sorbitol in Water for Injection.

This Patient Information has been approved by the U.S. Food and Drug Administration.



Neulasta® (pegfilgrastim)

#### **Manufactured by:**

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

US License No. 1080

Patent: <http://pat.amgen.com/neulasta/>

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[www.neulasta.com](http://www.neulasta.com)

1-844-MYNEULASTA (1-844-696-3852)

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## {SIDE 1 Information}

### Patient Instructions for Use

#### On-body Injector for Neulasta Description

The On-body Injector for Neulasta is intended for delivery of Neulasta. The On-body Injector is small, for one-time use, lightweight, battery-powered, and waterproof up to 8 ft for 1 hour. Your healthcare provider will use a prefilled syringe with Neulasta to fill the On-body Injector prior to applying it. The On-body Injector is applied directly to your skin using a self-adhesive backing. The On-body Injector informs you of its status with sounds and lights.

The On-body Injector contains electronic components as well as: a plastic housing, acrylic adhesive, batteries, a cannula introducer (needle) and a cannula. The On-body Injector is approximately: 2.4 in long, 1.6 in wide, 0.7 in height (62 mm long, 41 mm wide, 17 mm height).

#### Warnings

- **Before** you receive Neulasta, tell your healthcare provider if you:
  - Have sickle cell trait or sickle cell disease
  - Have any other medical problems
  - Are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.
  - Are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breastmilk.
- **DO NOT** take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta<sup>®</sup>) or to filgrastim (Neupogen<sup>®</sup>).
- Tell your healthcare provider if you are allergic to latex. A prefilled syringe is used to fill the On-body Injector by your healthcare provider prior to applying the On-body Injector. The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex. Latex may be transferred to your skin.
- Tell your healthcare provider if you have had severe skin reactions to acrylic adhesives.
- Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, **AVOID** traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector for Neulasta (this includes the 45-minute dose delivery period plus an hour post-delivery). If you must travel by airplane **before** the approximately 45-minute dose delivery period with the On-body Injector, avoid airport X-ray scans. Request a manual pat down instead. Use care during a manual pat down to help prevent the On-body Injector from being accidentally removed. For more information go to <http://www.tsa.gov/traveler-information/travelers-disabilities-and-medical-conditions>  
If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
- Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.
- Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.

- Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of acute respiratory distress syndrome (ARDS): fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- Keep children away from the used On-body Injector.
- You should only receive a dose of Neulasta on the day your healthcare provider tells you.
- You should not receive your dose of Neulasta any sooner than 24 hours after you finish receiving your chemotherapy. The On-body Injector for Neulasta is programmed to deliver your dose about 27 hours after your healthcare provider places the On-body Injector on your skin.
- It is not known if Neulasta is safe and effective in children.
- **DO NOT** expose the On-body Injector to the following because the On-body Injector may be damaged and you could be injured:
  - MRI
  - X-ray
  - CT-Scan
  - Ultrasound
  - Oxygen rich environments, such as hyperbaric chambers
- **DO NOT** use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
- **DO NOT** expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
- **DO NOT** sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect the On-body Injector performance.
- **DO NOT** peel off or disturb the On-body Injector's adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

## Precautions

### Environmental:

- Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
- Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C-40°C).
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

### Activity Related:

- Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
- Be careful not to bump the On-body Injector or knock the On-body Injector off your body.

### Biohazard:

#### Properly dispose of the On-body Injector:

- The On-body Injector contains batteries, electronics, and a needle. The On-body Injector should be placed in a sharps disposal container, with an appropriate sized opening, regardless of whether or not the needle is exposed. Follow instructions provided by your healthcare provider or by state or local laws.

- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit [www.neulasta.com](http://www.neulasta.com) to enroll.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

## Risks

You can avoid most risks related to using the On-body Injector for Neulasta by following the Patient Instructions for Use. Immediately call your healthcare provider if any of the following occur:

- The adhesive becomes noticeably wet (saturated) with fluid, or you see dripping
- If the On-body Injector fill indicator is not at the empty position after On-body Injector removal (You should see a black line next to the EMPTY indicator.)
- The On-body Injector comes off from the skin before or during a dose delivery (**DO NOT re-apply it.**)
- Status light is flashing red
- Allergic reaction
- Persistent or worsening redness or tenderness at the application site (may be a sign of infection)
- Severe pain or skin discomfort around your On-body Injector
- Any concern about your medication
- If the needle is exposed after On-body Injector removal

{SIDE 2 Information}

## On-body Injector for Neulasta® (nu-las-tah) (pegfilgrastim) Injection Patient Instructions for Use

### Dose Delivery Information

Your On-body Injector was applied:

---

Day	Time	AM / PM
-----	------	---------

Your dose delivery will start around:

---

Day	Time	AM / PM
-----	------	---------

Name of Healthcare Provider:

---

Last, First

Healthcare Provider contact number:

---

Lot number:

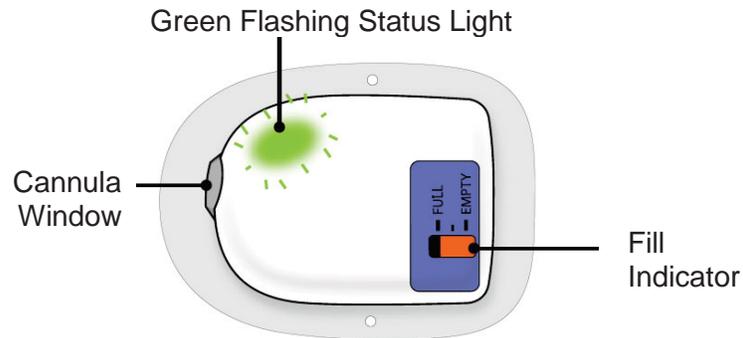
### Important Information

- !** This On-body Injector delivers Neulasta with an under-the-skin (subcutaneous) injection. See Patient Information for medicine information.
- !** If you have concerns about your medication, call your healthcare provider immediately. Serious allergic reactions can happen with Neulasta. Ask your caregiver to be nearby for the first use.
- !** Plan to be in a place where you or your caregiver can appropriately monitor the On-body Injector for Neulasta during the approximately 45 minute Neulasta delivery and for an hour after the delivery.
- !** Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector (hours 26-29).

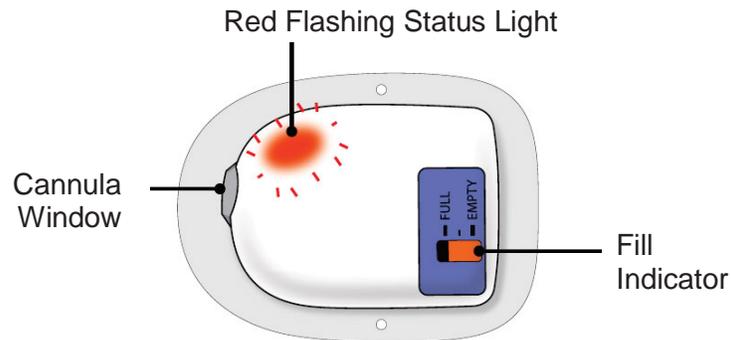
- ❗ If you have an allergic reaction during the delivery of Neulasta, remove the On-body Injector by grabbing the edge of the adhesive pad and peeling off the On-body Injector. Get emergency medical help right away.
  - ❗ The On-body Injector should be applied to intact, non-irritated skin on the stomach area (abdomen) or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
  - ❗ Call your healthcare provider immediately if you have severe pain or skin discomfort around your On-body Injector.
  - ❗ Be careful not to bump the On-body Injector or knock the On-body Injector off your body.
  - ❗ Avoid getting body lotions, creams, oils or cleaning agents near the On-body Injector as these products may loosen the adhesive.
  - ❗ Keep the On-body Injector dry for the last 3 hours prior to the dose delivery start.
  - ❗ Only expose the On-body Injector to temperatures between 41°F and 104°F (5°C and 40°C).
  - ❗ After On-body Injector removal, properly dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
  - ❗ Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.
- ⊘ **DO NOT:**
- ✗ use hot tubs, whirlpools, or saunas while wearing the On-body Injector. This may affect your medicine.
  - ✗ expose the On-body Injector to direct sunlight. If the On-body Injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the On-body Injector under clothing.
  - ✗ sleep on the On-body Injector or apply pressure during wear, especially during dose delivery. This may affect On-body Injector performance.
  - ✗ peel off or disturb the On-body Injector adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

A healthcare provider who is familiar with Neulasta should answer your questions. For general questions or support call 1-844-MYNEULASTA (1-844-696-3852) or visit [www.neulasta.com](http://www.neulasta.com).

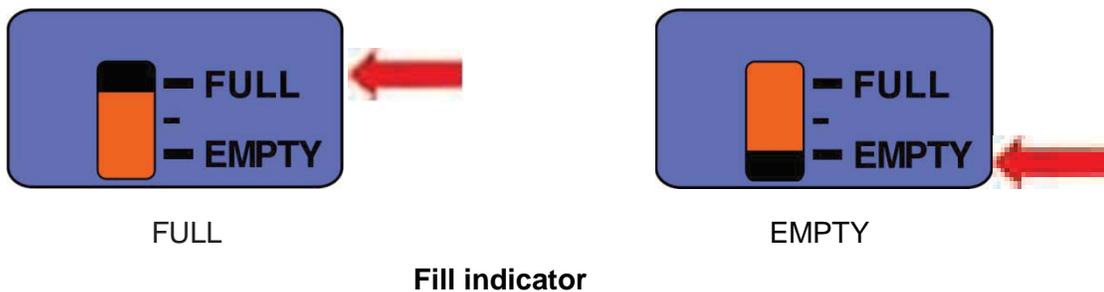
## Guide to Parts for On-body Injector for Neulasta



The On-body Injector is working properly.

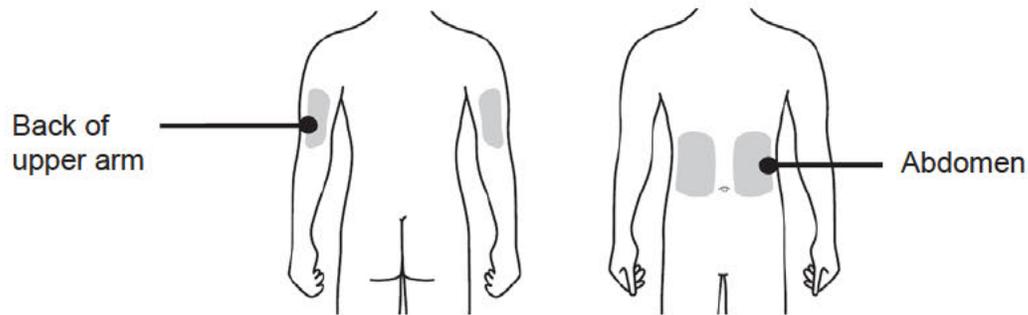


If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.



After your dose delivery is complete, check to see if the black line on your On-body Injector fill indicator is at empty.

## On-body Injector Placement

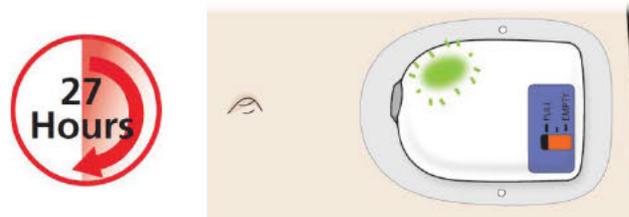


### Step 1: Monitor On-body Injector

- A** Check your status light occasionally for approximately 27 hours. Since it flashes slowly, watch for at least 10 seconds. If the status light is flashing green, it is okay.
- !** If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

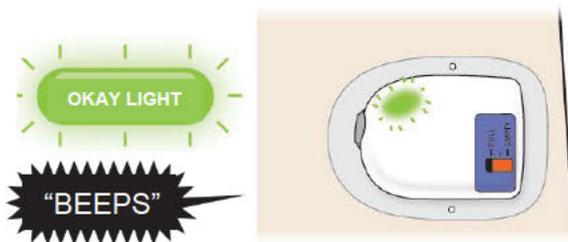


If the On-body Injector for Neulasta was placed on the back of your arm, a caregiver must be available to monitor the status of the On-body Injector.



**B** After approximately 27 hours, your On-body Injector will beep to let you know your dose delivery will begin in 2 minutes. When the dose delivery starts, it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.

**!** If at any time you hear beeping, check the status light. If it is flashing red, call your healthcare provider immediately.

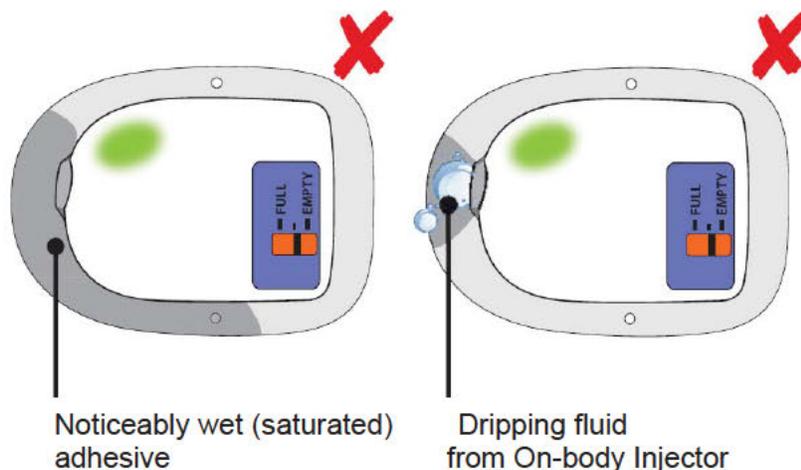


⊘ DO NOT remove the On-body Injector before the dose delivery is complete.

## Step 2: Monitor Dose Delivery



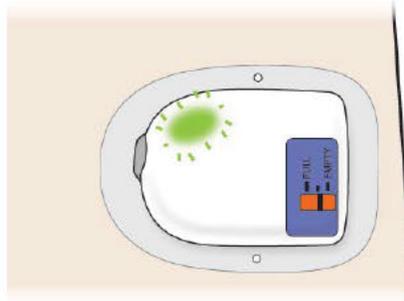
For the next 45 minutes, monitor your On-body Injector frequently for leaks during dose delivery. If the On-body Injector was placed on the back of your arm, a caregiver must be available to monitor your On-body Injector.



If the adhesive becomes noticeably wet (saturated) with fluid, or you see dripping, call your healthcare provider immediately.

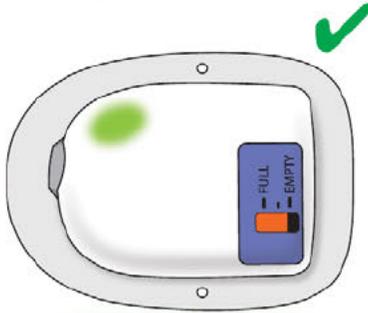
**A Your dose delivery will take around 45 minutes to complete.**

- You may hear a series of clicks. This is okay.
- A beep will sound when the dose delivery is complete.

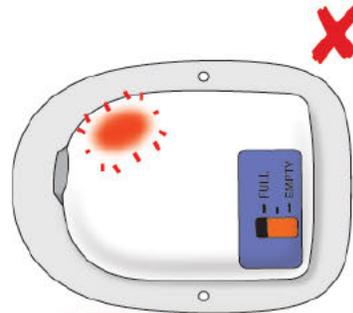


**Step 3: Remove On-body Injector When Dose Delivery Is Complete**

**A When beeping starts, check to see the color of the status light.**



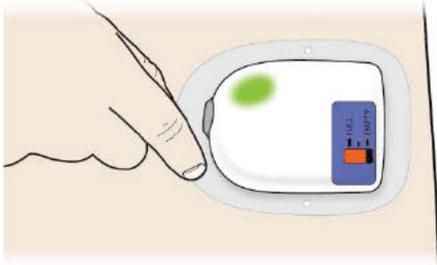
Check to see if the status light is **SOLID GREEN** or has switched off. This means the dose is complete. Remember, **any time you see a leak, call your healthcare provider immediately.** If complete, go to the next step.



If you see the status light is flashing red, your On-body Injector is not functioning properly. Call your healthcare provider immediately, as you may not have received a full dose.

**B Grab the edge of the adhesive pad. Slowly peel off the On-body Injector.**

- If medicine has leaked or the adhesive is noticeably wet (saturated), call your healthcare provider immediately as you may not have received your full dose.
- Remove any extra adhesive using soap and water.



**!** After On-body Injector removal, place the On-body Injector in a sharps disposal container whether the needle is exposed or not. If the needle is exposed, call your healthcare provider immediately.

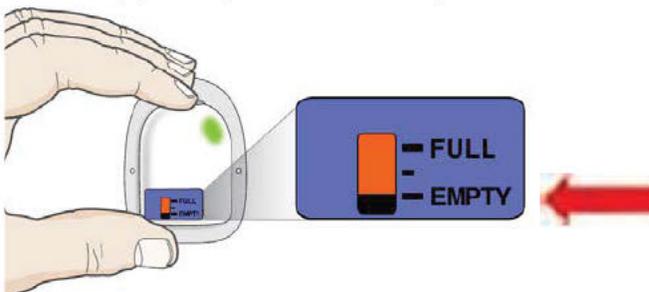
- ⊘ **DO NOT** grasp the On-body Injector itself to try to pull it off of your body.

## Step 4: Finish



**Check to see if your On-body Injector is empty.**

- You should see a black line next to the EMPTY indicator. If the On-body Injector is not empty, call your healthcare provider immediately.



- Check your status light again. Watch for at least 10 seconds. If the status light is solid green or it has switched off, it is okay.
- If you hear beeping, or when you check the status light and it is flashing red, call your healthcare provider immediately.

**A Record the end state of your On-body Injector.**

- Mark the box of the description that represents your On-body Injector after it has been used.

Status light is solid green or the status light has switched off. This means that the delivery is complete.

On-body Injector leaked, call your healthcare provider immediately.

Status light is red, call your healthcare provider immediately.

**B Properly dispose of the On-body Injector.**

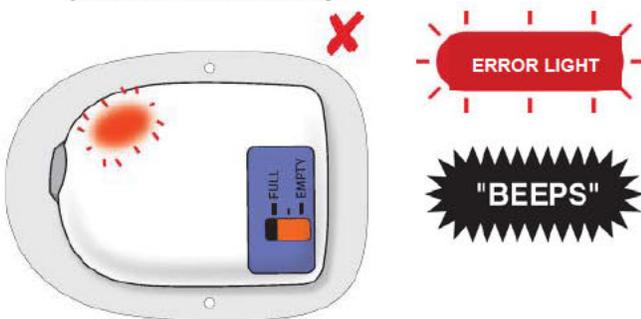
- The On-body Injector contains batteries, electronics, and a needle. Dispose of it in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- To participate in Amgen's voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit [www.neulasta.com](http://www.neulasta.com) to enroll. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

**!** Keep children away from the used On-body Injector.

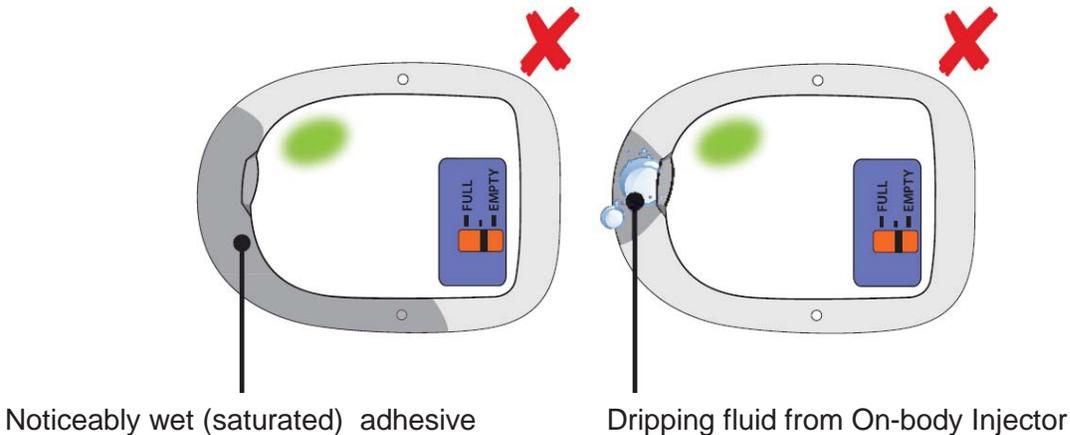
**Attention!**

**What to do if you hear beeping or when you look at the status light and it is flashing red.**

**!** If the status light is flashing red, you may not have received your full dose. Call your healthcare provider immediately.



**What to do if the On-body Injector adhesive becomes noticeably wet (saturated) with fluid, or you see dripping.**



- ! If the adhesive becomes saturated with fluid, or you see dripping, your medicine may have leaked out.
- ! Even with a leak, the status light may remain green and the fill indicator may be at EMPTY.
- ! Call your healthcare provider immediately as you may not have received your full dose.

**Note:** It is normal to see a few drops of fluid at the application site, but not normal to see a noticeably wet (saturated) adhesive.

**What do I do if the On-body Injector comes off before the full dose is delivered?**

Call your healthcare provider immediately if the On-body Injector at any time comes away from your skin before your full dose delivery, **DO NOT** reapply it.

**What if there is blood at my application site after the On-body Injector has been removed?**

If there is blood, press a clean cotton ball or gauze pad on the application site. Apply an adhesive bandage if needed.

**What if my application site is red or tender after On-body Injector removal?**

Call your healthcare provider immediately if you experience persistent or worsening redness or tenderness at the application site, as this can be a sign of infection.



Neulasta® (pegfilgrastim)

**Manufactured by:**

Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, California 91320-1799  
US License No. 1080

Patent: <http://pat.amgen.com/neulasta/>

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[www.neulasta.com](http://www.neulasta.com)

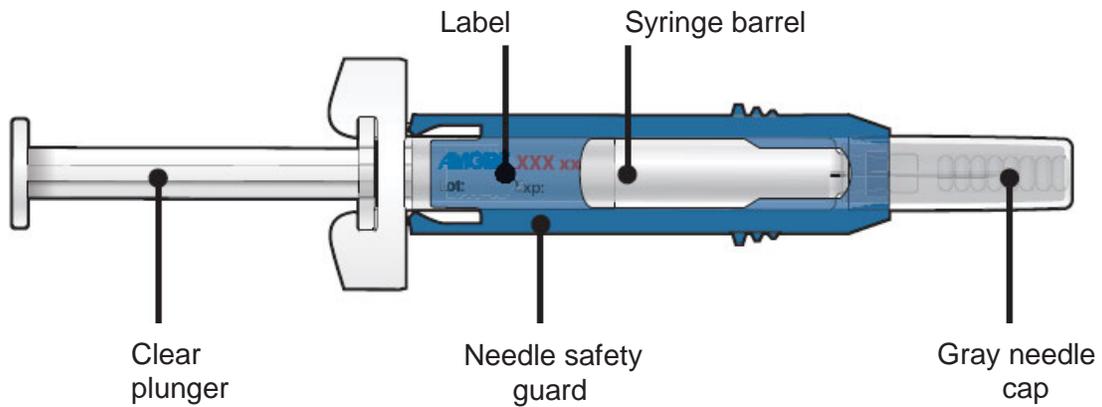
1-844-MYNEULASTA (1-844-696-3852) Issued: 12/2014 v1

# Neulasta® (pegfilgrastim) Delivery Kit

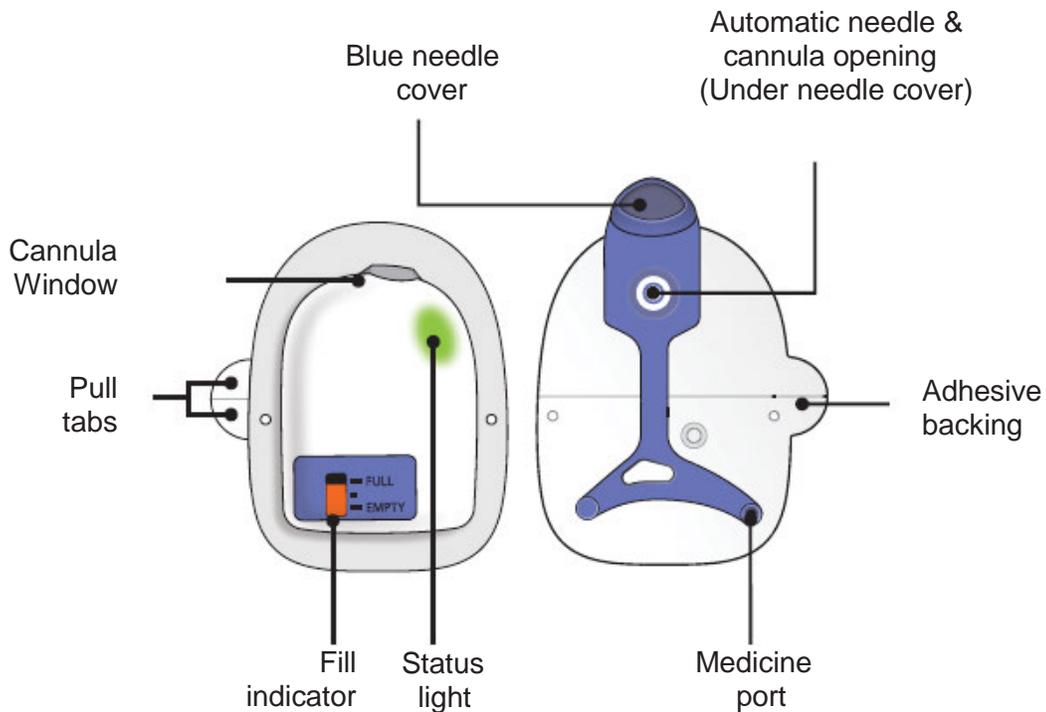
## Healthcare Provider Instructions for Use

### Guide to Parts

#### Neulasta Prefilled Syringe with Manual Needle Guard



#### On-body Injector for Neulasta



### Important

**READ THE FOLLOWING INSTRUCTIONS BEFORE USING THE ON-BODY INJECTOR**

**Warning:** Do not use the Neulasta Delivery Kit (the Kit) to deliver any other drug product.

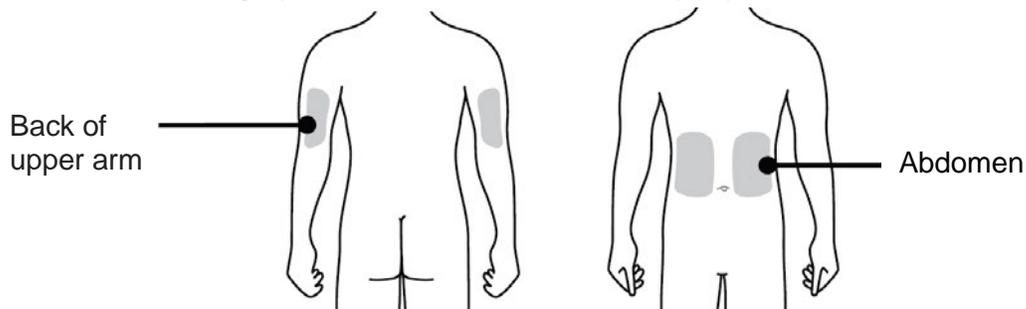
- !** See Prescribing Information for information on Neulasta.
- !** Store the Kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. If the Kit is stored at room temperature for more than 12 hours, do not use. Start again with a new Kit.
- !** Keep the prefilled syringe in the Kit carton until use to protect from light.
- !** For patients who have had severe skin reactions to acrylic adhesives, consider the benefit:risk profile before administering pegfilgrastim via the On-body Injector for Neulasta.
- !** The On-body Injector should be applied to intact, non-irritated skin on the abdomen or back of the arm. The back of the arm may only be used if there is a caregiver available to monitor the status of the On-body Injector.
- ⊘** DO NOT:
  - x** freeze the Kit.
  - x** shake the prefilled syringe.
  - x** separate the components of the Kit until ready for use.
  - x** modify the On-body Injector.
  - x** warm the Kit components using a heat source.
  - x** use Kit if expiry date on the Kit or any of the Kit components has passed.
  - x** use if the name Neulasta does not appear on the Kit.
  - x** attempt to reapply On-body Injector.
  - x** use if either the On-body Injector or prefilled syringe is dropped. Start again with a new Kit.

For all questions, call Amgen at 1-800-772-6436. If a patient calls you regarding any On-body Injector problems, call Amgen at 1-800-772-6436.

## Step 1: Prepare

- A Remove the Kit from refrigerator. Check to make sure it contains:**
- One Neulasta prefilled syringe
  - One On-body Injector for Neulasta
  - Neulasta package insert
  - Instructions for use:
    - for healthcare provider
    - for patient
  - Reference guide
- ⊘** DO NOT use On-body Injector if its packaging has been previously opened.

**B Wash hands thoroughly. Prepare and clean On-body Injector application site.**



**Choose the flattest site for On-body Injector application. Consult with your patient regarding their ability to remove and monitor the entire On-body Injector.**

You can use:

- Left or right side of abdomen, except for a 2-inch area right around navel.
- Back of upper arm, only if there is a caregiver available to monitor the status of the On-body Injector.

Choose an area larger than the adhesive pad, and clean it with an alcohol swab. Allow skin to completely dry.

**⊘ DO NOT touch this area again before attaching On-body Injector.**

You should avoid:

- x** Areas with scar tissues, moles, or excessive hair. In case of excessive hair, carefully trim hair to get On-body Injector close to skin.
- x** Areas where belts, waistbands, or tight clothing may rub against, disturb, or dislodge On-body Injector.
- x** Surgical sites.
- x** Areas where On-body Injector will be affected by folds in skin.



**The following is an overview of On-body Injector preparation steps. Read this section first.**

**When ready, proceed to Step 2: Get Ready Section.**

Before you apply On-body Injector to your patient, locate medicine port on blue needle cover to fill the On-body Injector with Neulasta.

**Please note:** During filling, beeping will sound and the On-body Injector will be activated.

**After activation, you will have 3 minutes to:**

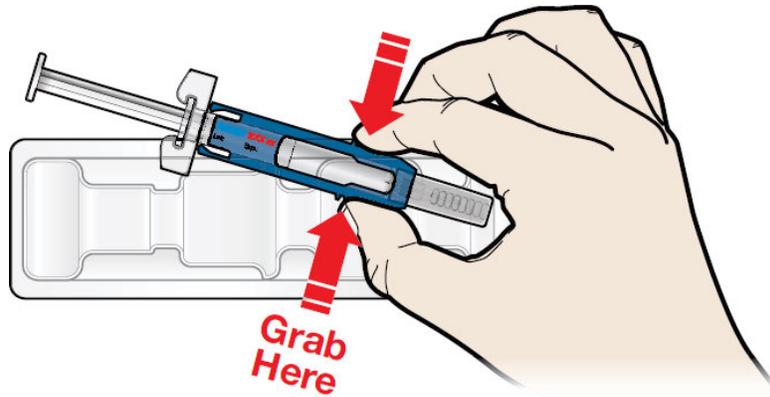
1. Completely empty syringe contents into medicine port.
2. Remove syringe from port and pull down needle safety guard over the exposed needle.
3. Remove blue needle cover from back of On-body Injector.
4. Peel away the two pieces of white adhesive backing on back of On-body Injector.
5. Attach On-body Injector to back of patient's upper arm or abdomen.

On-body Injector will deploy cannula in 3 minutes, even if not applied to patient. If not on patient's body in 3 minutes, do not use the On-body Injector. Start again with a new Kit.

**When you feel you are ready, please continue...**

## Step 2: Get Ready

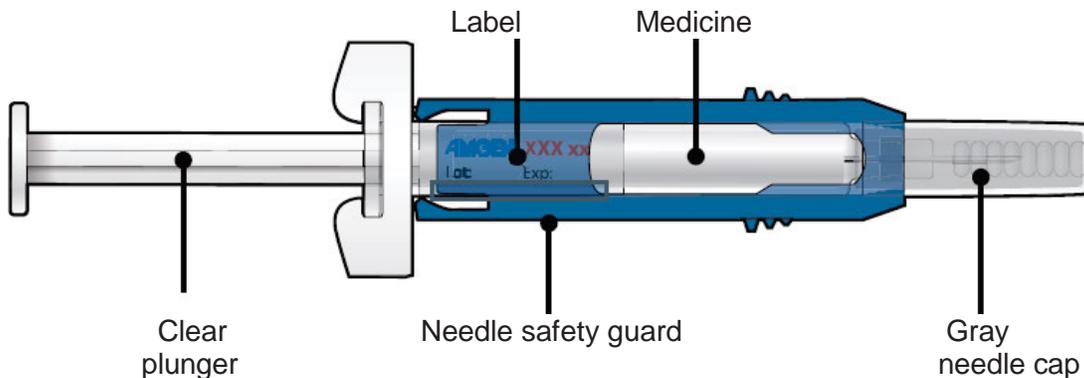
**A** Remove Neulasta prefilled syringe from tray.



For safety reasons:

- ⊘ DO NOT grasp gray needle cap.
- ⊘ DO NOT put the gray needle cap back onto syringe.
- ⊘ DO NOT grasp clear plunger.

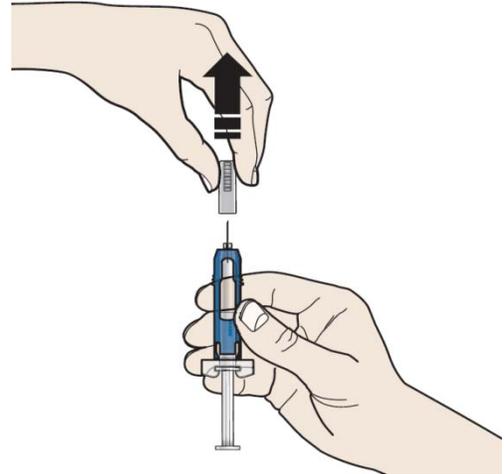
**B** Inspect medicine and Neulasta prefilled syringe. The Neulasta liquid should always be clear and colorless.



- ⊘ DO NOT use Neulasta prefilled syringe if:
  - ✗ Liquid contains particulate matter or discoloration is observed prior to administration.
  - ✗ Any part appears cracked or broken.
  - ✗ The gray needle cap is missing or not securely attached.
  - ✗ The expiration date printed on the label has passed.
- ⊘ DO NOT remove gray needle cap until ready to fill On-body Injector.
- ⊘ DO NOT pull needle safety guard down over the needle until filling is complete.
- ❗ In all the above cases, start again with a new Kit. Call Amgen at 1-800-772-6436.

**!** The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex.

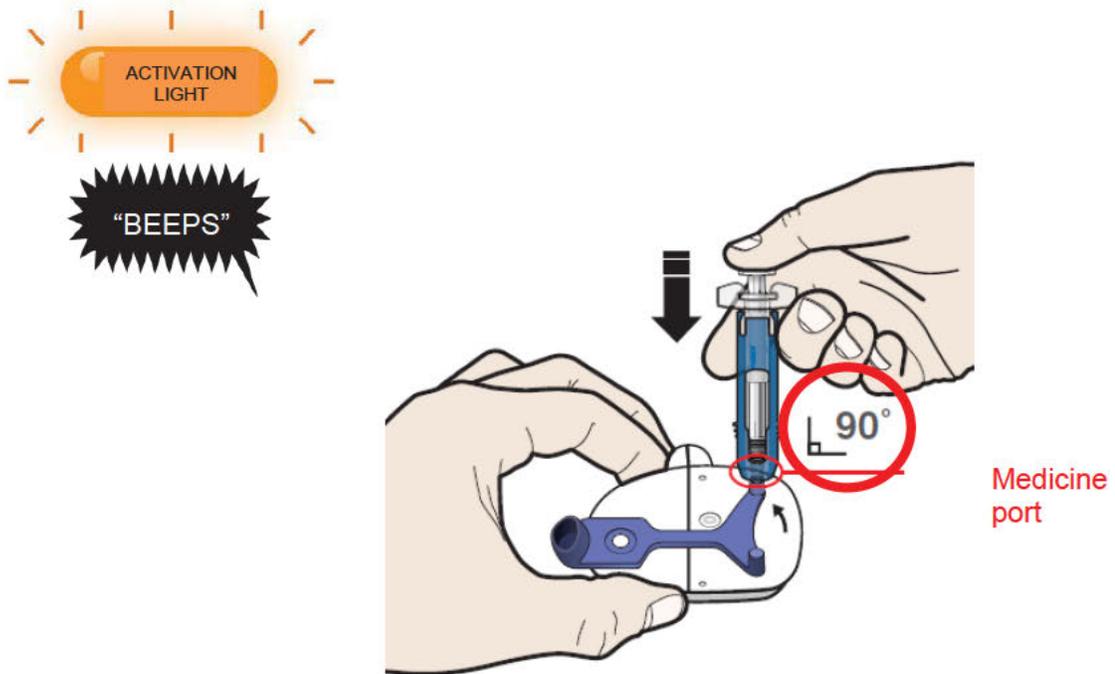
**C** Carefully remove gray needle cap straight out from the syringe and away from your body. Check syringe, and remove air bubbles.



**!** Take care to expel air only and not medicine. A small droplet at the tip of the needle during air purging is normal.

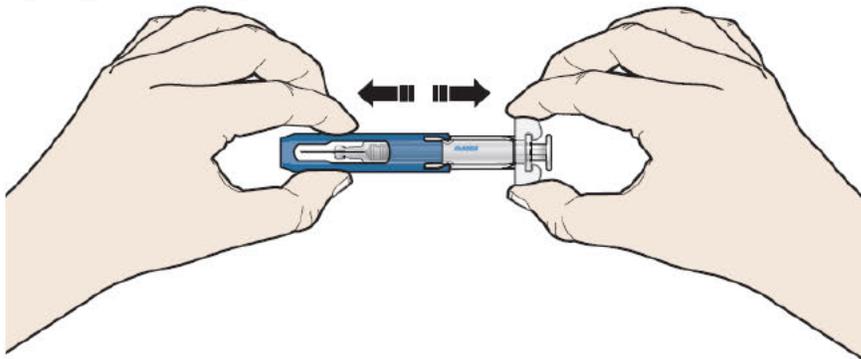
⊘ DO NOT recap syringe.

- D** Using blue needle cover, to avoid bending the needle and spilling medicine, insert syringe needle at 90 degrees all the way into medicine port. Slowly empty the entire syringe contents. Remove empty syringe from the medicine port. When beeping sounds and the status light flashes amber, the 3-minute countdown begins.

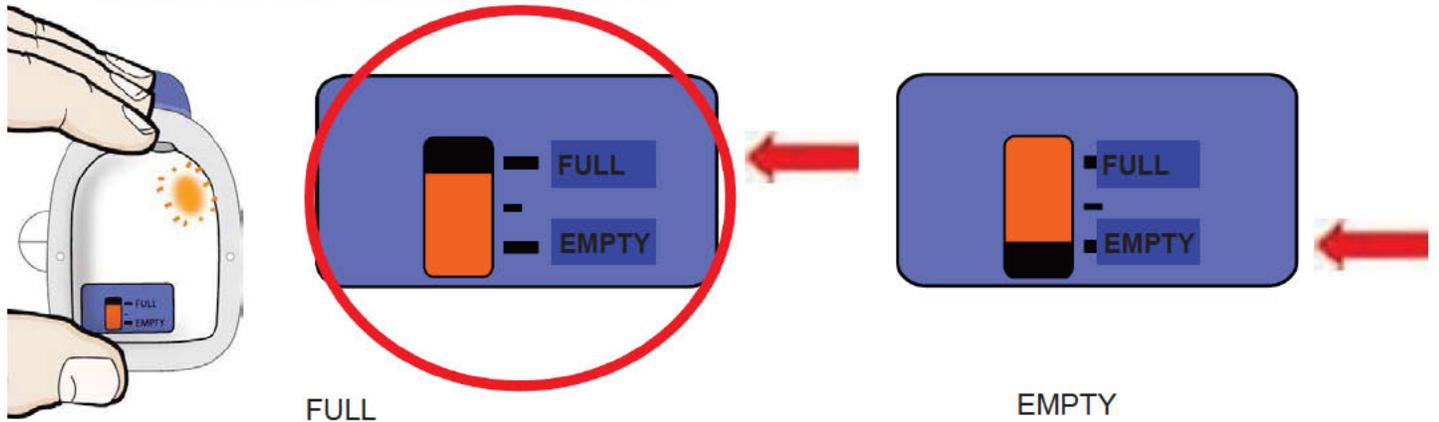


- | **Ø DO NOT** insert needle into medicine port at other than a 90 degree angle
- Ø DO NOT insert needle more than once.
- Ø DO NOT remove blue needle cover before filling the On-body Injector.

- E** Pull needle safety guard down until it clicks and covers needle. Dispose of empty syringe in a sharps container.



**F Check to see if the On-body Injector is full.**



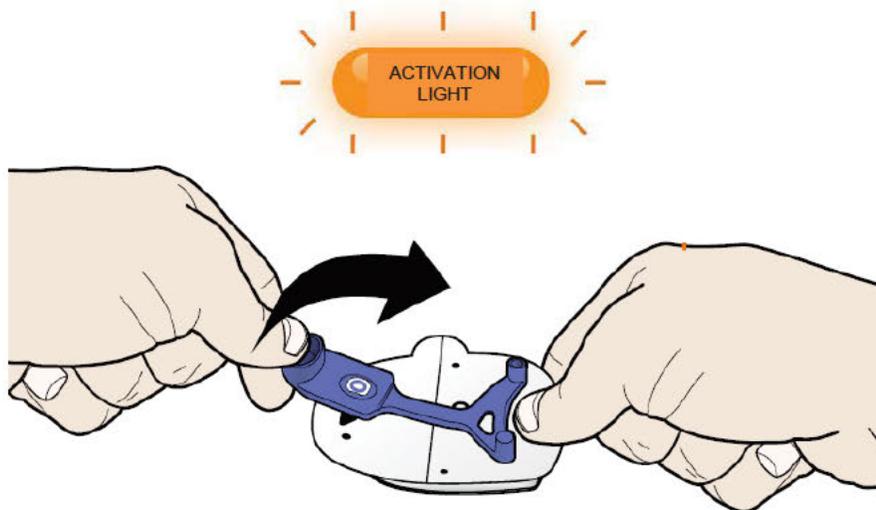
You should see:

- amber status light flashing.
- black line next to FULL on the fill indicator

If this is not the case, do not use. Start again with a new Kit, and call Amgen at 1-800-772-6436.

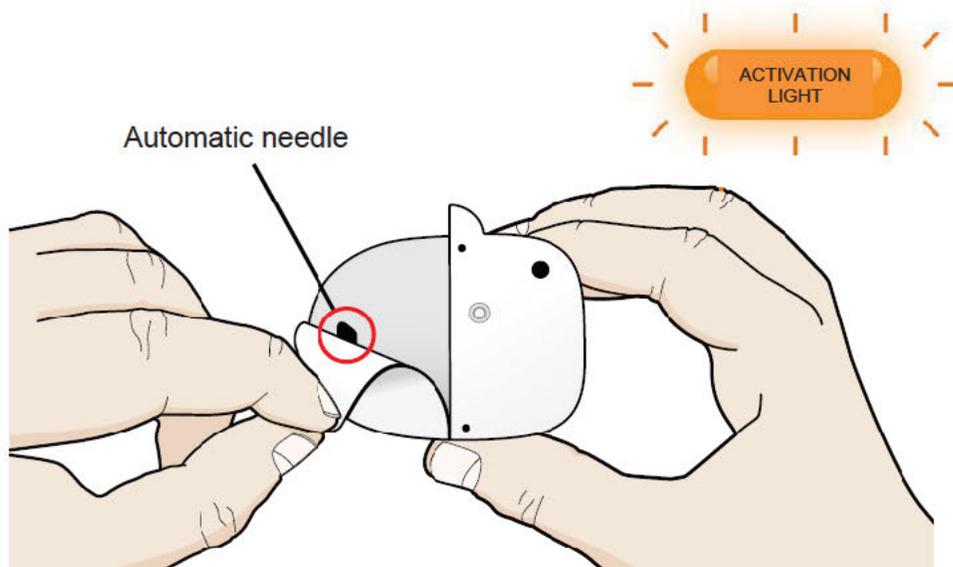
**Step 3: Apply**

**A Firmly lift and remove blue needle cover away from On-body Injector.**



A drop of medicine may be visible on needle tip when blue needle cover is removed.

- B** To expose the adhesive pad, use both pull tabs, one at a time, to peel the two pieces of white adhesive backing away from On-body Injector.



- ⊘ DO NOT touch or contaminate automatic needle area.
- ⊘ DO NOT pull off adhesive pad or fold it.
- ⊘ DO NOT use if the needle or cannula is extended past the adhesive or is extended before the On-body Injector is placed on patient.

**!** In all cases, start again with a new Kit. Call Amgen at 1-800-772-6436.

- C** Apply On-body Injector securely to patient with entire On-body Injector visible so it can be monitored by patient or caregiver.  
Before cannula deploys, place On-body Injector on your selected site, and run your finger around entire adhesive pad to make sure it is securely attached.

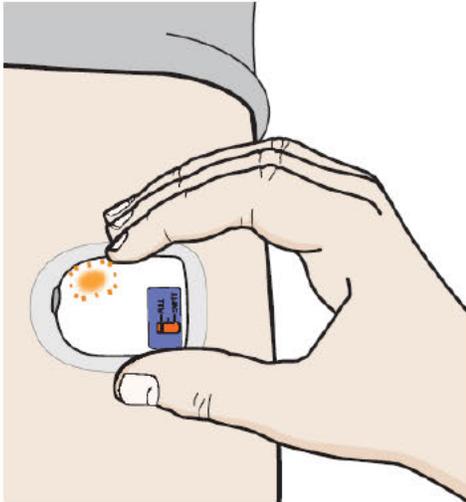
**Back of Upper Arm**



Vertical with light facing down toward navel

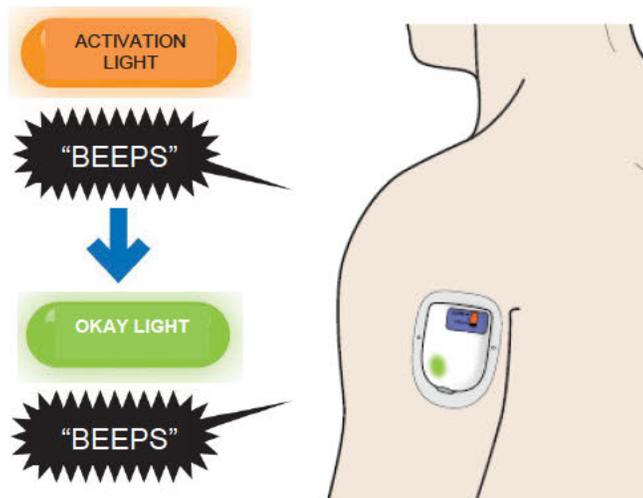
**Abdomen**

Horizontal  
with light  
facing  
navel



**STOP! Do not worry if On-body Injector is quiet. When 3 minutes are up, On-body Injector will beep.**

- D Beeping will tell you the cannula is about to insert. You may hear a series of clicks. This is okay.  
A long beep will sound, and the status light will turn to green. This means the cannula insertion is complete.**



If the adhesive folds over near the cannula window or there are folds anywhere that prevent the On-body Injector from securely adhering, remove the On-body Injector. Start again with a new Kit and call Amgen at 1-800-772-6436.

## Step 4: Finish

- A Fill in the Dose Delivery Information section in the patient instructions. Be sure to include when the On-body Injector was applied, when the dose will begin, and your contact information. Review this information with the patient.**

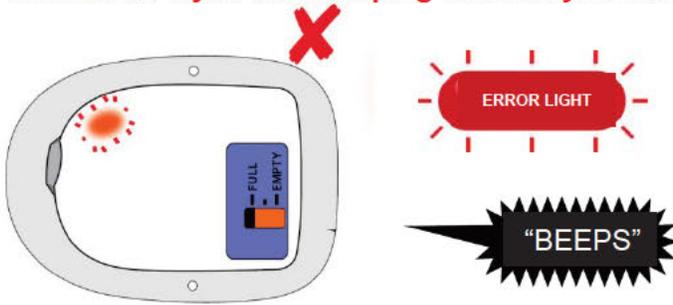
Review each step in the patient instructions with your patient. Give your patient the instructions, and reference guide to take home.

Before your patient goes home, make sure your patient understands:

- The On-body Injector will always flash a slow green light to let them know it is working properly.
- **After approximately 27 hours, beeps will signal that the dose delivery will begin in 2 minutes.**
- **When the dose delivery starts it will take about 45 minutes to complete. During this time, the On-body Injector will flash a fast green light.**
- The patient should remain in a place where they can monitor the On-body Injector for the entire dose delivery. The patient should avoid activities and settings that may interfere with monitoring during the dosing of Neulasta administered by the On-body Injector. For example, avoid traveling, driving, or operating heavy machinery during hours 26-29 following application of the On-body Injector (this includes the approximately 45-minute delivery period plus an hour post-delivery).
- If the patient has an allergic reaction during the delivery of Neulasta, the patient should remove the On-body Injector and call his or her healthcare provider or seek emergency care right away.
- If placed on the back of the arm, remind the patient that a caregiver must be available to monitor the On-body Injector.
- When the dose delivery is complete, the patient or caregiver will hear a beep and see a solid green light.
- Always dispose of the empty On-body Injector in a sharps disposal container as instructed by your healthcare provider or by state or local laws.
- Keep the On-body Injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the On-body Injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

## Attention!

What to do if you hear beeping or when you look at status light and it is flashing red.

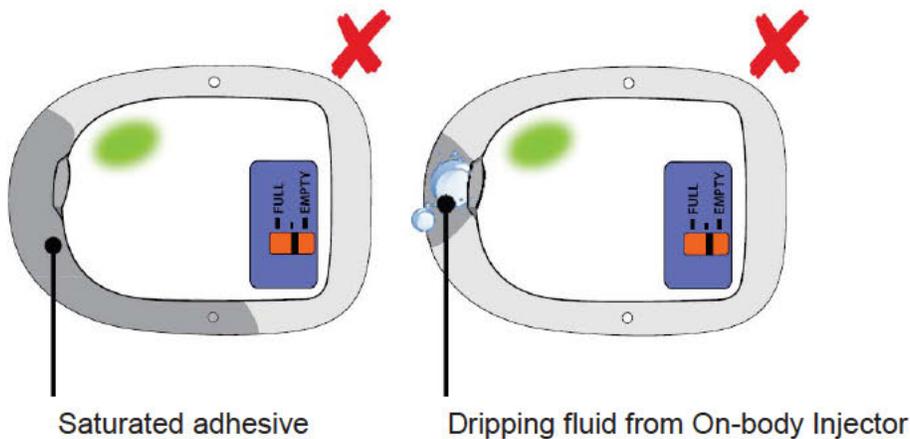


If at any time the On-body Injector beeps continuously for 5 minutes, and the status light is flashing red, take the On-body Injector off of the patient.

- ⊘ DO NOT apply On-body Injector to patient if red error light is on.
- ⊘ DO NOT leave On-body Injector on patient if red error light is on.

In all cases, do not use. Start over with a new Kit, and call Amgen at 1-800-772-6436.

What to do if the adhesive becomes saturated with fluid or the On-body Injector is dripping.



If patient reports an On-body Injector leak, they might not have received full dose. Schedule a follow-up appointment, and report the incident to Amgen at 1-800-772-6436.

Neulasta® (pegfilgrastim)

**Manufactured by:**

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, California 91320-1799

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www.neulasta.com 1-800-772-6436 (1-800-77-AMGEN)

Issued: 12/2014

v1

Do not expose the On-body Injector for Neulasta to the following environments as the On-body Injector may be damaged and the patient could be injured:

- MRI
- X-ray
- CT-Scan
- Ultrasound
- Oxygen rich environments such as hyperbaric chambers

Symbol	Meaning
	Do not reuse this On-body Injector. Single-use only
	Refer to Instructions for Use
	Do not use if packaging is damaged.
	Temperature Limitation
	Humidity Limitation
	Expiration Date (use by date)
	Reference/model number
	Lot Number
	Type BF medical device (protection from electrical shock)
	Sterilized by ethylene oxide
	Watertight to 8 feet for 30 minutes
	Prescription use only
	Not MRI-safe
	On-body Injector for Neulasta® (pegfilgrastim)
	Neulasta® (pegfilgrastim) Prefilled Syringe

## Electromagnetic Compatibility

The information contained in this section (such as separation distances) is, in general, specifically written in regard to the On-body Injector for Neulasta. The numbers provided will not guarantee faultless operation but should provide reasonable assurance of such. This information may not be applicable to other medical electrical equipment; older equipment may be particularly susceptible to interference.

### General Notes:

Medical electrical equipment requires special precautions regarding electromagnetic compatibility (EMC), and needs to be installed and put into service according to the EMC information provided in this document.

Portable and mobile RF communications equipment can affect medical electrical equipment.

Cables and accessories not specified within the instructions for use are not authorized. Using cables and/or accessories may adversely impact safety, performance, and electromagnetic compatibility (increased emission and decreased immunity).

Care should be taken if the On-body Injector for Neulasta is used adjacent to other electrical equipment; if adjacent use is inevitable, the On-body Injector for Neulasta should be observed to verify normal operation in this setting.

Electromagnetic Emissions		
The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of the On-body Injector for Neulasta should ensure that it is used in such an environment.		
Emissions	Compliance according to	Electromagnetic environment
RF Emissions (CISPR 11)	Group 1	The On-body Injector for Neulasta uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby equipment.
CISPR B Emissions Classification	Class B	

## Electromagnetic Immunity

The On-body Injector for Neulasta is intended for use in the electromagnetic environment specified below. The user of this equipment should ensure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment – Guidance
ESD IEC 61000-4-2	±6kV Contact ±8kV Air	6kV Contact ±8kV Air	Floors should be wood, concrete or ceramic tile. If floors are synthetic, the r/h should be at least 30%.
Power Frequency 50/60 Hz Magnetic Field IEC 61000-4-8	3A/m	3A/m	Power frequency magnetic fields should be that of typical commercial or hospital environment.
Radiated RF Fields 61000-4-3	3 V/m 80 MHz to 2.5 GHz	(E1)=3V/m	<p>Portable and mobile communications equipment should be separated from the On-body Injector for Neulasta by no less than the distances calculated/listed below:</p> <p><math>D=(3.5/V1)(\sqrt{P})</math> 150 kHz to 80 MHz</p> <p><math>D=(3.5/E1)(\sqrt{P})</math> 80 to 800 MHz</p> <p><math>D=(7/E1)(\sqrt{P})</math> 800 MHz to 2.5 GHz</p> <p>Where P is the max power in watts and D is the recommended separation distance in meters. Field strengths from fixed transmitters, as determined by an electromagnetic site survey, should be less than the compliance levels (V1 and E1). Interference may occur in the vicinity of equipment containing a transmitter.</p>

## Recommended separation distances between portable and mobile RF communications equipment and the On-body Injector for Neulasta

You can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the On-body Injector for Neulasta, as recommended below, according to the maximum power of the communication equipment.

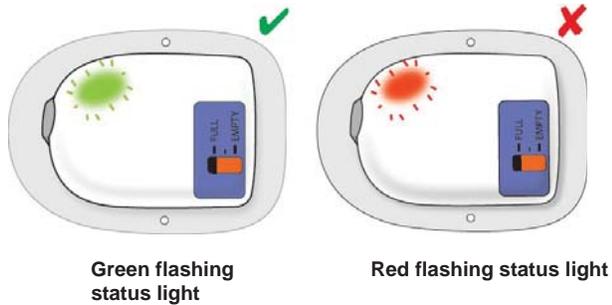
Rated maximum output power of transmitter, in watts	Separation distance according to frequency of transmitter, in meters		
	150 kHz to 80 MHz $D=(3.5/V1)(\sqrt{P})$	80 to 800 MHz $D=(3.5/E1)(\sqrt{P})$	800 MHz to 2.5 GHz $D=(7/E1)(\sqrt{P})$
0.01	0.11667	0.11667	0.23333
0.1	0.36894	0.36894	0.73785
1	1.1667	1.1667	2.3333
10	3.6894	3.6894	7.3785
100	11.667	11.667	23.333

## On-body Injector for Neulasta® (pegfilgrastim): Reference Guide

(barcode)  
XXXXXXXXXX

### Monitoring Your On-body Injector

- Check your status light occasionally for 27 hours. Since it flashes slowly, watch for at least 10 seconds. If status light is flashing green, it is okay.
- If placed on the back of your arm, a caregiver must be available to monitor the status of the On-body Injector.
- After approximately 27 hours, your On-body Injector will beep to let you know your dose delivery will begin in 2 minutes.
- For the next 45 minutes, monitor your On-body Injector frequently for leaks.
- A beep will sound when dose delivery is complete.



The On-body Injector is working properly.

Any time you hear beeping, check the status light. If flashing red, call your healthcare provider immediately.

6 mg/  
0.6 mL\*

AMGEN

Neulasta®  
(pegfilgrastim)



Delivery Kit

Pegylated Recombinant Methionyl Human Granulocyte Colony-Stimulating Factor (PEG-r-methHuG-CSF) derived from *E. Coli*

See package insert for full prescribing information and Instructions for Use

AMGEN

Neulasta®  
(pegfilgrastim)



Delivery Kit

Pegylated Recombinant Methionyl Human Granulocyte Colony-Stimulating Factor (PEG-r-methHuG-CSF) derived from *E. Coli*

6 mg/  
0.6 mL\*



Each 0.64 mL syringe delivers 0.6 mL dose through the on-body injector containing: 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP. Each syringe contains sufficient drug product to compensate for liquid loss during delivery through the on-body injector.

On-body Injector for Neulasta Sterilized Using Ethylene Oxide

Single Use Only  
Sterile Solution - No Preservatives  
Dosage - See Package Insert  
Do Not Use if Package is Damaged  
No U.S. standard of potency  
Type BF Applied Part  
Not MRI-safe  
© 2014 Amgen Inc. All rights reserved.  
Device Assembled in China

Lot:  
Exp.:



MCK20150y10.0



Neulasta®  
(pegfilgrastim)

Pegylated Recombinant Methionyl Human Granulocyte Colony-Stimulating Factor (PEG-r-methHuG-CSF) derived from *E. Coli*

AMGEN

6 mg/  
0.6 mL\*



Patent statement:  
<http://pat.amgen.com/neulasta/>

1 - Single Use Neulasta Prefilled Syringe  
1 - sterile On-body Injector for Neulasta  
NDC 55513-192-01

AMGEN

Neulasta®  
(pegfilgrastim)



Delivery Kit

Pegylated Recombinant Methionyl Human Granulocyte Colony-Stimulating Factor (PEG-r-methHuG-CSF) derived from *E. Coli*

6 mg/  
0.6 mL\*



6 mg/0.6 mL\*

\* Prefilled syringe contains 0.64 mL to deliver 6 mg/0.6 mL when used with on-body injector

For Subcutaneous Use Only

Carton Contents (intended to be dispensed as a unit):

- 1 sterile On-body Injector for Neulasta
- 1 - Neulasta prefilled syringe labeled for use with on-body injector only
- 1 patient instructions for use
- 1 healthcare provider instructions for use, 1 package insert
- 1 reference guide

This Product Contains Dry Natural Rubber

Store at 2° to 8°C (36° to 46°F).

Do Not Freeze or Shake. Keep in Carton to Protect from Light.

Rx Only

Manufactured by Amgen Inc.  
Thousand Oaks, CA 91320-1799

U.S. License No. 1080

6 mg/  
0.6 mL\*

AMGEN

Neulasta®  
(pegfilgrastim)



Delivery Kit

Pegylated Recombinant Methionyl Human Granulocyte Colony-Stimulating Factor (PEG-r-methHuG-CSF) derived from *E. Coli*

See package insert for full prescribing information and Instructions for Use



Neulasta® (pegfilgrastim)  
**Manufactured by:**  
Amgen Inc.  
Thousand Oaks, California 91320-1799

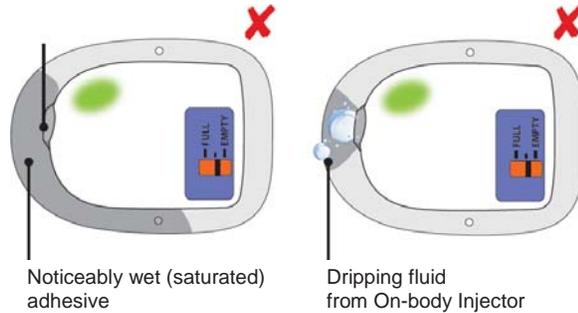
© 2002 to 2014 Amgen Inc. All rights reserved.  
www.neulasta.com  
1-800-77-AMGEN (1-800-772-6436)  
Issued: 12/2014  
v1

### Attention!

If medicine has leaked or the adhesive is noticeably wet (saturated), call your healthcare provider immediately as you may not have received your full dose.

Even with a leak, the status light may remain green and the fill indicator may be at EMPTY.

Cannula  
Window



Description:	Laser Marked Artwork:
1. Product Description	For use with Neulasta
2. Company Information	Amgen Inc. 1-844-696-3852
3. LOT # Sequence #	AXXXXX XXXXXXXX

\*AW not to scale. Approval of text only

NOTES:

A Device product identifier per 15126-AW has a prefix “A” and contains a total of 6 alpha numeric characters “AXXXXX”. Sub-contractor (b)(4) will uniquely laser inscribes each Device product identifier starting with A40000. Upon closeout of a Device product identifier, the next Device product identifier will be incremented by one (e.g. A40000, A40001, A40002, etc.).

For internal tracking of Device during the manufacturing process, a unique sequence number is added. The sequence number contains a total of 7 alpha numeric characters “XXXXXXXX”.

## 15126-AW Rev F

**On-body Injector for  
Neulasta®  
(pegfilgrastim)  
(1x)**

**REF ZXA390**  
Catalogue number

36° F - 86° F  
Temperature Limitation

**STERILE EO**  
Sterilized Using Ethylene Oxide

**IPX8**  
Submersible

20% - 85%  
Humidity Limitation

**MR**  
Non MRI-safe

**S**  
Single Use

**I**  
Refer to Instructions For Use

**D**  
Do Not Use If Package is Damaged

**BF**  
Type BF Applied Part

**U** YYYY-MM  
Use By

**LOT** AXXXXX  
Lot Number

Manufactured for:  
Amgen Inc.  
Thousand Oaks, CA 91320-1799 USA

**Rx ONLY**  
Assembled in China  
16207-AW Rev B



(b) (4)

**Neulasta®**  
(pegfilgrastim)  
**6 mg/0.6 mL\***

\* Contains 0.64 mL to deliver 6 mg/0.6 mL when used with on-body injector

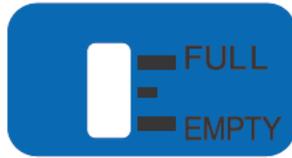
**Use With On-body Injector for Neulasta Only** **Rx Only**

Amgen Inc. U.S. Lic. No. 1080

Exp:  Lot:

MCK1931V5.0

**On-body Injector**  
for  
**Neulasta®**  
(pegfilgrastim)  
**1-844-696-3852**



(b) (4)

AMGEN®

# Neulasta® (pegfilgrastim)



6 mg/  
0.6 mL\*



Pegylated Recombinant Methionyl Human Granulocyte Colony-Stimulating Factor (PEG-r-methHuG-CSF) derived from *E. Coli*

\* Contains 0.64 mL to deliver 6 mg/0.6 mL when used with on-body injector

**Use With On-body Injector for Neulasta Only**

Dosage - See Package Insert  
Amgen Inc. Thousand Oaks, CA 91320

1 - Single Use Prefilled Syringe

NDC 55513-102-01

Each 0.64 mL syringe delivers 0.6 mL dose through the on-body injector containing: 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP. Each syringe contains sufficient drug product to compensate for liquid loss during delivery through the on-body injector.

No U.S. standard of potency.

Store at 2° to 8°C (36° to 46°F).

Do Not Freeze or Shake. Protect from Light.

This Product Contains Dry Natural Rubber

Sterile Solution - No Preservative

U.S. License No. 1080

Rx Only



MCK2060v6.0

Lot  
Exp.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125031Orig1s175**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

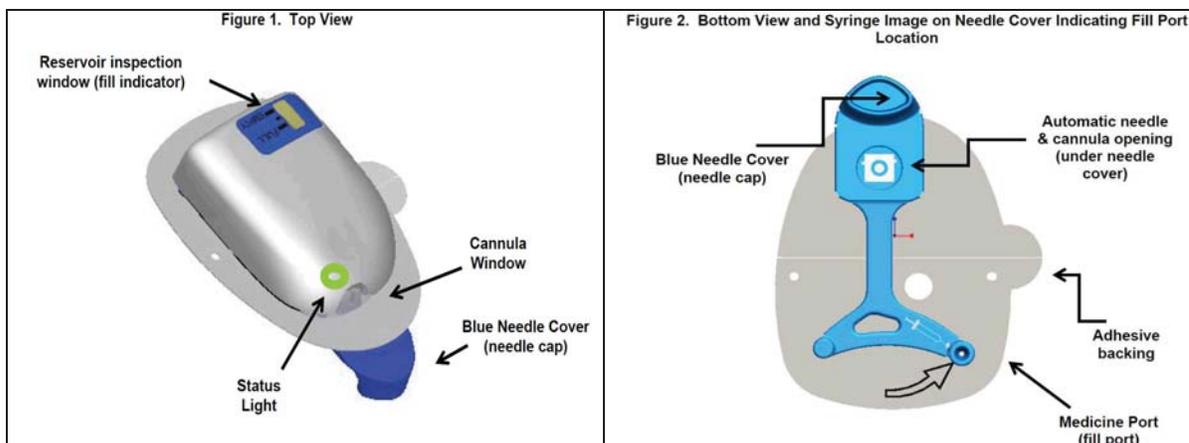
<b>Date</b>	December 19, 2014
<b>From</b>	Christopher Downey, PhD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	BLA 125031
<b>Supplement#</b>	Supplement 175
<b>Applicant</b>	Amgen
<b>Date of Submission</b>	June 27, 2014
<b>PDUFA Goal Date</b>	October 27, 2014, extended to December 27, 2014
<b>Proprietary Name / Established (USAN) names</b>	NEULASTA / pegfilgrastim
<b>Dosage forms / Strength</b>	6 mg once per chemotherapy cycle
<b>Proposed Change(s)</b>	Co-package pre-filled syringe with on-body injector device
<b>Recommendation:</b>	<i>Approval</i>

## 1. Introduction

On June 27, 2014, Amgen submitted a prior approval supplement (sBLA 125031/175) requesting approval of a combination product consisting of a Neulasta pre-filled syringe and a drug delivery device. The delivery device, called an on-body injector, is intended to deliver a single dose of the same 0.60 mL volume as the currently approved Neulasta pre-filled syringe 27 hours after application.

The proposed use of the device is that the healthcare provider will inject the drug into the device using the co-packaged pre-filled syringe. The act of filling activates the device. The provider then will apply the device to the patient. Three minutes after activation, the device will deploy a rigid needle to insert a soft cannula into the patient's subcutaneous tissue. The needle then retracts, leaving the soft cannula implanted in the tissue. Twenty-seven hours after device activation, the device delivers the drug through the cannula over a period of 45 minutes. The device gives light and sound signals to inform the patient, caregiver, or healthcare provider of the device status, including drug delivery initiation, completion, deactivation, and errors. Upon completion of dose delivery, the patient removes the device and disposes of the device.

An illustration of the on-body injector device is pasted below.



The Applicant's rationale for developing the on-body injector device is that the device can be filled with Neulasta and applied by a healthcare provider at the time of chemotherapy, and the device will then administer the drug 27 hours later. This method of administration will improve compliance with the recommended dosing schedule, eliminate the need for some patients to return to a hospital or other clinical setting the day after chemotherapy to receive Neulasta, and provide an alternative for patients who do not wish to self-administer or to be administered by a caregiver.

The on-body injector will be packaged in a clamshell kit with a single Neulasta pre-filled syringe (PFS). The manufacture and testing of Neulasta in the PFS is unchanged from the approved commercial product, with the exception that the PFS to be packaged exclusively with the on-body injector are filled with 0.64 mL solution instead of 0.60 mL to compensate for the volume held up in the on-body injector. The PFS packaged with the on-body injector are labeled as for use with the device only.

All the review disciplines recommend in favor of approval, and I agree with their recommendations. The product quality data presented support stability of the drug in the device. The device performance and manufacturing data support that the device will consistently deliver the intended dose 27 hours after application and will do so throughout the proposed 36 month device shelf life. The human factors study demonstrated that, with the current revisions to the instructions to the patients and healthcare providers, users will be able to apply and operate the device and interpret its light and sound prompts. The clinical pharmacology data demonstrate no impact to the pharmacokinetics of Neulasta administered by the device as compared to administered manually. The labeling information agreed to by the sponsor meets regulatory requirements and is sufficient to ensure proper use by healthcare providers, patients, and caregivers. There is little risk to patient safety or drug efficacy from administering Neulasta by the on-body injector, and the added convenience and improved compliance from using the device will benefit patients. I therefore recommend approval of this supplement.

This memorandum summarizes the information contained in sBLA 125031/175 and discusses the recommendations made by each review discipline.

## 2. Background

Neulasta is approved to decrease the incidence of infection, as presented by febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. The drug is administered once per chemotherapy regimen, the day after chemotherapy treatment. The currently approved format is a single-use pre-filled syringe administering 0.60 mL of 10 mg/mL pegfilgrastim in liquid solution.

The on-body injector is manufactured by Insulet Corporation (Bedford, MA). Insulet makes a similar device called OmniPod that injects insulin. The OmniPod is FDA-approved as a 510(k) device. Amgen worked with Insulet to develop the on-body injector for Neulasta. The device is designed to give the same dose as by manual injection 27 hours after the device is applied on the day of chemotherapy treatment.

### Submission and Review

The supplemental BLA was received electronically on June 27, 2014 and filed as a prior-approval supplement. The FDA extended the review clock from October 27 to December 27, 2014 upon receipt of amendments requiring substantial review by the CDRH team.

All of the relevant review disciplines have written review documents. The primary review documents relied upon in my CDTL memo is listed below:

<b>Review discipline</b>	<b>Name(s) of reviewers</b>
Product Quality (OBP/DTP)	J. Chung, Ph.D., 12/18/2014
Microbiology (BMAB)	Lakshmi Rani Narasimhan, 10/27/2014
Device Engineering (CDRH/GHDB/ODE)	Commander Alan Stevens, 10/13/2014
Device Manufacture Compliance (CDRH/OC)	Crystal Lewis, 11/19/2014
Clinical Pharmacology (DHP/CDP V)	Vicky Hsu, PhD, 9/16/2014
CDRH Human Factors (CDRH/ODE/DAGRID)	QuynhNhu Nguyen, PhD, 10/3/2014
Labeling review (DMEPA)	Neil Vora, PharmD, MBA, 10/26/2014
Labeling review (DTP/OBP)	Jibril Abdus-Samad, PharmD, 12/18/2014
Patient Labeling review (DMPP)	Sharon R. Mills, BSN,RN, CCRP, 10/16/2014
Patient Labeling review (OPDP)	Adam George, PharmD, 10/16/2014
Labeling review (CDRH/OCE/DHC/SCB)	Harriet Albersheim, 10/16/2014

### 3. Product Quality

#### CMC/Product Quality Review

The Division of Therapeutic Proteins (DTP) reviewer, Jee Chung, PhD recommended approval of the supplement, and I served as her team lead and agree with her recommendation. The reader is referred to the Product Quality review by Dr. Chung, dated December 18, 2014, for complete information. I summarize the key review findings below.

To support the approval of the combination product consisting of the Neulasta pre-filled syringe (PFS) co-packaged with the on-body injector, the sponsor provided the following product quality information:

- extractables and leachables study for the material held in the on-body injector
- study of the impact of and a specification control for residual levels the device sterilizing agent ethylene oxide
- in-use stability data for the drug in the on-body injector
- photostability data for the drug in the on-body injector
- process validation study for manufacture of the Neulasta PFS intended for the kit
- process controls for assembling the co-packaged PFS and device kit
- kit shipping validation
- shelf life limit and stability commitment

The leachables and extractables study identified no risk associated with storing the product in the on-body injector. The extractables study identified small levels of organic compounds and trace metals. Building from these data, Amgen examined 4 organic compounds and 5 inorganic elements in a leachables study, and found all levels >1000-fold lower than in the extractables study. Because all compounds from the extractables study had a margin of safety of 6 to 9 million-fold relative to the permissible daily exposure, the levels are acceptable.

The sponsor's proposed a specification limit (b) (4) for residual levels of ethylene oxide is sufficient to prevent risk of ethylene oxide oxidizing the drug during the 27 hour storage period in the device. This limit is supported by a study of ethylene oxide spiked into the drug under temperature conditions similar to intended use in the device. This study found no impact to product quality (b) (4) ethylene oxide.

Stability data for the drug in the on-body injector held at for 27 hours at temperatures ranging from 37 – 42 °C in 3 separate experiments support that the drug is stable in the on-body injector at body temperature for the labeled duration of use. In all 3 cases, there were no impacts to product quality detected. A “dynamic” stability study assessed stability of the drug in the on-body injector subjected to vibration and motion. In separate experiments, a drug-filled device was held at 37°C for 27 hours. During this time, one sample was agitated at (b) (4) and the other at (b) (4). In both cases, there was no significant impact on product quality.

The photostability data indicated increased, but within-specification limits, levels of in non-proteinaceous sub-visible particles on exposure to the equivalent of 27 hours of ambient light. There were no other significant impacts to product quality. The increasing trend of non-

proteinaceous particles is acceptable (b) (4)  
(b) (4) Therefore, the safety risk for capillary occlusion from particulates in patients using the delivery device is low. The label of the product carries a warning to protect drug-containing on-body injector from light, mitigating risk from the potential for sub-visible particle formation in response to light.

The sponsor validated filling the Neulasta pre-filled syringe (PFS) to be packaged with the device to 0.64 mL instead of the 0.60 mL of the stand-alone PFS. The extra 0.04 mL compensates for dead volume in the device, and the delivered dose is unchanged. The sponsor filled (b) (4) and met all criteria for fill weight. Dr. Chung concluded that the process limits for the 0.64 mL fill are sufficiently narrow to achieve the target volume and that the process is validated.

(b) (4)  
(b) (4) Dr. Chung noted that 21 CFR 610.14 requires an identity test on the final packaged drug product. The sponsor therefore agreed to conduct its (b) (4) (b) (4) identity test on samples pulled from the final packaged kit.

The sponsor assessed stability of the kit for shipping by simulating dropping, repetitive shock, and vibration. No damage to the device or PFS functionality or labeling was observed. The shipping validation study from the original BLA examined 0.60 mL prefilled syringes shipped over much larger distances than apply to the proposed kit, supporting stability of the product in the syringes during shipping. The difference in the 0.64 mL kit syringe and the 0.60 mL syringe is too small impact stability with respect to shipping.

The expiration dating for the packaged kit is determined by the component that expires first, assuring that neither the PFS or device component will expire prior to the kit expiry. Stability of the PFS component is covered by the approved stability protocol for monitoring PFS used for direct injection. Stability of the device is also monitored separately. The sponsor commits to (b) (4)  
(b) (4)

### **CMC/microbiology**

The Biotechnology Manufacturing Assessment Branch (BMAB) reviewer recommended approval of the supplement, and I agree with her recommendation. The reader is referred to the Product Quality Microbiology review by Dr. Lakshmi Rani Narasimhan, dated October 27, 2014, for complete information. I summarized the key review findings below.

A microbial challenge study demonstrates that pegfilgrastim does not support microbial growth over the timescale and temperature to be encountered during use of the device. Consequently, the growth of possible contaminating microorganisms during transfer or the use of the device is not supported by the drug product. The challenge organisms *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus brasiliensis* were spiked into the drug product solution (b) (4)

(b) (4) No growth was detected. The reviewer also notes that the acidic pH 4.0 drug formulation is inhibitory to microbial growth and proliferation.

There is no change to the microbial controls in the manufacturing process to manufacture the 0.64 mL PFS intended to be packaged with the device from the approved process to produce the 0.60 mL PFS intended for direct injection to the patient. There are no changes to the release or stability testing of the PFS.

The sponsor provided sufficient information on its inventory control and tracking systems to assure that the on-body injector will be co-packed 0.64 mL PFS intended to be packaged with the device rather than the 0.60 mL PFS intended for direct injection to the patient.

Dr. Narasimhan reviewed the shipping validation information and concluded that the container closure integrity of the PFS component is maintained over the intended shipping conditions and duration. Dye-ingress testing was used to demonstrate container closure integrity of PFS in its primary, pre-kitting packaging at the end of the shipping study. Upon request, the sponsor provided clarifying information on the study report numbers and PFS lots that were tested. The data for shipping PFS in its primary packaging is sufficient to support that the PFS container can be shipped in the kit with the on-body injector.

The reviewer requested and the sponsor provided satisfactory information on the FEI numbers of the manufacturing facilities for the device. The sponsor provided all needed information, and the reviewer found the information acceptable.

### **Device Engineering**

The General Hospital Devices Branch, Office of Device Evaluation, CDRH reviewer, Cdr. Alan Stevens, recommended approval of the supplement. He concluded that the on-body injector will perform reliably and will function adequately to yield safe and effective infusion of Neulasta. I agree with his recommendation. Refer to Cdr. Stevens' review dated October 23, 2014, for complete information. I summarized the key review findings below.

Dr. Stevens evaluated the device requirements, device risk assessments, and performance data for the on-body injector. He also evaluated the PFS component for its interaction with the on-body injector. He reviewed device labeling and instructions for use. He concluded that the sponsor provided a comprehensive set of design documents that supports a conclusion that the on-body injector will perform reliably and is adequately safe and effective for infusion of Neulasta.

The review covered a large quantity of information submitted by Amgen on October 3, 2014 and October 6, 2014. These documents were submitted in response to an information request sent on September 26, 2014. Receipt of the substantial new information triggered extension of the review clock by 2 months for this supplement.

The review covered the following aspects of on-body injector performance and concluded that the information was acceptable to support system performance and reliability:

- 1) Device software and firmware.
- 2) Biocompatibility of device materials (consulted to CDRH reviewer, Dr. BiFeng Qian, MD, PhD)
- 3) Sterilization with ethylene oxide
- 4) Stability of the device during 36 months accelerated aging, including package integrity, and device functionality
- 5) Filling of the correct volume from the PFS into the on-body injector reservoir
- 6) Applying the device to patient, including adhesive peel strength, the timing of actuation, the cannula insertion process, device self-tests, and alerts, lights, and notifications
- 7) Automatic needle and cannula insertion and needle retraction
- 8) Cannula insertion depth
- 9) Performance during the wearing period by the patient, including fluid ingress, adhesive reliability, cannula patency, kink resistance, fatigue resistance, reliability, occlusions, environmental exposure, and power requirements and reliability
- 10) Leakage during the cannula fill, after the fill, and after dose delivery
- 11) Device resistance to water
- 12) Battery life and LED indicators
- 13) Operational environmental conditions
- 14) Delivery accuracy and reliability and error conditions
- 15) Delivery time
- 16) Mechanical vibration and shock studies.
- 17) Dry heat and cold storage, operating, post-delivery drop studies
- 18) Free fall testing
- 19) Electrostatic discharge & radiofrequency immunity
- 20) Occlusion detection and delivery pressure

The data demonstrated that the dose is delivered with a reliability of (b) (4). The CDER review team concluded that the (b) (4) chance of mis-dosing is acceptable compared to the benefit of the device in providing increased convenience to patients and improved compliance for dose administration at the correct time. I concur with this risk assessment.

Cmdr. Stevens identified that the device contains a “pink slide indicator” that visibly moves during cannula insertion. For the similar insulin delivery device produced by the same manufacturer, the motion of the indicator signals to the patient that cannula insertion is taking place. For the Neulasta device, the indicator is not described to the patient nor intended to be used to communicate to the patient. The originally proposed labeling (b) (4), but labeling negotiations with the FDA resulted in the (b) (4). Car. Stevens expressed concern that the visible indicator may lead to patient confusion. The review team discussed the matter and determined that *i*) the cannula insertion takes place in the presence of the healthcare provider, *ii*) device lights and sounds communicate that cannula insertion is taking place, reducing the potential for confusion from observing visible motion within the device, and *iii*) the Neulasta on-body injector is more opaque than the insulin device, making the indicator barely visible. The team therefore concluded that the visible pink slide indicator is acceptable.

The 36 month shelf life for the device is adequately supported by accelerated stability data. The reviewer noted that the accelerated data may not sufficiently characterize the storage conditions for the battery. Because real-time stability studies are ongoing, the risk for battery life is mitigated. The real-time shelf life evaluations will be included as part of the relevant annual reports submitted to BLA 125031.

#### **Compliance of device manufacturer**

The compliance reviewer from CDRH Office of Compliance, Crystal Lewis, recommended approval of the supplement. I agree with her recommendation. Refer to Ms. Lewis' November 19, 2014 review for complete information. I summarized the key review findings below.

The reviewer performed a desk review of the following 4 topics related to components of 21 CFR 820 regulations:

- 1) management control (21 CFR 820.20)
- 2) design control (21 CFR 820.30)
- 3) purchasing controls (21 CFR 820.50)
- 4) corrective and preventative actions (21 CFR 820.100)

The reviewer determined that the information provided adequately addressed the regulatory requirements for all 4 topics.

The reviewer analyzed of the firm's inspection history over the past 2 years and found that a device inspection conducted 9/8/14 to 9/15/14 found no deficiencies and recommended no action indicated (NAI). The inspection report included enough information about the facility and the manufacture of the finished combination product to evaluate the facility's compliance with applicable 21 CFR part 820 regulations. Therefore, a preapproval application inspection was not necessary.

## **4. Clinical Pharmacology**

Vicky Hsu, Ph.D. of the Office of Clinical Pharmacology determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the sBLA to support a recommendation of approval of the Neulasta Delivery Device. I concur with her recommendation. Refer to Dr. Hsu's review dated September 16, 2014, for complete information. I summarized the key review findings below.

The sponsor completed a phase 1 trial to support comparability of pharmacokinetics and safety of the two pegfilgrastim delivered by the on-body injector and by the currently approved PFS injected manually.

Pharmacokinetics: The pharmacokinetics of pegfilgrastim are comparable when delivered manually from a pre-filled syringe and when delivered automatically from the Neulasta on-body injector (C<sub>MAX</sub> ratio = 0.97, 90% CI: 0.83, 1.14; AUC<sub>0-INF</sub> ratio = 1.00, 90% CI: 0.84,

1.20). The sponsor measured pharmacokinetic data in healthy volunteers following a single 6 mg subcutaneous dose of pegfilgrastim when delivered manually from a pre-filled syringe versus when delivered automatically from the Neulasta Delivery Device in a parallel group study (Study 20101153).

**Safety:** The reported incidences of adverse events were similar between the device-injected and manually injected groups, and the incidences were consistent with the known safety profile of pegfilgrastim. A higher incidence of non-serious adverse events, including contact dermatitis and medical device site reaction, were observed in the on-body injector group. These events are attributable to the device. These non-serious events are acceptable given the convenience and compliance benefit to patients from the device.

**Immunogenicity:** At baseline, 1.6% subjects (2/128) in the manually administered group and 3% subjects (4/134) in the device-administered group tested positive for anti-pegfilgrastim antibodies. After dosing, zero manually-administered subjects (0/127) and 2.2% of device-administered subjects (3/131) developed anti-pegfilgrastim antibodies. No sample for anti-drug antibodies tested positive for neutralizing antibodies.

The reviewer recommended a revision to the label to include a statement describing PK comparability when administering pegfilgrastim sub-cutaneously with a manual PFS versus with the Neulasta on-body injector. This revision was incorporated into the final labeling.

## 5. Device Human Factors

### CDRH Human Factors Review

QuynhNhu Nguyen, Ph.D. of CDRH's Office of Device Evaluation, Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices reviewed the human factors studies for the proposed device. The reviewer did not make a recommendation for or against approval. All issues the reviewer raised were addressed. Refer to Dr. Nguyen's review dated September 16, 2014 and to Dr. Nguyen's addendum dated December 22, 2014 for complete information. I summarized the key review findings below.

The sponsor performed a human factors validation study that included 93 participants from three user groups, 1) health care professionals (n=32), 2) patients (n=31), and 3) caregivers (n=30). Of the 93 participants, 46 participants were trained by the moderators on the Instructions for Use (IFU), while 47 participants were assigned to read the IFU on their own as training. Each user group included both moderator-trained and self-trained participants.

The reviewer identified several task failures and "close calls," including:

- failure to pull adhesive liners completely off the device (1 instance)
- failure to attach the device to the application site in less than 3 minutes (4 instances)
- premature removal of the device 1 minute into the 45 minute drug delivery period (1 instance)
- failure to correctly interpret device hazard alarm (2 instances)
- failure to correctly insert the syringe into the device fill port (2 instances)

The reviewer recommended the Instructions for Use for both the patient and healthcare provider (HCP) be revised to mitigate these types of issues:

- provide additional clarity on the adhesive removal step for the HCP IFU
- provide additional clarity on the correct device orientation for placing the device on the skin, on when is the appropriate time to place the device on the skin, and the meaning of the flashing green light in the Patient IFU
- provide additional information to user on the appropriate action to take if the cannula is deployed prior to placing the device on the patient in the HCP IFU
- emphasize the section in the Patient IFU to call user attention to the device hazard alarm (red flashing light), and to communicate to users that the device hazard alarm means that the device is not properly functioning, the patient may not get the dose, and the patient needs to take appropriate action to reduce further delay of treatment

The final revisions to the labeling and IFU document addressed these concerns.

The reviewer recommended the sponsor be asked to provide additional analysis of the close calls associated with inserting the PFS into the on-body injector and, if necessary, implement additional mitigation to address these reported close calls. FDA requested this information from the sponsor on December 19, 2014, Amgen responded the same day, and the information was reviewed by the QuynhNhu Nguyen, who had since transferred from CDRH to DMEPA in CDER (see next section).

#### DMEPA Human Factors Review

Neil Vora, PharmD, MBA reviewed the human factors study for the Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management. The review is dated September 26, 2014. The reviewer recommends approval of this supplement, and I agree with her assessment. I summarized the key findings for this initial DMEPA human factors review below.

The reviewer noted the same errors from the human factors as the CDRH human factor reviewer described above. The reviewer communicated revised instructions to the patient and healthcare provider to mitigate these issues. These revisions included clarification the instructions to remove adhesive from the back of the device. The reviewer inquired about the possibility of adding voice commands to the device's repertoire of communications to the patients. Such a modification is not feasible. The review team concluded that, with the clarifications in the final instructions to providers and patients, the current device communication system with lights and audio beeps is acceptable.

The reviewer concluded that overall the human factors study results demonstrate that the product can be used safely and effectively by patients, caregivers, and healthcare professionals who receive formal training or have training materials (Instructions for Use) available. The DMEPA reviewer examined the incidences of medication errors for the currently approved manually injected PFS, and she identified seven medication error cases associated with the

incorrect route of administration. Use of the device may mitigate this type of error, because it would be placed by a healthcare provider in the correct application site.

#### Addendum for close calls associated with inserting the PFS into the device

QuynhNhu Nguyen, now of DMEPA, filed an addendum to the DMEPA review on December 22, 2014 that covered the information provided by Amgen on “close calls” associated with inserting the PFS into the device. Dr. Nguyen had previously recommended the sponsor provide additional information on this topic in the CDRH human factors review. The review addendum recommends approval, and I agree with the recommendation. I summarize the findings below.

Amgen’s 12/19/2014 response stated that the close calls occurred when the healthcare providers (HCP) experienced difficulty filling the on-body injector on the first attempt. These users were able to recognize they made a mistake and were subsequently able to successfully fill the on-body injector. Amgen determined that the root cause was lack of clarity in the instructions on the correct angle of inserting the needle. As a corrective action, Amgen modified the HCP Instructions for Use (IFU) to clarify the correct angle of insertion to avoid bending the needle and spilling medication.

The review concluded that Amgen’s response to the IR and its corrective action of revisions to step 6 of the HCP IFU are acceptable. The team has no additional concerns regarding the human factors validation study report.

## **6. Labeling**

The carton and container labels were reviewed by Jibril Abdus-Samad, PharmD, of the Office of Biotechnology products. The review is dated December 18, 2014.

The patient labeling review was performed by Sharon R. Mills, BSN, RN, CCRP, Division of Medical Policy Programs. The review is dated October 16, 2014.

The patient package insert and instructions for use were reviewed by Adam George, PharmD, Office of Prescription Drug Promotion (OPDP). The review is dated October 16, 2014.

The labeling review from CDRH was performed by Harriett Albershiem, Strategic Communication Branch, Division of Health Communication. Her review is dated September 30, 2014.

Neil Vora, PharmD, MBA reviewed the labeling for the Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk Management. The review is dated September 26, 2014.

All labeling reviewers recommend approval of the supplement with the final label and labeling submitted by the sponsor. I concur with their recommendation.

The FDA recommended and the sponsor agreed to revisions to the label and labeling, including the Patient Package Insert and patient and healthcare provider Instructions for Use. These revisions brought the materials into compliance with 21 CFR regulations and current FDA Guidance. The changes simplified wording and clarified concepts, ensured that the PPI is consistent with the Prescribing Information (PI), removed unnecessary or redundant information, and ensured that the PPI is free of promotional language.

The labeling negotiations with the sponsor included several key issues described below.

- 1) The original instructions were to place the on-body injector on the abdomen or the back of the arm. Multiple reviewers raised the concern that the indicator lights on the device would not be visible to the patient if attached to the back of the arm. Therefore, the final labeling instructs that the on-body injector should be applied on the abdomen or back of the arm but that the back of the arm may only be used if there is a caregiver available to monitor the status of the on-body injector.
- 2) The labeling negotiations resulted in a change to the name of the device from (b) (4) (b) (4) to "On-body Injector." This change required the sponsor to alter the (b) (4) label applied to the device. Because the revised (b) (4) will not be available before the review goal date, the sponsor proposed (b) (4). The OBP reviewer raised the concern that the small laser-etched markings on the side of the device lacked prominence and do not enable easy identification of the device or the drug contained within should a patient experience an urgent medical condition while wearing the device. The CDRH labeling reviewer raised the same issue. The clinical team acknowledged the concern but determined that use of laser-etched label on the underside of the On-body Injector does not pose undue risk in the event of an emergency. Clinical concluded that likely interventions if the device is mistakenly identified as an insulin pump are removal of the device and administration of glucose, and these interventions would not be of grave risk to the patient.
- 3) (b) (4) label on the device exposed the "pink slide indicator." The CDRH reviewer noted that there were no instructions for how to interpret the now-visible indicator. The review team concluded that confusion due to movement of the pink slide insert is unlikely and that if confusion were to occur, it would not likely result in any harm to the patient. See CDRH engineering section above for more details.
- 4) The label for the device co-packaged PFS was revised to state explicitly that it is to be used with the on-body injector.
- 5) The instruction that the patient should remain in a place where they can monitor the device for the entire dose delivery was added to the (b) (4) (b) (4) and the (b) (4): Reference Guide. The original information only included this instruction in the Healthcare Provider Instructions. The OPDP review concluded that this information was important to be communicated to the patient in the patient instructions.

- 6) The word “kit” to describe the co-packaged PFS and on-body injector was added to the (b) (4). This made the wording consistent throughout the various labeling documents.
- 7) To mitigate risk of allergic reaction to latex, additional warnings about the latex cap on the PFS were added to the labeling.

## 7. Recommendations/Risk Benefit Assessment

### **Recommended Regulatory Action**

I recommend approval of BLA 125031/Supplement 175 to package a 0.64 mL Neulasta PFS in a kit with on-body device for delivery.

### **Risk Benefit Assessment**

The device-based method of administration will automatically deliver the correct dose of Neulasta at the proper interval after chemotherapy administration. This feature will improve patient compliance with the recommending dosing schedule, eliminate the need for some patients to return to a hospital or other clinical setting the day after chemotherapy to receive Neulasta, and provide an alternative for patients who do not wish to self-administer or to be administered by a caregiver. The dosing and indication are unchanged from the currently approved manually injected PFS. The significant benefits to the patient offset the very low (<1%) risk of device failure, errors arising from human factors, or the minor adverse effects that may arise from the adhesive irritating the skin. I therefore concur with the assessments of the review team and recommend approval.

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/s/  
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CHRISTOPHER D DOWNEY  
12/23/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125031Orig1s175**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY (OCP):**

<b>BLA (SDN)</b>	125031 (1006), Supplement-175 Manufacturing
<b>Submission Number (Date)</b>	06/27/2014
<b>Compound</b>	Pegfilgrastim (NEULASTA <sup>®</sup> )
<b>Sponsor</b>	Amgen
<b>Indication(s)</b>	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.
<b>Dosing Regimen</b>	6 mg SC once per chemotherapy cycle
<b>Clinical Division</b>	Division of Hematology Products
<b>OCP Division</b>	Division of Clinical Pharmacology V
<b>Primary Reviewer</b>	Vicky Hsu, Ph.D.
<b>Team Leader</b>	Sarah J. Schrieber, Pharm.D.
<b>Clinical Safety Reviewer</b>	Patricia Dinndorf, M.D.
<b>Clinical Safety Team Leader</b>	Albert Deisseroth, M.D., Ph.D.

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## 1.0 Executive Summary

In this supplemental BLA, the sponsor is seeking approval of a combination product comprising of a pegfilgrastim pre-filled syringe (PFS) co-packaged with a drug delivery device designed to administer pegfilgrastim according to the route of administration and dosing schedule for which pegfilgrastim is currently approved (as a single use PFS for subcutaneous (SC) injection). The sponsor completed a phase 1 trial to support pegfilgrastim pharmacokinetic comparability and safety of the two drug delivery methods.

**Pharmacokinetics:** Pharmacokinetic data were obtained in healthy volunteers following a single 6 mg subcutaneous dose of pegfilgrastim when delivered manually from a pre-filled syringe versus when delivered automatically from the Neulasta Delivery Device in a parallel group study (Study 20101153). Pegfilgrastim pharmacokinetics when delivered manually from a pre-filled syringe is comparable to pegfilgrastim pharmacokinetics when delivered automatically from the Neulasta Delivery Device ( $C_{MAX}$  ratio = 0.97, 90% CI: 0.83, 1.14;  $AUC_{0-INF}$  ratio = 1.00, 90% CI: 0.84, 1.20).

**Safety:** The reported incidences of adverse events were similar between both groups, and were consistent with the known safety profile of pegfilgrastim. A higher incidence of non-serious adverse events, such as contact dermatitis and medical device site reaction, were observed in the drug delivery device group and these were attributed to be device-related.

**Immunogenicity:** At baseline, 1.6% subjects (2/128) in Group A and 3% subjects (4/134) in Group B tested positive for anti-pegfilgrastim antibodies. After dosing, no subjects (0/127) in Group A and 2.2% subjects (3/131) in Group B developed anti-pegfilgrastim antibodies. No sample for APA tested positive for neutralizing antibodies.

## 1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the sBLA to support a recommendation of approval of the Neuasta Delivery Device.

### Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

## 1.2 Signatures

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Vicky Hsu, Ph.D.  
Reviewer  
Division of Clinical Pharmacology V

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Sarah J. Schrieber, Pharm.D.  
Acting Team Leader  
Division of Clinical Pharmacology V

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Patricia Dinndorf, M.D.  
Clinical Safety Reviewer  
OND, Division of Hematology Products

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Albert Deisseroth, M.D., Ph.D.  
Clinical Safety Team Leader  
OND, Division of Hematology Products

### 1.3 Clinical Pharmacology Summary

Pegfilgrastim (NEULASTA<sup>®</sup>) is a leukocyte growth factor. Neulasta is FDA-approved to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

In this supplemental BLA, the sponsor is seeking approval of a combination product comprising of a pegfilgrastim pre-filled syringe co-packaged with a drug delivery device designed to administer pegfilgrastim according to the route of administration and dosing schedule for which pegfilgrastim is currently approved (as a single use pre-filled syringe for subcutaneous injection).

Pharmacokinetics: Pharmacokinetic data were obtained in healthy volunteers following a single 6 mg subcutaneous dose of pegfilgrastim when delivered manually from a pre-filled syringe versus when delivered automatically from the Neulasta Delivery Device in a parallel group study (Study 20101153). Pegfilgrastim pharmacokinetics when delivered manually from a pre-filled syringe is comparable to pegfilgrastim pharmacokinetics when delivered automatically from the Neulasta Delivery Device ( $C_{MAX}$  ratio = 0.97, 90% CI: 0.83, 1.14;  $AUC_{0-INF}$  ratio = 1.00, 90% CI: 0.84, 1.20).

Safety: The reported incidences of adverse events were similar between both groups, and were consistent with the known safety profile of pegfilgrastim. A higher incidence of non-serious adverse events, such as contact dermatitis and medical device site reaction, were observed in the drug delivery device group and these were attributed to be device-related.

Immunogenicity: At baseline, 1.6% subjects (2/128) in Group A and 3% subjects (4/134) in Group B tested positive for anti-pegfilgrastim antibodies. After dosing, no subjects (0/127) in Group A and 2.2% subjects (3/131) in Group B developed anti-pegfilgrastim antibodies. No sample for APA tested positive for neutralizing antibodies.

### 2.0 Question Based Review

#### **What are the proposed dosage(s) and route(s) of administration?**

The recommended dosage is 6 mg pegfilgrastim administered subcutaneously (SC) once per chemotherapy cycle (do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy).

#### **Is pegfilgrastim PK comparable when delivered subcutaneously via the Neulasta Delivery Device versus when delivered manually via a pre-filled syringe?**

Yes, the PK of pegfilgrastim appears to be comparable when pegfilgrastim is delivered SC via a manual pre-filled syringe versus when it was delivered automatically via the proposed co-packaged Neulasta Delivery Device.

### Study Design

In Study 20101153, a subcutaneous (SC) dose of 6 mg pegfilgrastim was administered to healthy subjects either manually via a pre-filled syringe (Group A, n=125 planned) or automatically via the investigational Neulasta Delivery Device (Group B, n=125 planned). Group B subjects received the Neulasta Delivery Device on Study Day -1, which was pre-programmed to automatically administer a single 6 mg SC dose pegfilgrastim on Study Day 1 (27 hours after activation and application). Group A subjects received a single 6 mg SC dose of pegfilgrastim administered manually via a pre-filled syringe on Study Day 1 at approximately the same time of day as those receiving the automatic dose in Group B. The following statistical method was used to assess pegfilgrastim PK comparability between Group A and B: one-way analysis of variance (ANOVA) of log-transformed pegfilgrastim AUC<sub>0-INF</sub> and C<sub>MAX</sub>, with PK comparability defined when the 90% confidence intervals of the ratios of the least-squares geometric means for AUC<sub>0-INF</sub> and C<sub>MAX</sub> for both Groups fall between 0.80 and 1.25.

### Results

#### Demographics:

Ninety-seven percent of enrolled subjects (258/267) completed the study. Nine subjects discontinued from the study (Group A: n=4, Group B: n=5) for various reasons, and of these, five subjects never received pegfilgrastim and were thus excluded from PK and safety analysis sets (Group A: n=2, Group B: n=3). A summary of subject demographics is provided in **Table 1**.

**Table 1.** Summary of subject demographics

Demographics		Group A (n=128)	Group B (n=134)
Sex	Male	85 (66%)	96 (72%)
	Female	43 (34%)	38 (28%)
Age (years)	Mean	35	35
	Range	18-50	19-50
Weight (kg)	Mean	76.5	77.0
	Range	50.7-107	54.4-106
Race	Caucasian	91 (71%)	93 (70%)
	African American	33 (26%)	32 (24%)
	Asian	1 (0.8%)	5 (3.7%)
	Other	3 (2.3%)	4 (3.0%)

**PK:** The PK of pegfilgrastim appears to be comparable when pegfilgrastim is delivered SC via a manual pre-filled syringe (PFS) versus when it was delivered automatically via the co-packaged Neulasta Delivery Device.

The least-squares geometric mean ratios for  $C_{MAX}$  and  $AUC_{0-INF}$  were 0.97 and 1.00, respectively, with corresponding 90% confidence intervals within the PK comparability limits of 0.80 and 1.25 (Table 2). A summary of the PK parameters are presented in Table 3 and the concentration vs. time profiles are presented in Figure 1.

**Table 2.** Least-squares geometric means of  $C_{MAX}$  and  $AUC_{0-INF}$  of pegfilgrastim delivered SC by manual injection or delivery device

Parameter (unit)	Group B (Test) (N=125)		Group A (Reference) (N=128)		Ratio of Group B / Group A (Test/Reference) <sup>b</sup>	
	n	LS Mean <sup>a</sup>	n	LS Mean <sup>a</sup>	LS Mean	90% CI
$C_{max}$ (ng/mL)	125	192.6	128	198.2	0.97	(0.83, 1.14)
$AUC_{0-inf}$ (ng*hr/mL)	125	7971.6	128	7941.5	1.00	(0.84, 1.20)

Group A = subjects randomized to receive pegfilgrastim with a manual syringe

Group B = subjects randomized to receive pegfilgrastim with the investigational delivery device

90% CI = 90% confidence interval;  $AUC_{0-inf}$  = AUC from time 0 to infinity;  $C_{max}$  = Maximum observed concentration; LS = least squares; n = Number of subjects for whom the corresponding PK parameter can be adequately estimated.

<sup>a</sup>LS Mean = least squares geometric mean from the SAS PROC MIXED procedure.

<sup>b</sup>The ratio and CI are based on natural log scale data converted back to the original scale.

(Source: Table 11-2 from Sponsor's Clinical Study Report 20101153)

**Table 3.** Pegfilgrastim PK parameter estimates after a single 6 mg SC dose of pegfilgrastim in healthy subjects

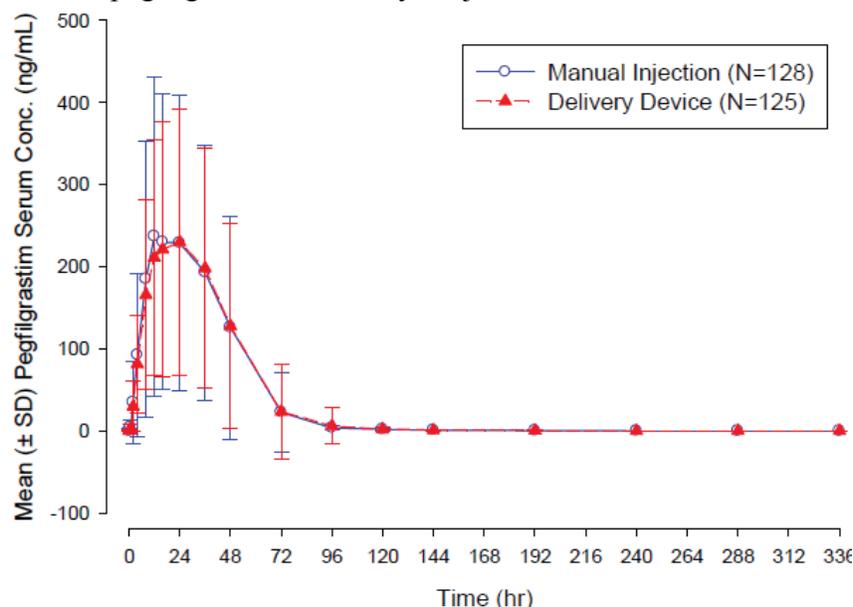
Descriptive Statistics	$t_{max}$ (hr)	$C_{max}$ (ng/mL)	$AUC_{0-t}$ (hr*ng/mL)	$AUC_{0-inf}$ (hr*ng/mL)
Group A				
n	128	128	128	128
Mean	-	262	11100	11100
SD	-	199	9590	9590
Min	8.0	21.5	1120	1140
Median	16	224	8920	8930
Max	48	1250	61700	61700
CV%	-	76.1	86.6	86.5
Group B				
n	125	125	125	125
Mean	-	248	10900	10900
SD	-	168	8530	8530
Min	4.0	23.2	248	259
Median	16	217	9110	9150
Max	48	925	46300	46300
CV%	-	68.0	78.2	78.0

Group A = subjects randomized to receive pegfilgrastim with a manual syringe

Group B = subjects randomized to receive pegfilgrastim with the investigational delivery device

(Source: Table 11-1 from Sponsor's Clinical Study Report 20101153)

**Figure 1.** Pegfilgrastim mean ( $\pm$ SD) serum concentration-time profiles after a single 6 mg SC dose of pegfilgrastim in healthy subjects.



(Source: Figure 11-1 from Sponsor's Clinical Study Report 20101153)

**What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

Immunogenicity samples were collected at: pre-dose (Day 1) and end of study (Day 42 $\pm$ 3).

At baseline, 1.6% subjects (2/128) in Group A and 3% subjects (4/134) in Group B tested positive for anti-pegfilgrastim antibodies. After dosing, no subjects (0/127) in Group A and 2.2% subjects (3/131) in Group B developed anti-pegfilgrastim antibodies.

**Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

Given the results of the study, there did not appear to be an impact of immunogenicity on PK in this study (**Table 3**). However, conclusions regarding the impact of immunogenicity on pegfilgrastim PK cannot be drawn at this time due to the low immunogenicity incidence rate. PD was not assessed in this study.

**Do the anti-product antibodies (APA) have neutralizing activity?**

No sample that tested positive for APA tested positive for neutralizing antibody formation.

**What is the impact of anti-product antibodies on clinical efficacy?**

Efficacy was not evaluated in this study.

**What is the impact of anti-product antibodies on clinical safety?**

The impact of APA on clinical safety is limited due to the low incidence rate of APA following pegfilgrastim administration.

**What is the safety profile of pegfilgrastim when delivered subcutaneously via the Neulasta Delivery Device versus when delivered manually via a pre-filled syringe?**

Approximately 85% of subjects in both Groups experienced at least one adverse event (**Table 4**). Most of the adverse events were mild to moderate in severity and were consistent with known safety profile of pegfilgrastim.

Syringe/Device-Related

A higher incidence of delivery-related adverse events, mainly dermatitis contact and medical device site reaction, occurred with the delivery device in Group B (13.4% (18/134)) than with the manual pre-filled syringe in Group A (3.9% (5/128)). None of these adverse events were serious in nature.

Serious Adverse Events (SAEs)

No subjects in Group A experienced SAEs. Two subjects in Group B experienced SAEs of anaphylactic reaction (Subject 15366005028) and arthritis (Subject 15366006035). The anaphylactic reaction was considered to be related to pegfilgrastim, and resolved quickly with oxygen administration. The arthritis case resolved with administration of non-steroidal anti-inflammatory drugs and antibiotics. Both subjects completed the study.

Both SAE cases appear to be isolated incidents and do not constitute as additional safety risks to patients using the proposed Neulasta combination product.

**What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.**

Serum pegfilgrastim concentrations were measured in plasma by a validated enzyme-linked immunosorbent assay (ELISA) method using (b) (4) (b) (4) from (b) (4) (MET-003315). The assay range was 0.170 – 3.33 ng/mL. The assay has been previously reviewed under BLA 125031, and the sponsor submitted additional Pharmacokinetic Information Report (Section 16.1.13.1) to summarize assay performance.

**What bioanalytical methods are used to assess the formation of the anti-product antibodies and neutralizing antibodies? Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.**

A Biacore biosensor immunoassay (MET-001908, version 5.0) was used to detect anti-pegfilgrastim and/or filgrastim antibodies. A cell-based bioassay assay (MET-001941, version 1.0) was used to test for neutralizing antibody formation against pegfilgrastim and/or filgrastim. These assays have been previously reviewed under BLA 125031, and the sponsor submitted additional Anti-pegfilgrastim Antibody Assays Report (Section 16.1.13.2) to summarize assay performance.

**3.0 Labeling Recommendations**

**Section 12.3 Pharmacokinetics:** Revised to include a statement regarding PK comparability when administering pegfilgrastim SC with a manual PFS vs. with the (b) (4)

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WENCHI HSU  
09/15/2014

SARAH J SCHRIEBER  
09/15/2014

PATRICIA A DINNDORF  
09/16/2014

ALBERT B DEISSEROTH  
09/16/2014

## Office of Clinical Pharmacology New Drug Application Filing and Review Form

This sNDA is to seek approval of a combination product comprising of a pegfilgrastim prefilled syringe co-packaged with a drug delivery device to facilitate administration of Neulasta<sup>®</sup> according to the same dose, dosing schedule and route of administration for which pegfilgrastim is currently approved. To support this change, the sponsor submitted results from a PK comparability study (Study 20101153) comparing AUC and Cmax in subjects receiving pegfilgrastim via the proposed combination product (which delivers drug automatically) vs. via the currently approved prefilled syringe (which requires manual injection).

<b>NDA Number:</b>	BLA 125031 (S-175, Manufacturing)	<b>SDN:</b>	1006
<b>Sponsor:</b>	Amgen	<b>Date of Submission:</b>	06/27/2014
<b>Brand Name:</b>	Neulasta <sup>®</sup>	<b>Generic Name:</b>	pegfilgrastim
<b>Drug Class:</b>	Leukocyte growth factor		
<b>Dosage Form:</b>	Subcutaneous injection: 6 mg per 0.6 mL in single dose prefilled syringe		
<b>Dosing Regimen:</b>	6 mg once per chemotherapy cycle		
<b>Route of Administration:</b>	Subcutaneous		
<b>Indication:</b>	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		
<b>OCP Division:</b>	DCPV	<b>OND Division:</b>	DHP
<b>OCP Reviewer:</b>	Vicky Hsu, Ph.D.		
<b>OCP Team Leader:</b>	Sarah Schrieber, Pharm.D.		
<b>PM Reviewer:</b>	N/A		
<b>PM Team Leader:</b>	N/A		
<b>PBPK Reviewer:</b>	N/A		
<b>PBPK Team Leader:</b>	N/A		
<b>GG Reviewer:</b>	N/A		
<b>GG Team Leader:</b>	N/A		
<b>Priority Classification:</b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Expedited	<b>PDUFA Due Date</b>	10/27/14
<b>OCP Review Due Date:</b>	09/26/14	<b>OND Division Due Date:</b>	10/13/14

### Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	<input checked="" type="checkbox"/>		
Tabular Listing of All Human Studies	<input checked="" type="checkbox"/>		
Human PK & BP Summary	<input checked="" type="checkbox"/>		
Labeling	<input checked="" type="checkbox"/>		
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/>	1	161-131 Clinical Study Report (supportive data for Study 20101153)
<b>I. Clinical Pharmacology</b>			
Mass balance:	<input type="checkbox"/>		
Isozyme characterization:	<input type="checkbox"/>		
Blood/plasma ratio:	<input type="checkbox"/>		
Plasma protein binding:	<input type="checkbox"/>		
Pharmacokinetics (e.g., Phase I) - <i>Healthy Volunteers:</i>	<input type="checkbox"/>		
single dose:	<input type="checkbox"/>		
multiple dose:	<input type="checkbox"/>		
<i>Patients:</i>			
single dose:	<input type="checkbox"/>		
multiple dose:	<input type="checkbox"/>		

<b>Dose proportionality -</b>			
fasting / non-fasting single dose:	<input type="checkbox"/>		
fasting / non-fasting multiple dose:	<input type="checkbox"/>		
<b>Drug-drug interaction studies -</b>			
In-vivo effects on primary drug:	<input type="checkbox"/>		
In-vivo effects of primary drug:	<input type="checkbox"/>		
In-silico effects on primary drug:	<input type="checkbox"/>		
In-silico effects of primary drug:	<input type="checkbox"/>		
Concomitant therapy:	<input type="checkbox"/>		
In-vitro:	<input type="checkbox"/>		
<b>Subpopulation studies -</b>			
ethnicity:	<input type="checkbox"/>		
gender:	<input type="checkbox"/>		
pediatrics:	<input type="checkbox"/>		
geriatrics:	<input type="checkbox"/>		
renal impairment:	<input type="checkbox"/>		
hepatic impairment:	<input type="checkbox"/>		
<b>PD -</b>			
Phase 2:	<input type="checkbox"/>		
Phase 3:	<input type="checkbox"/>		
<b>PK/PD -</b>			
Phase 1/2, proof of concept:	<input type="checkbox"/>		
Phase 3 clinical trial:	<input type="checkbox"/>		
<b>Population Analyses -</b>			
Data rich:	<input type="checkbox"/>		
Data sparse:	<input type="checkbox"/>		
<b>QT evaluation:</b>	<input type="checkbox"/>		
<b>II. Biopharmaceutics</b>			
<b>Absolute bioavailability:</b>	<input type="checkbox"/>		
<b>Relative bioavailability -</b>			
solution as reference:	<input type="checkbox"/>		
alternate formulation as reference:	<input type="checkbox"/>		
<b>Bioequivalence studies -</b>			
traditional design:	<input checked="" type="checkbox"/>	1	Study 20101153
replicate design:	<input type="checkbox"/>		
<b>Food-drug interaction studies:</b>	<input type="checkbox"/>		
<b>Bio-waiver request based on BCS</b>	<input type="checkbox"/>		
<b>BCS class</b>	<input type="checkbox"/>		
<b>Alcohol induced dose-dumping</b>	<input type="checkbox"/>		
<b>III. Other CPB Studies</b>			
<b>Genotype/phenotype studies</b>	<input type="checkbox"/>		
<b>Immunogenicity Testing</b>	<input checked="" type="checkbox"/>	1	161-132 Clinical Study Report (supportive data for Study 20101153)
<b>Chronopharmacokinetics</b>	<input type="checkbox"/>		
<b>Pediatric development plan</b>	<input type="checkbox"/>		
<b>Literature References</b>	<input checked="" type="checkbox"/>		
<b>Total Number of Studies</b>		3	

On **initial** review of the NDA/BLA application for filing:

<b>Criteria for Refusal to File (RTF):</b> This OCP checklist applies to NDA, BLA submissions and their supplements					
<b>No</b>	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			PK comparability study (biologic drug)
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
<b>Complete Application</b>					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

**Is the Clinical Pharmacology Section of the Application Fileable?**

- Yes**  
 **No**

**If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant: N/A**

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. N/A**

**Signatures:**

---

Vicky Hsu, Ph.D.  
 Reviewer  
 Division of Clinical Pharmacology V

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Sarah J. Schrieber, Pharm.D.  
 Acting Team Leader  
 Division of Clinical Pharmacology V

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/s/  
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WENCHI HSU  
08/12/2014

SARAH J SCHRIEBER  
08/12/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125031Orig1s175**

**OTHER REVIEW(S)**

## Division of Hematology Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** BLA 125031/S-175

**Name of Drug:** Neulasta® (Pegfilgrastim) – 6mg/0.6mL solution in a single prefilled syringe co-packaged with the On-body Injector for Neulasta.

**Applicant:** Amgen

### Labeling Reviewed

**Submission Date:** June 27, 2014

**Receipt Date:** June 27, 2014

#### Background and Summary Description:

Neulasta was approved in January 2002 for the following 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.”

Amgen submitted a CMC Prior Approval labeling supplement on June 27, 2014. This submission contains a combination product comprising a pegfilgrastim prefilled syringe co-packaged with a drug delivery device.

#### Review

This review compares the labeling submitted on June 27, 2014 to the currently approved labeling dated May 25, 2012. This supplemental application proposes the following change(s): combination product comprising a pegfilgrastim prefilled syringe co-packaged with a drug delivery device designed to facilitate the administration of Neulasta® (pegfilgrastim) according to the approved dosing schedule and route of administration for which pegfilgrastim is currently approved. The applicant also proposes partial labeling for the device. This included an Instructions for Use (IFU) for the Health Care Provider.

Numerous editorial changes were made throughout the PI, PPI, IFUs and carton container labels, i.e. capitalization, active voice, formatting and layout etc.

**USPI:** Information on the dosage forms and strengths was updated to include information on latex allergies as well as recommendations for device placement (arm and abdomen) and appropriate monitoring of the device by a caregiver. Additional information on administration of the on-body injector and monitoring for correct dose delivery were provided. Information on monitoring for a missed dose as a result of device failure or leakage was included. Information

on allergies to acrylics was added under warnings and precautions. Information related to the Delivery Kit was added under how the drug is supplied, stored and should be handled. Patient counseling information was updated to reflect advice with regard to a range of safety considerations including prohibited activities, recommendations for caregivers, device storage, disposal and dose monitoring. The sponsor has included the team's proposed changes to the PI, which was reviewed by the team and deemed acceptable.

**PPI:** Patient Information was updated for the On-body Injector, to include advice regarding device placement, dose monitoring, and a range of safety considerations including prohibited activities, device storage and disposal. The sponsor has included the team's proposed changes to the PPI and ensured that advice is consistent across the PI, PPI, and IFUs. The final version of the PPI was reviewed by the team and deemed acceptable.

**Patient and HCP Instructions for Use (IFU)/ Reference Guide:**

The sponsor has included the team's proposed changes to the above mentioned documents. These include adding appropriate signage i.e. arrows to denote if the device is full or empty and audio and visual signals to help patients and providers monitor dose delivery and device status. Additionally, the sponsor accepted team recommendations regarding device orientation and placement as well as having a caregiver close by to assist the patient in monitoring dose delivery. In response to HF comments from DMEPA, the sponsor has amended the HCP IFU which instructs providers to insert the needle at a 90 degree angle to avoid bending the needle and spilling medicine. This adequately addresses the HF issue of task failures and close calls. DMEPA provided an HF addendum to their review dated December 22, 2014 which confirmed Amgen's response was acceptable. The final versions were reviewed by the team and deemed acceptable.

**Carton and Container Labels:**

The sponsor has complied with the edits proposed by the FDA review team with regard to font size, symbols and label placement, and has incorporated these into the labels as directed. The OBP product labeling reviewer completed a review of the carton/container labels and confirmed acceptance on December 18, 2014. The sponsor has included the team's proposed changes to the Carton Container Labels, which was reviewed by the team and deemed acceptable.

**Recommendations**

A final clean label was received from the sponsor via email on December 16, 2014. The final label has been reviewed by the RPM as well as the review team who have found the labeling changes acceptable. This supplement can be approved with the final clean labeling.

Rachel McMullen, MPH	12/16/14
Regulatory Project Manager	Date
Amy Baird/ Theresa Carioti	12/22/14
Chief, Project Management Staff	Date

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/s/  
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RACHEL S MCMULLEN  
12/22/2014

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**HUMAN FACTORS CONSULT REVIEW ADDENDUM**

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\*\*\***

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**Date of This Review:** 12/22/2014  
**Requesting Office or Division:** Division of Hematology Products (DHP)  
**Application Type and Number:** sBLA 125031-175  
**Product Name:** Neulasta (pefgilgrastim) prefilled syringe and on-body injector  
**Product Type:** Combination Product (Device-Biologic)  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Amgen  
**Submission Date:** 12/19/2014  
**OSE RCM #:** N/A  
**Human Factors Specialist:** QuynhNhu Nguyen, MS  
**Associate Division Director:** Lubna Merchant, MS, PharmD

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## **1 REASON FOR REVIEW**

The Division of Hematology Products requested DMEPA evaluate Amgen's response to an information request (IR) regarding the results of the human factors validation study for a combination product which consists of a prefilled syringe, an on-body injector (OBI) and Neulasta drug product.

## **2 MATERIALS REVIEWED**

We reviewed Amgen's response to the IR issued by FDA requesting additional information on the reported close calls that were identified in the human factors validation study report as well as the revisions made to the healthcare providers' Instructions for Use (IFU).

## **3 DISCUSSION**

On 12/19/2014, FDA issued an IR to Amgen requesting additional information on the reported close calls that were identified in the human factors validation study report. There were two trained healthcare providers (HCPs), who could not insert the prefilled syringe into the medication port. One HCP bent the needle, and the other HCP caused the drug to spill out of the port in the process. However, the human factors validation study did not provide sufficient subjective data from these HCPs as to why they experienced the difficulty while performing the steps and whether they have any recommendations to address the difficulty. Amgen was requested to provide additional analysis of these close calls, and depending on the root cause that the HCPs identified, and to implement additional mitigation to address these reported close calls. This concern was originally identified within the CDRH Human Factors review.

Amgen's response dated 12/19/2014 indicated that the reported close calls occurred when the HCP users experienced difficulty filling the on-body injector on the first attempt. These HCP users were able to recognize they made a mistake and subsequently, were able to successfully fill the on-body injector. Amgen reported that the root cause is lack of clarity of the instructions to emphasize the importance of correct angle of inserting the needle. As a result, the HCP Instructions for Use (IFU) was modified to emphasize the importance of inserting the needle at the correct angle to avoid bending the needle and spilling medication.

The following excerpt provides Amgen's proposed modifications (in blue text) made to step D on page 6 of the HCP IFU:

#### **4 CONCLUSION & RECOMMENDATIONS**

We found Amgen's response to the IR and additional revisions made to (b) (4) of the HCP IFU acceptable. We do not have any further concerns with regards to the human factors validation study report.

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/s/  
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LUBNA A MERCHANT  
12/22/2014

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

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

**Memorandum**

**Date:** October 16, 2014

**To:** Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products (DHP)

**From:** Adam George, PharmD. Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Davis, Acting Team II Leader, OPDP

**Subject:** Comments on draft labeling (Package Insert and Instructions for Use) for sBLA 125031/supplement 175 Neulasta (pegfilgrastim) injection, for subcutaneous use

In response to your consult dated July 22, 2014, we have reviewed the draft Package Insert and instructions for use for supplement 175 for Neulasta (pegfilgrastim) injection and offer the following comments. For this BLA, the instructions for use include the Neulasta (pegfilgrastim) Delivery Device Kit Healthcare Provider Instructions for Use and the Neulasta (pegfilgrastim) Delivery Device: Reference Guide. OPDP has made these comments based on review of the October 9, 2014 version of the substantially complete labeling and the September 23, 2014, version of the instructions for use. Please note that OPDP's comments pertaining to the (b) (4) (also known as patient prescribing information) will be communicated in the joint consult response with the patient labeling group.

Section	Statement from draft	Comment
Neulasta Delivery (b) (4) Healthcare Provider Instructions for Use, Step 2: Get Ready, section C	The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex	OPDP recommends including the statement from section 2.2 ADMINISTRATION of the PI that "persons with latex allergies should not administer this product". This information is important to communicate to healthcare providers with latex allergies that may attempt to administer Neulasta.
Neulasta Delivery (b) (4) Healthcare	Review each step in the patient instructions with your patient. Give your	This statement may be confusing to prescribers as the generic words "patient

Section	Statement from draft	Comment
<p>Provider Instructions for Use, Step 4: Finish, section A</p>	<p>patient the instructions, reference guide and (b) (4) to take home.</p>	<p>instructions” and “reference guide” do not adequately describe these documents. The statement should be revised to reflect the correct titles of the documents which are (b) (4) and (b) (4) (b) (4) Reference Guide.”</p>
<p>Neulasta Delivery (b) (4), Healthcare Provider Instructions for Use, Step 4: Finish, section A, bullet 4.</p>	<p>The patient should remain in a place where they can monitor the (b) (4) for the entire dose delivery.</p> <p>A similar statement is also made in section 17 PATIENT COUNSELING INFORMATION of the Neulasta prescribing information</p>	<p>This important information is not communicated in the (b) (4) (b) (4) or (b) (4) (b) (4) Reference Guide. OPDP recommends that this important information be communicated in either or both of these documents so that the patient is aware of this recommendation.</p>

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/s/  
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ADAM N GEORGE  
10/16/2014

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

**PATIENT LABELING REVIEW**

Date: October 16, 2014

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**  
Robert Kane, MD  
Deputy Director for Safety  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Adam George, PharmD.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): Neulasta (pegfilgrastim)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA125031/175

Applicant: Amgen, Inc.

## 1 INTRODUCTION

On June 27, 2014, Amgen, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) to their approved Biologics License Application (BLA) 125031/175 for Neulasta (pegfilgrastim) injection. In this supplement, the Applicant proposes the addition of a Neulasta Delivery Device Kit as an alternate way to administer Neulasta (pegfilgrastim) for patients who are not able to return for observed therapy. Neulasta (pegfigrastim) injection 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 a clinically significant incidence of febrile neutropenia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on July 22, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Neulasta (pegfilgrastim) for injection.

The Center for Devices and Radiologic Health will be providing a separate review of the Instructions for Use that is intended for patients, which was submitted by the Applicant and attached at the end of the proposed PPI.

## 2 MATERIAL REVIEWED

- Draft Neulasta (pegfilgrastim) injection PPI received by DMPP and OPDP on June 27, 2014.
- Draft Neulasta (pegfilgrastim) injection Prescribing Information (PI) received on June 27, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 7, 2014.
- Approved Neulasta (pegfilgrastim) injection patient labeling dated May 25, 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

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

#### **4 CONCLUSIONS**

The PPI is 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 is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.
- Please request that the Applicant update the PPI for the Neulasta prefilled syringe dosage form, where applicable, to be consistent with the revisions we have made to the PPI for the Neulasta Delivery Device.

Please let us know if you have any questions.

10 Pages of Draft Labeling have been Withheld in Full immediately following this page.

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/s/  
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SHARON R MILLS  
10/16/2014

ADAM N GEORGE  
10/16/2014

BARBARA A FULLER  
10/16/2014

LASHAWN M GRIFFITHS  
10/16/2014

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

## Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

**When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes.** For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

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## APPLICATION INFORMATION

PDUFA Action Date: **October 27, 2014**  
Applicant Name: **Amgen Inc.**  
U.S. License #: **# 1080**  
STN(s): **STN 125031/175**  
Product(s): **Neulasta® (pegfilgrastim)**  
Summary: **Request for approval of a new combination product presentation**

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## FACILITY INFORMATION

Firm Name: Amgen Inc.  
Address: Thousand Oaks, CA  
FEI: 2026154  
Short summary of manufacturing activities performed: release and stability testing for both drug substance and drug product

THIS SITE WAS INSPECTED BY LOS-DO FROM NOVEMBER 15 - DECEMBER 12, 2012 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTB PROFILE WAS UPDATED AND IS ACCEPTABLE.

Firm Name: Amgen Manufacturing, Limited  
Address: P.O. Box 4060, Road 31 km 24.6, Juncos, Puerto Rico  
FEI: 1000110364

Short summary of manufacturing activities performed: Drug substance manufacturing (fermentation, purification, PEGylation, bulk filtration, release testing, stability testing). Drug product manufacturing (formulation, sterile filtration, fill and finish, packaging/labeling, release testing, stability testing)

THIS SITE WAS INSPECTED BY SJN-DO FROM 7/24/2013 - 8/15/2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE AND PRODUCT MANUFACTURING OPERATIONS. THE BTP AND TRP PROFILES WERE UPDATED AND ARE ACCEPTABLE.



Firm Name: Insulet Corporation  
Address: Oak Park Drive, Bedford, MA 01730  
FEI: 3004464228

Short summary of manufacturing activities performed: Device design and manufacture

THIS SITE WAS INSPECTED BY NWE-DO FROM 9/4/2013 - 9/19/2013 AND CLASSIFIED VAI. THIS WAS CLASS II MEDICAL DEVICE MANUFACTURING INSPECTION. THE DKA PROFILE WAS UPDATED AND IS ACCEPTABLE.





OVERALL RECOMMENDATION

THERE ARE NO PENDING OR ONGOING COMPLIANCE ACTIONS THAT PREVENT APPROVAL OF THIS SUPPLEMENT.

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/s/  
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CHRISTINA A CAPACCI-DANIEL  
10/15/2014



Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**CDRH Human Factors Review**

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

DATE: October 2, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID  
TO: Pat Dinndorf, Medical Officer, CDER/OND/OHOP/DHP  
Rachel McMullen, Regulatory Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: **sBLA 125031 - 175**  
Applicant: Amgen  
Device Constituent: prefilled syringe  
Drug Constituent: neulasta (pefgilgrastim)  
Intended Treatment: to decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer  
CDRH CTS Tracking No. 1400465

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Digitally signed by Quynhnhu T. Nguyen -S  
Date: 2014.10.03 14:50:14 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist  
(Human Factors Premarket Evaluation Team - HFPMET)



Digitally signed by Richard C.  
Chapman -S  
Date: 2014.10.03 15:21:39 -04'00'

for

Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

## CDRH Human Factors Review

### *Overview and Recommendation*

The Office of Hematology and Oncology Products, Office of New Drugs, Center for Drug Evaluation and Research, requested CRH Human Factors Premarket Evaluation Team (HFPMET) consultative review of the human factors validation study report included in the sBLA 125031 (available in global submit, SDN: 1003; eCTD Sequence Number: 0186, submission dated June 27, 2014).

This study included 93 participants from three user groups, 1) Health Care Professionals (HCPs) (n=32) 2) Patients (n=31) and 3) Caregivers (n=30). As in formative study testing, each group consisted of both moderator-trained and self-trained participants. Of the 93 participants, 46 participants were trained by the moderators on the Instructions for Use (IFU), while 47 participants were assigned to read through the IFU on their own as training.

The study results showed the following notable task failures and close calls:

- 1 trained HCP failed to pull off both adhesive liners completely in moderator-trained session 1, and stated that the IFU illustration which shows only one piece of adhesive removed.
- 1 untrained HCP and 2 trained HCPs failed to secure the devices to the application site in less than 3 minutes and did not attempt to apply the device on the skin pad after 3 minutes. The untrained participants stated that they were either unsure of the correct orientation for device placement, did not fully understand when to place the device on the body, and had to wait for the green light before placing the device on patient.
- 1 untrained HCP failed to secure the device to the site within 3 minutes therefore the device was applied to the skin pad and after the cannula was deployed. This participant indicated that she was confused by the instructions.
- 1 trained caregiver prematurely removed the device after a minute into start of the nominal 45 minute delivery period and therefore the simulated patient did not get a full dose. The participant misinterpreted the rapidly flashing green light to indicate a dose delivery completion.
- 1 trained patient and 1 trained caregiver detected, but failed to interpret the device hazard alarm. Both participants were able to visually confirm the device's blinking red light with beeps. However, they did not perform the appropriate action by simulating calling the appropriate party per IFU due to their belief that the fill indicator was at empty.
- 2 close calls were observed with 2 trained HCP where they could not insert the prefilled syringe into the medication port. One participant bent the needle, and the other caused the drug to spill out of the port in the process. No specific objective follow-up obtained from participants on these close calls but they were able to start over with a new kit. In addition, 3 close calls were observed with 3 untrained HCPs when they were trying to fill the device. All three realized that they had to start over, and were able to complete the task successfully with the new kit.

Recommendation: The analysis of the task failures and the subjective data from study participants indicated that some task failures occurred because users were confused by the instructions for use, and the other task failures occurred because users misinterpreted the device indicators i.e. flashing green light and the device hazard alarms. In addition, there were some close calls that were directed at step of filling medication that will need to be performed that resulted in difficulty in inserting the prefilled syringe into the medication port and in the needle becoming bent, and difficulty in filling the medication in general. Review of the Instructions for Use indicated that they should be further optimized to address the report failures and closed calls. This human factors reviewer recommends that the follow deficiency be issued and addressed by the Sponsor:

1. Our analysis of the task failures and the subjective data from study participants indicated that some task failures occurred because users were confused by the instructions for use, and the other task failures occurred because users misinterpreted the device indicators i.e. flashing green light and the device hazard alarms. In addition, there were some close calls associated with filling medication step performed by HCP, which resulted in user experiencing difficulty in inserting the prefilled syringe into the medication port and in the needle becoming bent, and difficulty in filling the medication in general. Because some of these failures could result in medication leakage that could lead to underdosing, and some could result in delay in therapy when the users did not take appropriate action to address the device hazard alarm state, we believe that additional mitigations are necessary. Please address the following:
  - a. We believe that the Instructions for Use should be further optimized to address the reported task failures.
    - i. Please provide additional clarity on the adhesive removal step for the HCP IFU.
    - ii. Please provide additional clarify on the correct device orientation for placing the device on the skin, on when is the appropriate time to place the device on the skin, and the meaning of the flashing green light in the Patient IFU.
    - iii. Please provide additional information to user to take appropriate action if the cannula has been deployed prior to placing the device on the patient in the HCP IFU.
    - iv. Please emphasize the section in the Patient IFU to call out the user attention on the device hazard alarm (red flashing light), and to communicate to users that the device hazard alarm means that the device not properly functioning and that the patient may not get the dose, and that they need to take appropriate action to reduce further delay of treatment.
  - b. We need additional information on the reported close calls. You reported that these HCPs experienced difficulty in inserting the prefilled syringe into the medication port and in the needle becoming bent, and difficulty in filling the medication in general. While you stated that these situations resolved when a new kit was made available, you did not provide sufficient subjective data from these HCPs as to why they experienced the difficulty while performing the steps and whether they have any recommendations to address the difficulty. Please provide additional analysis of these close calls, and depending on the root cause that the HCPs identified, we ask that you implement additional mitigation to address these reported close calls.

## **CDRH Human Factors Review**

### **Combination Product Device Information**

**Submission No.:**sBLA 125031

Applicant: Amgen

Device Constituent: prefilled syringe

Drug Constituent: neulasta (pegfilgrastim)

Intended Treatment: to decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer

### **CDRH Human Factors Involvement History**

- 7/18/2014: CDRH HFPMET received a request to review human factors validation study report
- 10/2/2014: CDRH HFPMET provided review recommendation to CDER.

### **Summary of Human Factors Related Information**

The intended user of the device may be a patient, the patient's caregiver, or a health care provider (HCP). The Sponsor notes that pegfilgrastim patients may have impairments, including, but not limited to, issues with manual dexterity due to age or their condition, arthritis, short-term memory issues, hearing impairment, visual impairment including color blindness; and may require the aid of a caregiver to assist in the confirmation of dose delivery and removal of the device.

Patients will wear the device for approximately 27 hours prior to the start of dose delivery, monitor the device for proper function and potential visual and audio notifications, and confirm that their dose has been delivered prior to removing the device from their body. Since the patient will wear the device for approximately 27 hours prior to start of dose delivery, and through the dose delivery cycle, it is anticipated that patients will conduct basic, daily activities, including routine showering for up to 30 minutes.

This study included 93 participants from three user groups, 1) Health Care Professionals (HCPs) (n=32) 2) Patients (n=31) and 3) Caregivers (n=30). As in formative study testing, each group consisted of both moderator-trained and self-trained participants. Of the 93 participants, 46 participants were trained by the moderators on the Instructions for Use (IFU), while 47 participants were assigned to read through the IFU on their own as training.

The following table shows the breakdown of the tasks and which user group is expected to perform the tasks.

Table 1. Essential and Critical Tasks

Task	Potential Cause(s) of Hazard(s) <i>Potential Consequence</i>	User(s)	Essential/ Critical	Summative Validation Study Technique	Success Criteria
Remove device and PFS from package	HCP drops components (PFS or device) and uses the combination product <i>Potential Consequence: Infection</i>	HCP	Essential	Participants will be observed if they remove the device and PFS from packaging.	Participant must be able to remove the device and PFS from packaging.
Identify application site	HCP places device on location other than subcutaneous site <i>Potential Consequence: Missed Dose</i>	HCP	Essential	Participants will be asked to state the preferred injection sites before they proceed to attach device to the patient's body.	Must respond "subcutaneous site" when asked by moderator.
Identify medicine port	HCP can't identify the medicine port <i>Potential Consequence: Customer Annoyance</i>	HCP	Essential	Participants will be observed if they correctly identify the medicine port.	Must correctly identify the medicine port
Task	Potential Cause(s) of Hazard(s) <i>Potential Consequence</i>	User(s)	Essential/ Critical	Summative Validation Study Technique	Success Criteria
Empty PFS into device medicine port	HCP doesn't fully empty the contents of PFS <i>Potential Consequence: Missed Dose</i>	HCP	Essential	Participants will be observed for their ability to successfully pierce the medicine port and fully depress PFS plunger and empty entire contents of the PFS into device	Must be able to do the following: Must pierce device medicine port with PFS Must fully empty the syringe into the device reservoir. Must remove the PFS from Device medicine port.
Remove device needle cover	HCP inserts needle too far (remove device needle cover prior to filling) <i>Potential Consequence: Missed Dose</i> HCP removes the device needle cover and attempts to replace prior to filling <i>Potential Consequence: Infection</i>	HCP	Essential	Participants will be observed regarding their ability to remove the device needle cover	Must completely remove the needle cover after filling the device
Remove adhesive liner	HCP folds adhesive over needle site while removing adhesive backing HCP removes only half of adhesive backing <i>Potential Consequence: Missed Dose</i>	HCP	Essential	Participants will be observed regarding their ability to completely remove both adhesive liners.	Must pull off both adhesive liners completely
Apply to application site	HCP fails to secure adhesive to skin HCP folds adhesive over while placing device on Patient. <i>Potential Consequence: Missed Dose</i>	HCP	Essential	Participants will be observed regarding their ability to apply device to application site in less than 3 minutes.	Must secure device backing to the application site in less than 3 minutes.
Allow device to remain on skin until delivery complete	Patient misinterprets dose delivery notification as dose completion notification (beeps) Patient unintentionally dislodges device during use Patient manipulates adhesive Patient attempts to put device back on after device is removed prior to complete delivery <i>Potential Consequence: Missed Dose</i>	Patient/ Caregiver	Essential	Participants will be observed regarding when they remove the device.	Must not remove device until dose delivery is complete, or if device is removed prematurely, must contact the appropriate party per IFU.
Respond appropriately to device hazard alarm states	Patient doesn't hear alarm due to excessive background noise Patient doesn't hear alarm due to clothing covering device Patient doesn't understand alarm due to complicated alarm Patient doesn't understand alarm due to complicated instructions Patient doesn't hear alarm due to patient's physical hearing limitation HCP places device in location where visual alarms cannot be seen <i>Potential Consequence: Missed Dose</i>	Patient/ Caregiver	Critical	Participants will be given a device pre-conditioned to produce error condition (beeps and light blinks red).	Must identify that an error has occurred prior to device disposal and state the next action would be to contact the appropriate party per IFU.

In practice, HCP users are expected to receive training. Patients and caregivers are expected to receive training from their HCPs. However, in some cases, neither the Hep nor the patient or caregiver may receive training. Therefore, participants will be divided into two sub-groups; trained, and self-trained. To assess learning decay, trained HCPs will perform device preparation and application tasks in a first trial and will return 3 days later in a second trial to repeat these same tasks. The following table provides a summary of the study results:

#	Task	Success Criteria	Pass Results
1	Remove device and PFS from package (Essential)	Participant must be able to remove the device and PFS from packaging.	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
2	Identify application site (Essential)	Must respond subQ when asked which device placement site they prefer (note: participants what the acceptable device placement locations were).	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
3	Identify medicine port (Essential)	Must correctly identify the medicine port	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
4	Empty PFS into device medicine port (Essential)	Must be able to do the following:	
		Must pierce device medicine port with PFS	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
		Must empty the syringe into the device reservoir	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
		Must remove the PFS from device medicine port	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
5	Remove device needle cover (Essential)	Must completely remove the needle cover after filling the device	47/47, 100% of HCPs (16/16 moderator-trained session 1, 15/15 moderator-trained session 2, 16/16 self-trained)
6	Remove adhesive liner (Essential)	Must pull off both adhesive liners completely	46/47, 97.9% of HCPs [P3] (15/16 moderator-trained session 1, 15/15 moderator-
			trained session 2, 16/16 self-trained)
7	Apply device to application site (Essential)	Must secure device backing to the application site in less than 3 minutes	43/47, 91.5% of HCPs [P43, P57, P75, P27] (14/16 moderator-trained session 1, 15/15 moderator-trained session 2, 14/16 self-trained)
8	Allow device to remain on skin until delivery complete (Essential)	Must not remove device until dose delivery is completed or if device is removed prematurely to contact the appropriate party per IFU	28/31, 90.3% of Patients/Caregivers [P12, P45, P34] (12/15 moderator-trained, 16/16 self-trained)
9	Respond appropriately to device hazard alarm state (Critical)	Must identify that an error has occurred prior to device disposal and state the next action would be to contact the appropriate party per IFU	28/30, 93.3% of Patients/Caregivers [P10, P48] (13/15 moderator-trained, 15/15 self-trained)

## Summary Discussion of the Task Failures and Close Calls:

### Remove Adhesive Liner: HCP Removes Only Half of Adhesive Backing

- 1 trained HCP failed to pull off both adhesive liners completely in moderator-trained session 1. This participant stated that he followed the IFU illustration which shows only one piece of adhesive removed. Amgen reaffirmed that if the HCP places the device on patient with only 1 adhesive liner, leakage may occur alerting the patient to call the HCP and return for a redose. In the summative validation study, 30/30 trained patients and caregivers and 30/31 untrained reported that they would call the HCP if a leak were detected.

### Apply to Application Site: HCP Fails to Place Device on Patient

- 1 untrained HCP and 2 trained HCPs failed to secure the devices to the application site in less than 3 minutes and did not attempt to apply the device on the skin pad after 3 minutes. The untrained participant stated that he was unsure of the correct orientation for device placement. Of the trained participants, one stated that she did not fully understand when she was supposed to place the device on the body, and the other thought he had to wait for the green light before placing the device on patient. Both of these participants were able to perform the task correctly on the second trial.

### Apply to Application Site: HCP Places Device on Patient After Cannula Deployment

- 1 untrained HCP failed to secure the device to the site within 3 minutes therefore the device was applied to the skin pad and after the cannula was deployed. This participant indicated that she was confused by the instructions. Amgen reaffirmed that if the HCP places the device on patient after the cannula is deployed, leakage will occur alerting the patient to call the HCP and return for a redose. In the summative validation study, 30/30 trained patients and caregivers and 30/31 untrained reported that they would call the HCP if a leak were detected.

### Removal of NDD device After Successful Delivery: Patient Misinterprets Device Indicators (Complete Dose)

- 1 trained caregiver and 1 trained patient removed the device prior to notification of a complete delivery via a beep and solid green light. Both removed the device because the fill indicator was at empty position and thereby believing the delivery was complete. These were considered to be study artifact. Amgen reaffirmed that the instructions clearly point out that dose delivery will take approximately 45 minutes; if a patient removes the device after the approximately 45 minutes and the fill indicator is at the 'empty' position, then the entire prescribed dose would have been dispensed.

### Removal of NDD device After Successful Delivery: Patient Misinterprets Device Indicators (Incomplete Dose)

- 1 trained caregiver also removed the device prior to dose delivery completion and therefore the simulated patient did not get a full dose. The caregiver prematurely removed the device after a minute into start of the nominal 45 minute delivery period. The participant misinterpreted the rapidly flashing green light to indicate a dose delivery completion.

#### Device Hazard Alarm State and Response: Patient Misinterprets Device Indications

- 1 trained patient and 1 trained caregiver detected, but failed to interpret the device hazard alarm. Both participants were able to visually confirm the device's blinking red light with beeps. However, they did not perform the appropriate action by simulating calling the appropriate party per IFU due to their belief that the fill indicator was at empty.

#### Close calls

- 2 close calls were observed with 2 trained HCP where they could not insert the prefilled syringe into the medication port. One participant bent the needle, and the other caused the drug to spill out of the port in the process. No specific objective follow-up obtained from participants on these close calls but they were able to start over with a new kit.
- 3 close calls were observed with 3 untrained HCPs when they were trying to fill the device. All three realized that they had to start over, and were able to complete the task successfully with the new kit.

## Appendix 1: Device Description Information

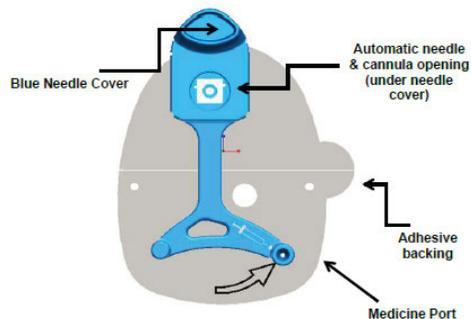
The device is a small, lightweight, disposable, battery-powered, sterile, non-pyrogenic, single-use, waterproof, electromechanical device that is applied directly to the patient's skin using a self-adhesive backing and is intended for delivery of pegfilgrastim. The device is intended to deliver a single dose of Neulasta contained in the co-packaged prefilled syringe (PFS) described. Drug product is loaded from the sterile PFS through the medicine port into a reservoir inside the device by the healthcare practitioner (HCP). The device is activated upon filling with drug product and the HCP immediately applies the filled activated device to the patient using the self-adhesive backing. Three minutes after device activation, a rigid needle and soft cannula are automatically deployed and inserted into the patient's subcutaneous tissue. After the soft cannula is inserted, the needle automatically retracts into the device. Twenty-seven hours after device activation, the device automatically delivers a 6 mg subcutaneous dose of pegfilgrastim to the patient, which takes approximately 45 minutes. The device is designed to provide both audio and visual signals to inform the HCP and patient of the status of the device from activation, needle and cannula insertion, 27-hour waiting period, drug delivery initiation, drug delivery completion, and deactivation. After confirmation of successful administration, the patient or caregiver will remove and dispose of the device. The NDD produces a visual and auditory alarm when the device malfunctions. The alarm consists of a flashing red light every 0.5 seconds and a beep every 0.25 seconds for 5 minutes. After 5 minutes, the beep ceases and the red light flashes once every second for at least the next 26 hours. Should the device produce an alarm, the patient and/or caregiver is expected to recognize this condition and report it to Amgen or to their HCP.

*Neulasta Delivery Device Description and Design Features*

Figure 1. Top View



Figure 2. Bottom View and Syringe Image on Needle Cover Indicating Medicine Port Location





Proposed Instructions for Use for Patients:



draft-label-text-uspp  
i-ifu.doc

Proposed Instructions for Use for Healthcare Providers:



draft-label-text-hcp-i  
fu.doc

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RACHEL S MCMULLEN

10/07/2014

Signing on behalf of CDRH reviewer Quynh Nhu Nguyen.

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**HUMAN FACTORS, 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\*\*\***

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**Date of This Review:** September 26, 2014

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

**Application Type and Number:** BLA 125031 / S-0175

**Product Name and Strength:** Neulasta (pegfilgrastim) Delivery Device Kit for Injection,  
6 mg / 0.64 mL

**Product Type:** Combination Product (Drug-Device)

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Amgen

**Submission Date:** June 27, 2014

**OSE RCM #:** 2014-1474

**DMEPA Primary Reviewer:** Neil Vora, PharmD, MBA

**DMEPA Team Leader:** Yelena Maslov, PharmD

**DMEPA Associate Director:** Lubna Merchant, PharmD, M.S.

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## 1 REASON FOR REVIEW

This review evaluates the results of the Human Factors Study (HFS), container label and carton labeling, Instructions for Use (IFU), and Prescribing Information (PI) for Neulasta Delivery Device (pegfilgrastim) for injection, 6 mg / 0.64 mL, BLA 125031/S-0175, submitted on June 27, 2014 for areas of vulnerability that could lead to medication errors. Neulasta is currently marketed as a prefilled syringe for subcutaneous administration. Amgen is proposing the use of a delivery device which would be placed on the patient's skin for 27 hours for the administration of Neulasta.

## 2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Overall, human factors study results demonstrated that the product can be used safely and effectively by patients, caregivers, and healthcare professionals (HCP) who receive formal training and/or have training materials (Instructions for Use) available for review. Although some errors have occurred that would lead to potential underdose and dose omission, the risk is acceptable because this error would be identified during monitoring of the patient's nadir within 7 to 10 days. Additionally, once learning regarding the use of the product occurs (i.e., after the initial use), the errors related to the incorrect placement or misinterpretation of the signals on the device should significantly decrease in occurrence.

With regard to the results of the Human Factors Study, a total of 10 users made errors during the study as follows:

1. One moderator-trained HCP failed to pull off both adhesive liners completely.
2. Two self-trained HCP, and two moderator-trained HCP failed to secure the devices to the application site in less than 3 minutes and did not attempt to apply the device on the skin pad after 3 minutes.
4. One moderator-trained caregiver and one moderator-trained patient removed the device prior to notification of a complete delivery via a beep and solid green light. Both participants removed the device because the fill indicator was at the empty position, indicating dose delivery had been completed. .
5. One moderator-trained caregiver removed the device prior to dose delivery completion (one minute after into the start of the 45 minute delivery period) after misinterpreting the rapidly flashing green light.
6. One moderator-trained patient and one moderator-trained caregiver detected but failed to interpret the device hazard alarm correctly.

#### **Types of Errors and from the HF study and their Analysis:**

1. *Inability to secure the device on a patient causing a potential underdose or dose omission:*
  - a. Placing the device on the patient with only one adhesive liner or failing to secure a device may cause leakage of the drug to occur, potentially causing underdose or dose omission. Although the majority of users (caregivers, patients, and HCP) were able to identify this error and re-dose though apparent leakage, formative studies showed that 3 participants were not able to detect a leak from the device. Although this error occurred, nadir monitoring within 7 to 10 days would identify this error. Furthermore, the proposed HCP Instructions for Use currently appear to be misleading by stating in step 3-B, (b) (4)  
However, only one piece of adhesive is shown on the Figure. Thus, revising this step will also provide clarity. Additionally, we recommend adding text regarding removal of the white adhesive backing on the backing itself to further mitigate this error.
2. *Removal of device after successful delivery, but before the final notification that medication was delivered:*
  - a. This error would not result in patient harm as entire dose should have been delivered. Thus, this risk is acceptable. The Applicant states that a possible reason for this error is the fact that the device was over-filled with air instead of actual drug to avoid drug spillage onto a participant. This caused the simulated delivery to be approximately 52 minutes, which is longer than

the expected time period of 45 minutes as mentioned in the training and IFU. The participants used this information to decide when to remove the device instead of the actual designed cues indicating end of delivery. However, based on the evaluation of the IFU for HCPs, it appears that the statements regarding when the device will activate and how long it will deliver the product are buried in the text and can be made more prominent.

3. *Removal of device prior to complete product delivery:*

- a. The participant prematurely removed the device after a minute into start of the 45 minute delivery period because they misinterpreted the rapidly flashing green light to indicate a dose delivery completion. Removing the device prior to dose delivery would result in a missed dose for the patient, which could lower the patient's neutrophil count and exposing the patient to acquire infections. Despite the risks associated with the patient not receiving their full dose, this risk is acceptable since the patient would either immediately notice the device leaking or nadir monitoring would occur within 7 to 10 days that will also identify this error. However, we recognize that potential contributing factor to this error is a light and beeps ambiguity with all possible interpretations what each light and beep means. Thus, if possible, Amgen should consider implementation of voice commands in addition to beeps.

4. *Misinterpretation of the device hazard alarm.*

- a. The two participants detected but failed to interpret the device hazard alarm. Both participants were able to visually confirm the device's blinking red light with beeps. However, they did not perform the appropriate action by simulating calling the appropriate party per IFU due to their belief that the fill indicator was at empty. This error could potential lead to underdose or missed dose and possible infections. However, this risk is acceptable due to frequent monitoring of nadir at 7 to 10 days after chemotherapy cycle. Again, as mentioned previously, the contributing factors for this error could be ambiguity in regards to multiple lights and beeps with all possible interpretations what each light and beep means. Thus, if possible, Amgen should consider implementation of the voice commands in addition to beeps.

Although the Applicant did not test it during Human Factors study, we also considered whether it is acceptable that the device will be on the patient for 27 hours prior to start of the dose delivery. This appears reasonable as Neulasta should not be administered less than 24 hours post-chemotherapy per cycle. Thus, it appears appropriate that the patient could be fitted with the device right after chemotherapy and receives medication 27 hours after without running a risk of administration prior to 24 hour period after chemotherapy.

In addition to the Human Factors Study evaluation, DMEPA evaluated the medication errors cases that occurred with the currently marketed Neulasta Prefilled Syringe. Following exclusions, DMEPA identified seven medication error cases associated with the incorrect route of administration (See Appendix B for additional details). Given that wrong route of administration error occurred with the prefilled syringe, addition of this device may help with mitigating this type of error by ensuring that the product is delivered via correct route provided it is placed on the correct body application site.

In addition, DMEPA reviewed the proposed patient and healthcare providers IFU, labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted that the proposed Neulasta Drug Delivery Device secondary label, healthcare provider instructions for use and patient instructions for use can be improved to avoid confusion for the end user. We provide recommendations in Section 4.

#### **4 CONCLUSION & RECOMMENDATIONS**

Overall, human factors study results demonstrated that the product can be used safely and effectively by patients, caregivers, and healthcare professionals (HCP) receive formal training and/or have training materials (Instructions for Use) available for review .

Additionally, the proposed labels and labeling can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information. Please refer to section 4.1 for our recommendations.

Furthermore, we defer to the Office of Biotechnology Products to provide recommendations regarding the strength of the product and the amount of overfill.

##### **4.1 RECOMMENDATIONS FOR THE DIVISION**

Recommend providing Monitoring of nadir in Section 2, Dosing and Administration.

##### **4.2 RECOMMENDATIONS FOR AMGEN**

Based on this review, DMEPA recommends the following be implemented prior to approval:

###### **A. Drug Device Adhesive Liner**

1. Currently there are two unmarked adhesive pull tabs on the device for placement of the device on the patient's skin. In order to safely secure the device on to the patient, both pull tabs must be removed prior to application. We recommend placing "peel this" or similar statement on the adhesive liner backing paper which will prompt users to remove two pieces of white adhesive backing instead of one. We provide this recommendation based on the Human Factors (HF) study results where one HCP

participant failed to remove both adhesives which resulted in insecure placement of the device and subsequently leaking. This error can result in an underdose or missed dose.

#### B. Drug Delivery Device

1. Consider implementing voice commands in the device (i.e. “injection starting,” and “injection complete”) to clarify any ambiguity that may occur when the device flashes and beeps. We provide this recommendation based on the Human Factors (HF) study results where one caregiver misinterpreted the rapidly flashing green light and removed the device prior to dose delivery completion. This error would result in the patient not receiving the full dose, thus resulting in an underdose or missed dose of the product.

#### C. Healthcare Provider Instructions For Use

1. Please bold the following bullets in Step 4:

After approximately 27 hours, beeps will signal that the dose delivery will begin in 2 minutes.

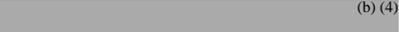
When the dose delivery starts it will take about 45 minutes to complete. During this time, the device will flash a fast green light.

We recommend this to draw attention to exactly when the device will start the injection and the time to inject the required dose. In addition, this recommendation is provided to ensure proper knowledge of device usage is understood by the healthcare provider to help them educate their patients.

#### D. Patient Instructions For Use

1. We recommend revising the format on page 4 titled, (b) (4) (b) (4) to have the statement “Green flashing status light” above the first picture of the device and to move the statement “Red flashing status light” above the second picture of the device to avoid potential confusion. We provide this recommendation to allow the patient to clearly read and understand what the green and red flashing lights translate to, and to minimize any ambiguity in these instructions.
2. In Step 2, we recommend bolding the statement “If the adhesive becomes noticeably saturated with fluid, or you see dripping, call your healthcare provider immediately” to increase the prominence and allowing the patient to clearly understand the actions needed to be taken if the adhesive becomes saturated with fluid. This recommendation is provided to prevent dose omissions or underdoses in the event this situation may occur.

#### E. Drug Delivery Device label

1. Revise the Device label to state  (b) (4) The way the label is currently presented, can be misinterpreted that the product is  (b) (4). Thus, wrong technique errors and dosing errors can occur. We recommend the revision of the statement as follows:



2. We recommend orienting the statement for the Delivery Device horizontally for optimal readability  (b) (4).

#### F. Drug Delivery Device Secondary Label

1. See recommendation in E.1 and revise the label accordingly.
2. Currently on the drug delivery device secondary label, there are 7 icons placed on the label to communicate information regarding the device. The icons are not readily understood, thus not communicating the intent. In addition, the use of the icons occupies space making the writing under the icons less prominent and difficult to read. Thus, remove all the picture icons and increase the prominence of the text by increasing the font size.

If you have further questions or need clarification, please contact Sarah Harris, OSE Project Manager, at 240-402-4774.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Neulasta that Amgen submitted on July 22, 2014.

Table 2. Relevant Product Information for Neulasta	
Initial Approval Date	January 31, 2002
Active Ingredient	Pegfilgrastim
Indication	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
Route of Administration	Subcutaneous Injection
Dosage Form	Delivery device and prefilled syringe
Strength	6 mg / 0.64 mL
Dose and Frequency	6 mg once per chemotherapy cycle. Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.
How Supplied	<b>Proposed:</b>  The kit is supplied with a prefilled single use syringe containing 0.64 mL with 0.6 mL of deliverable pegfilgrastim, used with the (b) (4) and supplied with a 27-gauge, 1/2-inch needle with an UltraSafe <sup>®</sup> Needle Guard.  The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).  The Neulasta Delivery (b) (4) kit is provided in a carton containing one sterile 0.64 mL prefilled syringe and one sterile (b) (4) (NDC 55513-192-01).
Storage	Store the kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until ready for use. Because the device is at room temperature during the period of use, the kit should not be held at room temperature longer than 12 hours prior to use. Discard the kit if stored at room temperature for more than 12 hours.

## APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### B.1 Methods

DMEPA previously performed a search of the FDA Adverse Event Reporting System (FAERS), reported in OSE Review #2010-1804 (dated October 18, 2010) to determine medication errors related to the use of this product.<sup>1</sup> Therefore, for this review, we searched the FDA Adverse Event Reporting System (FAERS) on August 13, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>2</sup>

Table 3: FAERS Search Strategy	
Date Range	November 1, 2010 to August 13, 2014
Product	Pegfilgrastim [active ingredient] Neulasta [product name]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]
Country	USA [Country]

### B.2 Results

Our search from November 1, 2010 to August 13, 2014 identified 44 cases, of which 7 describe errors for this review.

We excluded 37 cases because they described adverse drug reaction not related to medication error (n = 13), dose omission (n = 6), drug being administered to the wrong patient (n = 6) and patients accidentally overdosing (n = 12).

#### Wrong Route of Administration (n = 7)

Seven cases described that either caregivers or patients mistakenly administered Neulasta Prefilled Syringe using an incorrect route of administration. 3 of the seven cases reported

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<sup>1</sup> Abate, R. Medication Error Review for Neulasta (pegfilgrastim) Injection (BLA 125031). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 October 18. 5 p. OSE RCM No.: 2010-1804.

<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

administration via intravenous route, 2 reported administration via intramuscular route, 1 of the seven cases reported administration via intradermal route and 1 case did not specify the route of administration, only stating it was incorrect. 1 case reported that patient outcome was hospitalization and 6 cases did not report patient outcome. None of the cases reported to this error.

### B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case Number	Version	Manufacturer Control Number
10136263	1	US-AMGEN-USASP2014029976
8435610	2	US-AMGEN-USASP2012012561
9256079	1	US-AMGEN-USASP2012022135
9256087	1	US-AMGEN-USASP2012023927
9256118	1	US-AMGEN-USASP2012049496
9256194	1	US-AMGEN-USASP2012067109
9256250	1	US-AMGEN-USASP2012082836

### B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

## APPENDIX C. PREVIOUS DMEPA REVIEWS

### C.1 Methods

We searched the L:Drive on August 13, 2014 using the terms, Neulasta to identify reviews previously performed by DMEPA.

### C.2 Results

Our search identified one previous reviews<sup>3</sup>, and we confirmed that our previous recommendations were implemented were considered.

- OSE Review #2010-1804 Neulasta Medication Error Review

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<sup>3</sup> Abate, R. Medication Error Review for Neulasta (pegfilgrastim) Injection (BLA 125031). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 October 18. 5 p. OSE RCM No.: 2010-1804.

- **APPENDIX D. HUMAN FACTORS STUDY**

**D.1 Study Design**

The Human Factors Study Results and IFU submitted on July 22, 2014 were evaluated. Below is a brief overview of the study objectives, description of the study participations, study design, data collection, and data analysis.

**Study Objective:**

The primary objective of the study was to assess that the Neulasta Delivery Device System can be safely and effectively operated by participants who are representative of the intended user groups (i.e. oncology nurses, patients with cancer, caregivers) under simulated dose administration conditions to identify any potential use errors/task failures that could lead to user harm.

**Study Participants:**

Ninety-three (93) participants were enrolled in the study. Table 4 provides a description of the user groups and Table 5 provides a summary of the participants' demographic information.

**Table 4: User Groups**

User Groups	Moderator-Trained		Self-Trained		Total
HCPs	16		16		32
	No Alarm	Alarm	No Alarm	Alarm	
Caregivers	8	7	8	7	30
Patients	7	8	8	8	31
Sub-Total	15	15	16	15	
Total	46		47		93

**Table 5: Overall Demographics**

Factor	Criteria Applied	Participant Demographic Summary
<b>Factors Applicable to Patient Participants (N=31)</b>		
Gender	Mix, if available	Male – 5/31 (16.1%) Female – 26/31 (83.9%)
Age	Mix desired, including ranges 21-75	Avg. Age 55 (range 26-66)
Cancer Type	Recruited for the following cancers: - Breast - Lung - Non-Hodgkin's Lymphoma (NHL)	Breast – 26/31 (83.9%) Lung – 3/31 (9.7%) NHL – 2/31 (6.4%)
Education Level	A mix of levels of education was desired	High School Grad: 1/31 (3.2%) Some College: 14/31 (45.1%) College Grad: 14/31 (45.1%) Graduate School: 2/31 (6.6%)
<b>Factors Applicable to Caregiver Participant (N=30)</b>		
Gender	Mix, if available. Caregivers skews female	Female: 21/30 (70%) Male: 9/31 (30%)
Age	Mix desired, including ranges 21-75	Avg. Age 43.1 (range 27-59)
Education Level	A mix of levels of education was desired	High School Grad: 3/30 (10%) Some College: 9/30 (30%) College Grad: 15/30 (50%) Graduate School: 3/30 (10%)
<b>Factors Applicable to HCP Participant (N=32)</b>		
Gender	Mix, if available. Nurses skew female.	Female: 23/32 (75%) Male: 8/32 (25%)
Age	Mix desired, including ranges 21-75	Avg. Age 41 (range 25-68)
Oncology Nursing Society (ONS) certification	Half of the HCP participants should currently hold ONS certification.	Yes – 17/32 (53.1%) No – 15/32 (46.9%)
Education Level	A mix of levels of education was desired	Associates Degree: 8/32 (25%) College Grad: 24/32 (75%)

### **Training and Test Sessions:**

As in formative study testing, each group (patients, caregivers, healthcare providers) consisted of both moderator-trained and self-trained participants. Of the 93 participants, 46 participants were trained by the moderators on the Instructions for Use (IFU), while 47 participants were assigned to read through the IFU on their own as training. Training included information regarding drug storage, preparation and device placement requirements, device operation, monitoring the device, dose administration, confirmation of dose completion, and device disposal. Participants in all groups performed their assigned use scenarios as appropriate. In addition, two situations of use were included:

- ***Training Scenarios: Moderator-Trained vs. Self-Trained:***

Because of the potential that some users, including all user groups, may not receive prior device familiarization or training, the simulated use study consisted of two arms: Moderator-Trained and Self-Trained.

- ***Alarm Resolution Scenarios***

In addition, the patient and caregiver groups were further divided into those encountering scenarios with forced alarm conditions to detect and resolve (Error Path requiring alarm resolution) vs. event-free scenarios with no errors or alarm conditions to detect or resolve (No Error Path, no alarms encountered).

This additional study breakdown resulted in the following assignment of participants to conditions for their use scenarios as shown in Table 4.

All components evaluated (e.g. devices, PFS, IFUs, labeling, packaging) were representative of the intended commercial product.

### **Data Collection and Analysis:**

During HFE testing, interaction between the users and the device, its accessories, and labeling was analyzed to understand user perception and assumptions; specifically how users handled packaging, labeling, and features on the device including visual and audible alarms and mechanisms for transferring the drug product from the prefilled syringe (PFS) to the device, and device disposal.

## D.2 Results

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
Remove device and PFS from package	Essential	Participant must be able to remove the device and PFS from packaging	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP drops components (PFS or Device) and uses the combination product	Infection	100% Success rate
Identify application site	Essential	Must respond subcutaneous site	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP places device on location other than a subcutaneous site	Missed Dose	100% Success rate
Identify medicine port	Essential	Must correctly identify the medicine port	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP can't identify the medicine port	Customer Annoyance	100% Success rate

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
Empty PFS into device medicine port	Essential	Must be able to do the following:	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP can't pierce device medicine port	Customer Annoyance	100% Success rate
		Must pierce device medicine port with PFS	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP does not fully empty the contents of the PFS	Missed Dose	100% Success rate
		Must fully empty the syringe into the device reservoir	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	N/A	None	100% Success rate
		Must remove the PFS from device medicine port	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)			

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
Remove Device Needle Cover	Essential	Must completely remove the needle cover after filling the device	47/47 HCPs (100% success) (16/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP removes the device needle cap and attempts to replace prior to filling	Infection	100% Success rate
Remove adhesive liner	Essential	Must pull off both adhesive liners completely	46/47 HCPs (97.8% success) (15/16 moderator-trained session 1 15/15 moderator-trained session 2 16/16 self-trained)	HCP removes only half of adhesive backing	Missed Dose	1 HCP Moderator-Trained Participant [P3] failed to pull off both adhesive liners completely in moderator-trained session 1.

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
Apply to application site	Essential	Must secure device backing to the application site in less than 3 minutes	43/47 HCPs (91.5% success) (14/16 moderator-trained session 1 15/15 moderator-trained session 2 14/16 self-trained)	HCP fails to place device on patient in 3 minutes and sticks themselves with device needle	Customer Annoyance	1 HCP Self-Trained Participant [P57] and 2 HCP Moderator-Trained Participants [P27] and [P75] failed to secure the devices to the application site in less than 3 minutes and did not attempt to apply the device on the skin pad after 3 minutes.

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
				HCP places device on patient after cannula deployment.	Missed Dose	1 HCP Self-Trained Participant [P43] failed to secure the device to the site within 3 minutes and therefore the device was applied to the skin pad <i>after</i> the cannula was deployed.

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
Allow device to remain on skin until delivery complete	Essential	Must not remove device until dose delivery is complete or if device is removed prematurely to contact the appropriate party per IFU.	28/31 (90.3%) patient and caregivers 12/15 moderator-trained 16/16 self-trained)	Patient or Caregiver misinterprets device indicators - (full dose)	No Medical Impact	1 Moderator-Trained Caregiver [P45] and 1 Moderator-Trained Patient [P12], removed the device prior to notification of a complete delivery via a beep and solid green light. Both removed the device because the fill indicator was at empty position and thereby believing the delivery was complete.

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
				Patient or Caregiver misinterprets device indicators - (incomplete dose)	Missed Dose	1 Moderator- Trained Caregiver [P34] also removed the device prior to dose delivery completion and therefore the simulated patient did not get a full dose. The caregiver prematurely removed the device after a minute into start of the nominal 45 minute delivery period. The participant misinterpreted the rapidly flashing green light to indicate a dose delivery completion.

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

Task	Essential/ Critical	Success Criteria	Results (success/total)	URA Potential causes of hazard(s) <sup>a</sup>	Potential Harm <sup>a</sup>	Result (Description)
Respond appropriately to device hazard alarm state	Critical	Must identify that an error has occurred prior to device disposal and state the next action would be to contact the appropriate party per IFU.	28/30 (93.3%) patient and caregivers 13/15 moderator-trained 15/15 self-trained)	Patient or Caregiver misinterprets device indicators	Missed Dose	1 Moderator- Trained Patient [P10] and one Moderator- Trained Caregiver [P45] detected, but failed to interpret the device hazard alarm.

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<sup>a</sup> The URA Potential cause of hazard(s) and Potential Harm in table 1 are based on worst case outcome, whereas; the URA Potential cause of hazard(s) and Potential Harm in this table are based on the Amgen disposition of the outcome in the summative validation study which may be different.

## Overall Observations

Below is a brief of summary of the six types of errors that occurred during the study:

- 1 HCP failed to pull off both adhesive liners completely.

- 3 HCPs failed to secure the devices to the application site in less than 3 minutes and did not attempt to apply the device on the skin pad after 3 minutes.
- 1 HCP failed to secure the device to the site within 3 minutes and after the cannula was deployed, the device was applied to the skin pad.
- 1 Caregiver and 1 Patient removed the device prior to notification of a complete delivery via a beep and solid green light because they saw the fill indication was in the empty position and believed delivery was complete. However, in these cases the patient still received the full dose.
- 1 Caregiver removed the device prior to dose delivery completion (1 minute after into the start of the nominal 45 minute delivery period) after misinterpreting the rapidly flashing green light.
- 1 Caregiver and 1 Patient detected, but failed to interpret the device hazard alarm.

## Detailed Observations

### **Remove Adhesive Liner: HCP Removes Only Half of Adhesive Backing**

One HCP moderator-trained participant [P3] failed to pull off both adhesive liners completely in moderator-trained session 1.

Residual Risk Analysis: To lead to an undetected missed dose, the following events need to occur:

1. HCP removes half of adhesive backing and applies device to patient.
2. Patient doesn't detect the adhesive has been disrupted
3. Device leaks to an unacceptable level.
4. Patient does not detect leakage.

As evidence of learning and remembering how they were debriefed in the moderator-trained session 1, 3 days later, in the test session, an HCP moderator-trained participant [P3] successfully pulled off both adhesive liners correctly in moderator-trained session 2.

As further reduction for this risk, if the HCP places the device on patient with only 1 adhesive liner, leakage may occur alerting the patient to call the HCP and return for a redose. As evidence that patients or caregivers would detect such a leak, Human Factors Formative Study 5 results showed that 27/30 (90%) patients and caregivers successfully detected leakage when this condition was simulated. Also, in the summative validation study 30/30 trained patients and caregivers and 30/31 untrained reported that they would call the HCP if a leak were detected.

Therefore, the residual risk of undetected missed dose is acceptable based upon the combination of the low probability of removing half the adhesive backing leading to leakage and the high detectability of leakage given an unacceptable level of leakage occurs.

**Apply to Application Site: HCP Fails to Place Device on Patient**

One HCP self-trained participant [P57] and 2 HCP moderator-trained participants [P27] and [P75] failed to secure the devices to the application site in less than 3 minutes and did not attempt to apply the device on the skin pad after 3 minutes.

Residual Risk Analysis: If the HCP self-identifies the use error and tries again with a new kit per IFU, only a risk of customer annoyance would occur.

As evidence of learning and remembering how they were debriefed in the moderator-training session, 3 days later, in the test session, both HCP moderator-trained participants [P27] and [P75] correctly secured the device to the application site in less than 3 minutes in moderator-trained session 2.

The residual risk of harm to the patient is low since the only risk is HCP annoyance, given that the HCP would try again with a new kit per IFU instructions as opposed to the outcome observed in this study. Therefore, the residual risk is deemed acceptable.

### **Apply to Application Site: HCP Places Device on Patient after Cannula Deployment**

One HCP self-trained participant [P43] failed to secure the device to the site within 3 minutes therefore the device was applied to the skin pad and after the cannula was deployed.

Residual Risk Analysis: In a recent clinical evaluation in 2013 (Study 20130237), results showed that 297/297 (100%) devices were successfully placed on the patients within 3 minutes. There were no complaint records reported for this event during this evaluation.

As further control for this risk, if the HCP places the device on patient after the cannula is deployed, leakage will occur alerting the patient to call the HCP and return for a redose. As evidence that patients or caregivers would detect such a leak, Human Factors Formative Study 5 results showed that 27/30 (90%) patients and caregivers successfully detected leakage when this condition was simulated. Also, in the summative validation study, 30/30 trained patients and caregivers and 30/31 untrained reported that they would call the HCP if a leak were detected.

Therefore, the residual risk is acceptable based on low probability of placing the device on the patient after cannula deployment and high detectability of leakage.

### **Removal of device After Successful Delivery: Patient or Caregiver Misinterprets Device Indicators (Complete Dose)**

One moderator-trained caregiver [P45] and one moderator-trained patient [P12] removed the device prior to notification of a complete delivery via a beep and solid green light. Both removed the device because the fill indicator was at empty position and thereby believing the delivery was complete.

Residual Risk Analysis: It is believed that the cause of this observation was the method used to simulate a delivery, in order to avoid actual drug spillage onto a participant and real drug administration. This technique involved over-filling the device with air instead of actual drug, which caused the simulated delivery to be approximately 52 minutes which is longer than the expected time period (45 minutes) mentioned in training and in the IFU. Therefore, these 2 participants used that information to decide when to remove the device instead of the actual designed cues indicating end of delivery.

Furthermore, this instance would not result in a dosing error. In a subsequent engineering analysis it was established that these participants would have received their minimum required dose.

Since the instructions clearly point out that dose delivery will take approximately 45 minutes and design verification testing (reference [3.2.P.7 \[Neulasta Delivery Device Design Verification\]](#)) has confirmed that a delivery period of approximately 45 minutes will ensure that the entire prescribed dose is expelled from the device; it is concluded that if a patient removes the device after approximately 45 minutes and the fill indicator is at the 'empty' position, then the entire prescribed dose would have been dispensed. Therefore the risk is considered acceptable.

### **Removal of Device after Successful Delivery: Patient or Caregiver Misinterprets Device Indicators (Incomplete Dose)**

One moderator-trained caregiver [P34] also removed the device prior to dose delivery completion and therefore the simulated patient (mannequin) would not have received a full dose. The caregiver prematurely removed the device after a minute into start of the nominal 45 minute delivery period. The participant misinterpreted the rapidly flashing green light to indicate a dose delivery completion.

Residual Risk Analysis: Based upon previous formative studies, participants have demonstrated to be able to clearly differentiate the delivery vs. completed delivery states. The delivery state is a rapidly flashing green light, while the state of the device after dose delivery completion is a solid green light. There have been no previous observations in formative studies of failures related to misinterpretation of the rapidly flashing green light as dose delivery completion.

Therefore, the risk associated with patient misinterpreting device indicators resulting in a missed dose has been evaluated and is considered acceptable based on the following risk control measures:

1. The Patient IFU instructs the User on the device alerts and notifications.
2. The Patient IFU instructs the User not to remove the device until they have confirmed their full dose is complete.
3. The Patient IFU instructs the User to check for dose delivery completion, by checking whether the status light is solid green or has switch off.
4. The Patient IFU instructs the User to confirm dose delivery by checking the black line next to the "empty" indicator. If the device is not empty, call their healthcare provider.

### **Device Hazard Alarm State and Response: Patient or Caregiver Misinterprets Device Indications**

One moderator-trained patient [P10] and one moderator-trained caregiver [P48] detected, but failed to interpret the device hazard alarm. Both participants were able to visually confirm the device's blinking red light with beeps. However, they did not perform the appropriate action by simulating calling the appropriate party per IFU due to their belief that the fill indicator was at empty.

Residual Risk Analysis: This error condition of both an empty fill indicator and a hazard alarm indicating lack of a full dose delivery is extremely unlikely from an engineering standpoint. Furthermore, results from a 2013 clinical evaluation (Study 20130237) showed that none of the 297 devices that were filled had an under fill alarm.

Also, two formative studies provide further evidence. Formative 6 results showed that 19/20 (95.0%) and Formative 5 results showed that 15/15 (100%) participants were able to successfully detect the hazard alarm. These two formative studies were executed with exact same alarm and simulated an under fill alarm in the same method as the simulated use summative validation study.

The residual risk of harm (missed dose) to the patient is acceptable based on the low occurrence of under fill condition and the high detectability of the hazard alarm.

## APPENDIX E. ISMP NEWSLETTERS

### E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on August 21, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Neulasta

### E.2 Results

Our search did not identify any medication errors or actions associated with the current use, labels and labeling for Neulasta.

## APPENDIX F. NOT APPLICABLE

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>4</sup> along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Amgen on July 22, 2014.

- Prefilled Syringe Label (*currently marketed*)
- Delivery Device Top Housing Label Options 1 and 2 (*proposed*)
- Delivery Device Secondary Label (*proposed*)
- Delivery Device Carton Labeling (*proposed*)
- Prefilled Syringe for use with Delivery Device Primary Label (*proposed*)
- Prefilled Syringe for use with Delivery Device Container Top Label (*proposed*)
- Prescribing Information (*no image*)
- Patient Medication Guide and Instructions for Use (*no image*)
- Healthcare Providers Instructions for Use (*no image*)

### G.2 Label and Labeling Images

#### Prefilled Syringe Label (*currently marketed*)



<sup>4</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NEIL H VORA  
09/26/2014

YELENA L MASLOV  
09/26/2014

LUBNA A MERCHANT  
09/26/2014

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

<b>Application:</b>	BLA125031/175	<b>Action Goal:</b>	
<b>Stamp Date:</b>	27-JUN-2014	<b>District Goal:</b>	22-SEP-2014
<b>Regulatory:</b>	27-OCT-2014		
<b>Applicant:</b>	(b) (4)	<b>Brand Name:</b>	NEULASTA
		<b>Estab. Name:</b>	
		<b>Generic Name:</b>	
<b>Priority:</b>	1	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
<b>Org. Code:</b>	161		001; INJECTION, SOLUTION; PEGFILGRASTIM; 6MG
<b>Application Comment:</b>	REQUEST FOR APPROVAL OF A NEW COMBINATION PRODUCT PRESENTATION (on 31-JUL-2014 by T. WILSON ()) 2404024226)		
<b>FDA Contacts:</b>	L. NARASIMHAN	Facility Reviewer	3017960059
	D. PLUZNIK	Prod Qual Reviewer (HFD-122)	2404029252
	A. BROWN	Product Quality PM	3017962066
	T. SENSIE	Regulatory Project Mgr	2404024230
<b>Overall Recommendation:</b>	PENDING	on 01-AUG-2014	by EES_PROD



**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 2650228 FEI: 1000110364  
AMGEN MANUFACTURING LIMITED, INC.  
RD 31 KM 24.6  
JUNCOS, PR 00777

**DMF No:** **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE OTHER TESTER  
FINISHED DOSAGE PACKAGER

**Establishment Comment:** DRUG PRODUCT MANUFACTURING (FORMULATION, STERILE FILTRATION, FILL AND FINISH, PACKAGING/LABELING, RELEASE TESTING, STABILITY TESTING) (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)  
DRUG SUBSTANCE MANUFACTURING (FERMENTATION, PURIFICATION, PEGYLATION, BULK FILTRATION, RELEASE TESTING, STABILITY TESTING).  
DRUG PRODUCT MANUFACTURING (FORMULATION, STERILE FILTRATION, FILL AND FINISH, PACKAGING/LABELING, RELEASE TESTING, STABILITY TESTING) (on 31-JUL-2014 by T. WILSON () 2404024226)  
FINAL KIT PACKAGING OF NEULASTA PREFILLED SYRINGE AND DRUG DELIVERY DEVICE (on 31-JUL-2014 by T. WILSON () 2404024226)  
DRUG SUBSTANCE MANUFACTURING (FERMENTATION, PURIFICATION, PEGYLATION, BULK FILTRATION); RELEASE AND STABILITY TESTING (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

**Profile:** BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) **OAI Status:** NONE  
STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

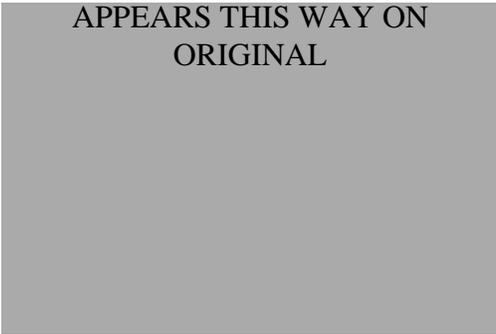
<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	01-AUG-2014				WILSONT
SUBMITTED TO BMR	11-AUG-2014	Request BMR Evaluation			PRABHAKARAR
THIS SITE WAS INSPECTED BY SJN-DO FROM JULY 24, 2013 - AUGUST 15, 2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG MANUFACTURING AND TESTING OPERATIONS. THE TRP PROFILE WAS UPDATED AND IS ACCEPTABLE. THIS SITE WAS ALSO INSPECTED BY CDER-OMPQ FROM MARCH 24-28, 2014 AND CLASSIFIED VAI. THIS WAS A PAI FOR ARANESP THAT FOUND BIOTECH DRUG MANUFACTURING OPERATIONS ACCEPTABLE.					
DOES BMAB PLAN TO PERFORM A PAI BEFORE APPROVING BLA 125031/175?					
SUBMITTED TO OC	01-AUG-2014				WILSONT
SUBMITTED TO BMR	11-AUG-2014	Request BMR Evaluation			PRABHAKARAR
THIS SITE WAS INSPECTED BY SJN-DO FROM JULY 24, 2013 - AUGUST 15, 2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG MANUFACTURING AND TESTING OPERATIONS. THE TRP PROFILE WAS UPDATED AND IS ACCEPTABLE. THIS SITE WAS ALSO INSPECTED BY CDER-OMPQ FROM MARCH 24-28, 2014 AND CLASSIFIED VAI. THIS WAS A PAI FOR ARANESP THAT FOUND BIOTECH DRUG MANUFACTURING OPERATIONS ACCEPTABLE.					
DOES BMAB PLAN TO PERFORM A PAI BEFORE APPROVING BLA 125031/175?					

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

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APPEARS THIS WAY ON  
ORIGINAL



**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

(b) (4)

Establishment:



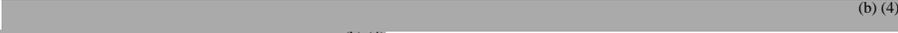
DMF No:

Responsibilities:



(b) (4)

Establishment Comment:



(b) (4)

Profile:



(b) (4)

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	01-AUG-2014				WILSONT
SUBMITTED TO BMR	29-AUG-2014	Request BMR Evaluation			PRABHAKARAR
THIS SITE HAS NO FDA INSPECTIONAL HISTORY. DOES BMAB PLAN TO PERFORM A PAI OF THIS SITE BEFORE APPROVAL OF THIS BLA?					

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA: [REDACTED]

Responsibilities: [REDACTED] (b) (4)

Establishment Comment: [REDACTED] (b) (4)

Profile: [REDACTED] (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	01-AUG-2014				WILSONT
SUBMITTED TO DO	29-AUG-2014	10-Day Letter	[REDACTED] (b) (4)		PRABHAKARAR



**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** [REDACTED] (b) (4)

**DMF No:** [REDACTED] (b) (4)      **AADA:** [REDACTED]

**Responsibilities:** [REDACTED]

**Establishment Comment:** [REDACTED] (b) (4)

**Profile:** [REDACTED] (b) (4)      **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<b>Comment</b>					
<b>OAI Submit To OC</b>					
<b>Request to Extend Re-eval Date To</b>					
<b>Extension Request Comment</b>					
<b>Reason</b>					

SUBMITTED TO OC	01-AUG-2014				WILSONT
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS [REDACTED] (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING [REDACTED] (b) (4) WAS UPDATED AND IS ACCEPTABLE.					

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA: [REDACTED]

Responsibilities: [REDACTED] (b) (4)

Establishment Comment: [REDACTED] (b) (4)

Profile: [REDACTED] (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	01-AUG-2014				WILSONT
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SUBMITTED TO DO	29-AUG-2014	GMP Inspection			PRABHAKARAR
THIS SITE WAS INSPECTED BY [REDACTED] (b) (4) AND CLASSIFIED NAI. THIS WAS A QSIT LEVEL I ABBREVIATED MEDICAL DEVICE INSPECTION COVERING [REDACTED] (b) (4) PROFILE WAS UPDATED AND WAS ACCEPTABLE FOLLOWING THAT INSPECTION.					

THE GMP STATUS OF THIS FIRM IS OUT-OF-DATE. HOWEVER, CDRH HAS INDICATED THAT THIS SITE WILL REQUIRE A DEVICE INSPECTION (COMBINATION PRODUCT) BEFORE APPROVAL OF THIS BLA. AN INSPECTION REQUEST WAS CREATED IN FACTS. THE FACTS ASSIGNMENT NUMBER IS [REDACTED] (b) (4).

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/s/  
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RANJANI PRABHAKARA  
08/29/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125031Orig1s175**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [McMullen, Rachel \(Rachel.Mcmullen@fda.hhs.gov\)](mailto:Rachel.Mcmullen@fda.hhs.gov)  
**Subject:** sBLA 125031/Neulasta: Please provide a response to HF comment by 5pm EST today.  
**Date:** Friday, December 19, 2014 2:46:00 PM  
**Importance:** High

---

Dear Dr. Silkaitis,

Please refer to your Supplemental New Biologics Application (sBLA) for BLA 125031/S-175 submitted under section 351(a) of the Public Health Service Act for BLA 125031/S-175, Neulasta<sup>®</sup> (pegfilgrastim).

The team is requesting a prompt response to the following Human Factors comment.

The analysis of the task failures and the subjective data from study participants indicated that some task failures occurred because users were confused by the instructions for use, and the other task failures occurred because users misinterpreted the device indicators i.e. flashing green light and the device hazard alarms. In addition, there were some close calls that were directed at step of filling medication that will need to be performed that resulted in difficulty in inserting the prefilled syringe into the medication port and in the needle becoming bent, and difficulty in filling the medication in general. Review of the Instructions for Use indicated that they should be further optimized to address the report failures and closed calls.

1. We need additional information on the reported close calls. You reported that these HCPs experienced difficulty in inserting the prefilled syringe into the medication port and in the needle becoming bent, and difficulty in filling the medication in general. While you stated that these situations resolved when a new kit was made available, you did not provide sufficient subjective data from these HCPs as to why they experienced the difficulty while performing the steps and whether they have any recommendations to address the difficulty. Please provide additional analysis of these close calls, and depending on the root cause that the HCPs identified, we ask that you implement additional mitigation to address these reported close calls.

Please provide a response by **4pm EST today** and confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
12/19/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [Baird, Amy](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: Final FDA Proposed Labeling: PI, PPI, IFU\_ Please respond by COB today  
**Date:** Monday, December 15, 2014 3:17:00 PM  
**Attachments:** [FINAL FDA proposed edits to PPI -Dec 15.doc](#)  
[FINAL FDA proposed labeling USPI- Neulasta Delivery Device. FDA edits Dec 15 .docx](#)  
[FINAL FDA proposed labeling-hcp-ifu Dec 15.doc](#)  
**Importance:** High

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Dear Dr. Silkaitis,

Please refer to your Supplemental New Biologics Application (sBLA) for BLA 125031/S-175 submitted under section 351(a) of the Public Health Service Act for BLA 125031/S-175, Neulasta<sup>®</sup> (pegfilgrastim).

We are in agreement with Amgen's proposed labeling. The FDA review team has proposed some minor editorial edits to the **PI, PPI and HCP IFU**. Please review and provide your concurrence to the attached FDA proposed labeling.

Please provide Amgen's confirmation regarding final FDA proposed labeling via email by **COB today, Monday December 15, 2014**. Following that, please submit the information formally to the BLA file.

Please ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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

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/s/  
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RACHEL S MCMULLEN  
12/15/2014

**From:** [McMullen, Rachel](#)  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [Baird, Amy](#); [McMullen, Rachel](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: Final FDA Proposed Labeling: PI, PPI, IFU  
**Date:** Friday, December 12, 2014 3:08:14 PM  
**Attachments:** [FINAL FDA proposed labeling USPI - Neulasta Delivery Device.docx](#)  
[FINAL FDA proposed edits to PPI - MS Word - Neulasta Delivery Device.doc](#)  
[FINAL FDA proposed edits Patient IFU - MS Word - Neulasta Delivery Device.doc](#)  
**Importance:** High

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Dear Dr. Silkaitis,

Please refer to your Supplemental New Biologics Application (sBLA) for BLA 125031/S-175 submitted under section 351(a) of the Public Health Service Act for BLA 125031/S-175, Neulasta® (pegfilgrastim).

FDA's current edits/comments on the **PI, PPI, and IFU** are attached. Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Additionally, with regards to device placement, the reviewer team would like Amgen to incorporate the comment below to all labeling documents (PI, PPI, IFU).

The back of the arm may be used but the PI, PPI, IFU and all instruction material must be revised to remove mention of (b) (4) The PI, PPI, IFU and all instruction material must be revised to indicate that the back of the arm may only be used if there is a caregiver available to monitor the device for signals, if the device is placed on the back of the arm.

Please provide a **revised** response via email by **10am EST on Monday December 15, 2014**. Following that, please submit the information formally to the BLA file.

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

Please ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
12/12/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [Baird, Amy](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: FDA Proposed Labeling: PI, PPI, IFU  
**Date:** Wednesday, November 19, 2014 10:41:00 AM  
**Attachments:** [FDA Proposed Changes to Neulasta USPI-draft-redline-2014-11-18.docx](#)  
[FDA proposed edits to Amgen updated PPI 11-3-14 \(2\).doc](#)  
[FDA Proposed changes to patient IFU-draft-redline-2014-10-29\\_rev 2014-11-10.doc .doc](#)  
**Importance:** High

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Dear Dr. Silkaitis,

Please refer to your Supplemental New Biologics Application (sBLA) for BLA 125031/S-175 submitted under section 351(a) of the Public Health Service Act for BLA 125031/S-175, Neulasta® (pegfilgrastim).

FDA's current edits/comments on the **PI, PPI, and IFU** are attached. Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Additionally, with regards to the IFU, the reviewers would like Amgen to address the comments described below.

1. The IFU **should be revised** to indicate that the on-body injector be placed in a sharps container, with an appropriate sized opening, regardless of whether or not the needle is exposed.
2. The entire printed IFU is on an 8x11 piece of paper, however the print is too small for patient to read. The team is requesting that Amgen tell us how the IFU will be presented in printed form to the patient.

Please provide a **revised** response via email by **4pm EST on Friday November 21, 2014**.

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

Following that, please submit the information formally to the BLA file.

Please **confirm** receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
11/19/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Subject:** BLA 125031/S-175: Information request  
**Date:** Friday, November 07, 2014 2:12:00 PM  
**Importance:** High

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Dear Dr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

Please provide a photo of the back side of the On-body Injector.

Please respond to the request no later than **4pm today Friday, November 7, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
11/07/2014

**From:** [McMullen, Rachel](#)  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](#)  
**Cc:** [McMullen, Rachel](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: FDA Proposed Labeling  
**Date:** Thursday, November 06, 2014 11:46:15 AM  
**Attachments:** [image001.png](#)  
[image002.png](#)  
**Importance:** High

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Dear Dr. Silkaitis,

With reference to your labeling submission for Neulasta BLA 125031/S-0175, the team has provided the following comments on the revised carton/container labels provided by Amgen.

### Carton Labeling and On-body Injector Label Comments for 125031/175

We reviewed your revised labels and labeling emailed on October 30, 2014 for BLA 125031/175. We identified a few deficiencies that require attention. Please respond by COB November 12, 2014.

#### **A. Carton Labeling**

1. Increase the font size of "6 mg/0.6 mL\*" within the blue circle to improve readability of the entire strength statement.



The appearance of "6 mg/0.6 mL\*" on the Inner Tray Labeling allows for easier reading of the entire strength statement.



#### **B. On-body Injector Label**

1. Provide a proposed label showing a horizontally oriented Top Housing Label for "On-body Injector for Neulasta (pegfilgrastim)".
2. We find the proposal for "Option 2" that provides for (b) (4) (b) (4) on the device is unacceptable. The laser-etched markings lack appropriate prominence and placement to allow for easy identification of the device and the contents being infused.

Furthermore, the originally proposed Top Housing Label would cover the Pink Slide Indicator that slides when the cannula implantation process is initiated.

(b) (4) (b) (4) The Pink Slide Indicator is not described in the Instructions for Use (HCP and patient). We understand the Pink Slide Indicator was not intended to be part of the user interface for this product.

3. If space is available, revise the laser-etched label "For use with Neulasta" to read "For use with Neulasta (pegfilgrastim)".

Please provide a **revised** response via email by **2pm EST on Wednesday November 12, 2014**. Following that, please submit the information formally to the BLA file.

Please ***confirm*** receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
11/06/2014

**From:** [McMullen, Rachel](#)  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [McMullen, Rachel](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: Labeling \_ FDA clarifications on labeling  
**Date:** Wednesday, October 29, 2014 3:29:19 PM  
**Importance:** High

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Dear Dr. Silkaitis,

With reference to your labeling submission for Neulasta BLA 125031/S-0175, the FDA has provided clarification responses to Amgen's questions sent last week on October 23, 2014. Based on the FDA responses provided below, please provide the following revised labeling documents for FDA to review.

1. **PPI**
2. **IFU**
3. **Carton/Container Labels:**
  - Carton Labeling
  - Inner Tray Labeling
  - Prefilled Syringe Container Label
  - On-body Injector Top Housing Label

Please provide a **revised** response via email by **4pm EST tomorrow, Thursday October 30, 2014**. Following that, please submit the information formally to the BLA file. Please **confirm** receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

## **SPONSOR QUESTIONS & FDA RESPONSES:**

### Question 1

Based on Amgen's experience, as well as from looking at IFUs for combination products recently approved by CDER, it does not appear to be typical to include the types of information requested by CDRH in patient IFUs. Can CDRH provide a specific example (web reference) for a combination

product patient instructions for use that Amgen will reference while drafting edits to the IFU?

**FDA Response:**

This kit is a first of its kind. There are other similar concepts in development, but none at the marketing application stage. Therefore there is no specific example which CDRH can provide at this time to the sponsor.

**Question 2**

Two sections in CDRH Patient or Consumer Labeling Review Comments (Information on Condition or Disease, Description of adverse Effect, Interpreted Summary of Clinical Data) request information on Neulasta (eg, side effects, 932 patient clinical trial information, dizziness). Please note that the Patients Information (PPI) and the Patient Instructions for Use (IFU) are intended to be printed on the same sheet of paper (two-sided printing; see attached artwork submitted in the original sBLA). Therefore specific Neulasta information will be readily available to the patient in direct connection to the IFU. Can CDRH confirm that there is no further request to add Neulasta information into the IFU?

**FDA Response:**

Because the sponsor states that examples of information such as those above will be available in the PPI, there is no need to include the additional Neulasta information to the IFU.

Confirmation/Questions 3 and 4

As submitted yesterday, Amgen was proposing the following information be included in the PPI; CDER responded today that it should not be included in the PPI and to work with CDRH on applicability to the IFU.

**Question 3**

Amgen provided the below information yesterday (responses submitted 10/22/2014 to FDA's questions/comments from 10/21/2014), (b) (4). Based on the e-mail received from FDA today, we have been directed to focus this information to the patient IFU. Please provide guidance on the acceptability of the below information for satisfying CDRH's comments [(CDRH Patient or Consumer Labeling Review Comments: Warnings, Precautions, Risks, Benefits); received 10/21/2014]. Again, this information is new from FDA to Amgen on combination product labeling being regulated through CDER. Therefore, we desire to ensure our understanding of the expectation is complete.

**FDA Response: This information should be included in the IFU.** (b) (4)

See recommended changes in Red.

Warnings:

- **Do not** take Neulasta if you have had a serious allergic reaction to pegfilgrastim (Neulasta®) or to filgrastim (Neupogen®).
- **Tell your healthcare provider if you are allergic to latex.** A pre-filled syringe is used to fill the

on-body injector by your Healthcare provider prior to applying the on-body injector. The prefilled syringe gray needle cap contains dry natural rubber, which is derived from latex. **Latex may be transferred to your skin.**

- **Tell your healthcare provider if you have had severe skin reactions to acrylic adhesives.**
  - Avoid activities and places that may interfere with monitoring during the dosing of Neulasta administered by the on-body injector. For example, (b) (4)  
(b) (4)  
(b) (4)
- If you have an allergic reaction during the delivery of Neulasta, remove the on-body injector by grabbing the edge of the adhesive pad and peeling off the on-body injector (b) (4)  
(b) (4).
- **Call your healthcare provider immediately** if you have severe pain or skin discomfort around your on-body injector.
- **Before you receive Neulasta**, tell your healthcare provider if you: **(These conditions should be listed first under Warnings)**
  - Have sickle cell trait or sickle cell disease
    - Have any other medical problems
    - Are pregnant or plan to become pregnant. It is not known if Neulasta may harm your unborn baby.
    - Are breastfeeding or plan to breastfeed. It is not known if Neulasta passes into your breastmilk.
- Call your healthcare provider right away if you have pain in your left upper stomach area or left shoulder area. This pain could mean your spleen is enlarged or ruptured.
- Call your healthcare provider or get emergency medical help right away if you get any of these symptoms of ARDS: fever, shortness of breath, trouble breathing, or a fast rate of breathing.
- **Keep children away from** (b) (4) the used on-body injector. (b) (4)  
(b) (4) **(“Keep children away from” is taken from a CPSC warning)**
- You should only receive a dose of Neulasta on the day your healthcare provider tells you.
- You should not receive your dose of Neulasta any sooner than (b) (4) after you finish receiving your chemotherapy. (b) (4) is programmed to deliver your dose about 27 hours after your healthcare provider places the on-body injector on your skin.
- It is not known if Neulasta is safe and effective in children.
- **Do not** expose the on-body injector to the following because the on-body injector may be damaged and you could be injured:
  - MRI
  - X-ray
  - CT-Scan
  - Ultrasound
  - Oxygen rich environments, such as hyperbaric chambers
  - **Do not** use hot tubs, whirlpools, or saunas while wearing the on-body injector. This may affect your medicine.
  - **Do not** expose the on-body injector to direct sunlight. If the on-body injector is exposed to direct sunlight for more than 1 hour, it may affect your medicine. Wear the on-body injector under clothing.

- **Do not** sleep on the on-body injector or apply pressure during wear, especially during dose delivery. This may affect the on-body injector performance.
- **Do not** peel off or disturb the on-body injector’s adhesive before your full dose is complete. This may result in a missed or incomplete dose of Neulasta.

Precautions:

Environmental:

- Keep the on-body injector dry for the last 3 hours prior to the dose delivery start.
- **Only expose** the on-body injector (b) (4) to temperatures between 41°F and 104°F (5°C-40°C).
- Keep the on-body injector at least 4 inches away from electrical equipment such as cell phones, cordless telephones, microwaves and other common appliances. Failure to keep the on-body injector at least this recommended distance may interfere with operation and can lead to a missed or incomplete dose of Neulasta.

Activity Related:

- Avoid getting body lotions, creams, oils or cleaning agents near the on-body injector as these products may loosen the adhesive.
- Be careful not to bump the on-body injector or knock the on-body injector off your body.

(b) (4)

Biohazard:

Properly dispose of the on-body injector:

- The on-body injector contains batteries, electronics, and a needle. (b) (4)
- (b) (4)
- To participate in Amgen’s voluntary disposal program, please call 1-844-MYNEULASTA (1-844-696-3852) or visit [www.neulasta.com](http://www.neulasta.com) to enroll.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to FDA’s website at: <http://www.fda.gov/safesharpsdisposal>.

Risks

You can avoid most risks related to using the Neulasta on-body injector by following (b) (4).

(b) (4) the Patient Instructions for Use. (b) (4) Immediately call (b) (4) your healthcare provider if (b) (4).

(b) (4) any of the following occur:

- The adhesive becomes noticeably wet (saturated) with fluid, or you see dripping
- If the on-body injector fill indicator is not at empty position after on-body injector removal (You should see a black line next to the EMPTY indicator.)
- The on-body injector comes off from the skin before or during a dose delivery (**Do not re-apply it.**)
- Red status light is flashing red
- Allergic reaction
- Persistent or worsening redness or tenderness at the application site (may be sign of

infection)

- Severe pain or skin discomfort around your on-body injector
- Any concern about your medication
- If the needle is exposed after on-body injector removal

(b) (4)

(CDER's opinion is that this information is not needed in the IFU and CDRH reviewer agrees. Additionally, the language used is too complex for most lay readers.)

#### Question 4

Amgen provided the attached PPI draft with information addressing the following CDRH's comments (CDRH Patient or Consumer Labeling Review Comments; received 10/21/2014): Device Description and Use, Need to Adhere to Care Regimen, Travel and International Use. The attached draft has the specific proposed text highlighted in yellow with an associated comment for ease of identification. Can CDRH confirm that this proposed text addressed the comments provided on 10/21/2104?

#### **FDA Response:**

Patients should stay in place in order to be monitored. As a result, the travel information should be removed. Language regarding staying in place was changed above to strengthen the language to read more as a warning, i.e., "**Do Not.**"

(b) (4) should be removed from the patient labeling.

**To the sponsor:** what is meant by (b) (4) under, "Record the end state of your on-body injector?" There is no explanation what this means and the patient should understand what (b) (4) means.

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/s/  
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RACHEL S MCMULLEN  
10/29/2014



BLA 125031/S-175

**REVIEW EXTENSION –  
CMC SUPPLEMENT**

Amgen Inc.  
Attention: Ray Silkaitis, RPh, PhD  
Director, Regulatory Affairs, Global Regulatory Affairs and Safety  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320

Dear Dr. Silkaitis:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 27, 2014, received June 27, 2014, submitted under section 351 of the Public Health Service Act for Neulasta<sup>®</sup> (pegfilgrastim).

On October 22, 2014, we received your three formal submissions dated October 22, 2014. These submissions provide for a significant amount of new information with updated reports and correction of data previously provided, as part of Amgen's responses to an extensive list of product quality and device information requests. We consider these submissions to constitute a major amendment. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is December 27, 2014.

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD  
Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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THERESA A CARIOTI

10/24/2014

Signing on behalf of Dr. Ann Farrell

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device - Information Request  
**Date:** Thursday, October 23, 2014 5:10:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

Upon reviewing the Human Factors Study submitted by Amgen on June 27, 2014 we were unable to find information regarding the placement of the device. Thus, please address the following questions:

1. Please specify the process of placing the Neulasta On-Body Injector on a patient body by a HCP participants (i.e., did they use a dummy, where did they place the device, how did they decide on the body area to place it on, how many “patients” have the device on the abdomen vs. the back of the arm).
2. For patient participants, please specify the process of how and what area of the body the Neulasta On-Body Injector was placed on (i.e. abdomen or back of the arm). Please provide the breakdown of patients who had the device placed on the abdomen vs. patients who had the device placed behind the arm.
3. Provide information regarding how the patients and caregivers monitored the device for proper placement and function after having it placed on to their skin?
4. Provide any comments from the patients regarding difficulties with monitoring the device after placement on to the skin. Specify what were they.

Please respond to the request no later than **3pm on Friday, October 24, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration

10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/23/2014

**From:** McMullen, Rachel  
**To:** ["Silkaitis, Ray"](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device - FDA comments on PI and Carton Labeling  
**Date:** Tuesday, October 07, 2014 12:53:00 PM  
**Attachments:** [annotated-draft-label-uspi.doc\\_RM.doc](#)  
[OBP DMEPA IR for 125031 175 10062014.doc](#)  
**Importance:** High

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Good morning Mr. Silkaitis,

Please refer to your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for BLA 125031/S-175, Neulasta<sup>®</sup> (pegfilgrastim).

FDA's current edits/comments on the **PI** and **Carton Container Labeling** are attached for your consideration. Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

Please note that FDA comments on patient labeling will be communicated in a separate email.

Please submit your labeling response via email by **4 pm EST on Monday, October 13, 2014.** followed by an official submission to the sBLA file. The resubmitted labeling will be used for further labeling discussions.

Please contact me if you have any questions.

Kind regards,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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

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/s/  
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RACHEL S MCMULLEN  
10/23/2014

**From:** [McMullen, Rachel](#)  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [McMullen, Rachel](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: FDA Proposed Labeling  
**Date:** Tuesday, October 21, 2014 3:59:00 PM  
**Attachments:** [OBP Container Carton comments for 125031\\_175\\_10172014.doc](#)  
[pegfilgrastim \(Neulasta\) B125031\\_175\\_DMPP-OPDP PPI Oct-2014 marked.doc](#)  
[Combined Recommendations from DMEPA and CDRH HF team.doc](#)  
[CDRH Patient or Consumer Labeling Review Comments.doc](#)  
**Importance:** High

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Good afternoon Mr. Silkaitis,

Please refer to your Supplemental New Biologics Application (sBLA) for BLA 125031/S-175 submitted under section 351(a) of the Public Health Service Act for BLA 125031/S-175, Neulasta® (pegfilgrastim).

FDA's current edits/comments on the **PPI, IFU and carton/container labeling** are attached. Please note that I am providing you these documents separately. Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please submit your labeling response via email by **4pm EST on Wednesday, October 22, 2014** followed by an official submission to the sBLA file. Per the discussion on Friday, October 17, regarding the clinical limitation of use, we are still awaiting Amgen's revised response to the PI. **Please include the PI in your response tomorrow.**

The resubmitted labeling will be used for further labeling discussions.

Please contact me if you have any questions.

Kind Regards,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products

Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
10/23/2014

**From:** [McMullen, Rachel](#)  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [McMullen, Rachel](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device: FDA Proposed Labeling  
**Date:** Thursday, October 23, 2014 11:57:16 AM  
**Attachments:** [pegfilgrastim \(Neulasta\) B125031\\_175\\_DMPP-OPDP PPI Oct-2014 marked.doc](#)  
**Importance:** High

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Good morning Mr. Silkaitis,

The team has reviewed your labeling submission received via email yesterday, October 22, 2014 and we have a few comments as noted below.

We acknowledge Amgen's agreement to the FDA to provide Container and Carton Comments. Actual labels need to be submitted for review before they are deemed acceptable. **Please provide the following revised carton/container labels:**

-

1. Carton Labeling
2. Inner Tray Labeling
3. Prefilled Syringe Container Label
4. On-body Injector Top Housing Label

With regards to the PPI with Amgen's revisions, the reviewers would like Amgen to address the comments described below. The PPI with FDA proposed revisions is re-attached here for your convenience.

- Use the document "DMPP-OPDP PPI Oct-2014 marked" as your base document.
  - This document incorporates the CDRH recommendations that CDER considers relevant. Therefore, do not utilize the separate document from CDRH with their patient labeling comments when you revise the Patient Package Insert (PPI). Instead, only use it in editing the Instructions for Use (IFU).
  - Submit a tracked changes copy of your proposed edits to the PPI in Word, making sure that all edits are based on information in the current working version of the PI.
  - Consistently reference the On-Body injector in the PPI. (b) (4)  
(b) (4) The device will be applied by a healthcare provider; therefore, do not refer (b) (4).

We need a **revised** response by **12pm EST tomorrow, Friday October 24, 2014.**

Please [confirm receipt](#) of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
10/23/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** RE: BLA 125031-S175, Neulasta Delivery Device - Clarification required; please submit by 4pm EST today  
**Date:** Tuesday, October 21, 2014 9:09:00 AM  
**Importance:** High

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Hi Ray,

With regard to the response provided below, the review team is requesting clarification on the following issues:

1. You claim that this device-drug combination product is not indicated for pediatric patients. Is this clearly labeled?
2. You claim that the DMSO extracts were tested undiluted in the *in vitro* genotoxicity assays. Please confirm that the DMSO extracts were tested undiluted in the *in vitro* Mouse Lymphoma Gene Mutation Assay, as DMSO is known toxic to cells at high concentrations.

Kindly provide the clarification requested by **2pm EST today, Tuesday, October 21, 2014.**

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

---

**From:** Silkaitis, Ray [mailto:[rsilkait@amgen.com](mailto:rsilkait@amgen.com)]  
**Sent:** Monday, October 20, 2014 12:13 PM  
**To:** McMullen, Rachel  
**Subject:** RE: BLA 125031-S175, Neulasta Delivery Device - Advice Information Request

Hello Rachel,

Amgen's responses to the FDA review team's request for information are attached. Please note that the Toxicology report was just submitted with a previous response sent earlier today. If you are not able to find that report or if you would like for Amgen to re-send a copy, we will be happy to do so.

A formal amendment via the CDER gateway will be submitted.

Please let me know if there is additional information that is needed or if there are any additional questions.

Also, if you could confirm receipt of this email, it is appreciated

Kind Regards,  
Ray

Ray Silkaitis  
Amgen Inc.  
Device Regulatory  
Desk: 805-447-6865

(b) (6)

---

**From:** McMullen, Rachel [<mailto:Rachel.Mcmullen@fda.hhs.gov>]  
**Sent:** Friday, October 17, 2014 11:55 AM  
**To:** Silkaitis, Ray  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Importance:** High

Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. (b) (4) of the Amgen Neulasta Delivery Device has introduced a new material, which is (b) (4). However, biocompatibility testing based on the (b) (4) has not been provided. In the Response to FDA Information Request of 03 October 2014, you state that the (b) (4) was evaluated following ISO 10993-17:2002, assuming 100% of each component would be released and have patient contact. You claim that under this maximum exposure assumption, the assessment showed negligible patient risk and acceptability of the (b) (4) material. However the risk assessment document cannot be located. Please provide a detailed risk assessment for the (b) (4), including toxicology evaluation of all three chemicals contained in the (b) (4). In your risk assessment report, please include all calculations, such as the calculations for the MOS, the body weight for various user populations (adults, pediatrics), the reference doses/LOAELs/NOAELs, the limit of detections (LODs), the limit of quantifications (LOQs), the exposure assessment, and etc.

2. In response to the deficiency regarding the two *in vitro* genotoxicity testing where non-polar test extracts were not tested, you state “*Genotoxicity testing is more relevant with polar extracts than with non-polar extracts with the Neulasta drug product because drug product is an aqueous formulation*”. You further state that DMSO was justified as a second *in vitro* extraction medium in addition to water. To determine if your testing and justification provided is adequate, please address the following:

- To support that your devices will only have indirect contact via a polar solution, please clearly describe the formulation and composition of the intended drug solution.
- Please clarify if the DMSO extracts were tested at the neat levels (without being diluted). This information was not provided in your test reports submitted.

Please respond to the request no later than **1pm EST on Wednesday, October 20, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/22/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Cc:** [McMullen, Rachel \(Rachel.Mcmullen@fda.hhs.gov\)](mailto:Rachel.Mcmullen@fda.hhs.gov)  
**Subject:** RE: BLA 125031/S-175, Neulasta Delivery Device: FDA Proposed Limitation of Use for PI: Response required by 10/22  
**Date:** Tuesday, October 21, 2014 5:36:00 PM  
**Importance:** High

---

Good afternoon Mr. Silkaitis,

Thank you for participating in the T-con with the FDA on Friday, October 17, 2014. We hope that you can propose additional wording as to the setting in which the timed infusion (b) (4) (b) (4) after being applied to the skin) should take place, as we discussed during our T-con to replace the language that you struck out in the following areas of the draft labelling that the FDA most recently sent to you for review: (b) (4) of the Indications and Usage section of the highlights, and (b) (4) of Section 1 (Indications and Usage).

Per the discussion on Friday, October 17, regarding the clinical limitation of use, we are still awaiting Amgen's revised response to the PI. Please provide your response via email by **4pm EST on Wednesday, October 22, 2014** followed by an official submission to the sBLA file.

The resubmitted labeling will be used for further labeling discussions.

Please contact me if you have any questions.

Kind Regards,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
10/22/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** RE: BLA 125031-S175, Neulasta Delivery Device - more clarification required; please submit by 5pm EST today  
**Date:** Tuesday, October 21, 2014 3:22:00 PM

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Good afternoon Ray,

Thank you for the requested clarification. The review team is requesting some follow up information to the information provided this afternoon.

1. You state that the mouse lymphoma gene mutation assay was not conducted on neat extracts, but was conducted on DMSO extracts at a dilution of (b) (4)

Testing based (b) (4) of the device extracts cannot adequately address the safety concerns on the neat levels of the extractables and leachables that may release from the subject device during a worst clinical use condition and be exposed to patients. We acknowledge that due to its toxic nature at higher concentrations, DMSO may not be cell compatible when used at a concentration (b) (4). Practically device extracts prepared in DMSO cannot be tested neat. Therefore, we recommend that the sponsor use a more appropriate, cell compatible solvent for extraction of the test samples. Please be advised that complete cell culture medium with serum can be used for extraction of both polar and non-polar samples and that the test extracts prepared in cell cultured medium can be tested neat. To adequately address the genotoxicity concerns on the subject device, please provide a revised test report for the mouse lymphoma gene mutation assay, based on neat device extracts, both polar and non-polar, of the final finished subject device.

2. Please also clarify if the DMSO extracts were also tested at a diluted level in the bacterial gene mutation (AMES) assay? If yes, please provide the testing based on neat test extracts.

Kindly provide the clarification requested by **6pm EST today, Tuesday, October 21, 2014.**

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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**From:** McMullen, Rachel  
**Sent:** Tuesday, October 21, 2014 9:09 AM  
**To:** 'Silkaitis, Ray'  
**Subject:** RE: BLA 125031-S175, Neulasta Delivery Device - Clarification required; please submit by 4pm EST today  
**Importance:** High

Hi Ray,

With regard to the response provided below, the review team is requesting clarification on the following issues:

1. You claim that this device-drug combination product is not indicated for pediatric patients. Is this clearly labeled?
2. You claim that the DMSO extracts were tested undiluted in the *in vitro* genotoxicity assays. Please confirm that the DMSO extracts were tested undiluted in the *in vitro* Mouse Lymphoma Gene Mutation Assay, as DMSO is known toxic to cells at high concentrations.

Kindly provide the clarification requested by **2pm EST today, Tuesday, October 21, 2014.**

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

---

**From:** Silkaitis, Ray [<mailto:rsilkait@amgen.com>]  
**Sent:** Monday, October 20, 2014 12:13 PM  
**To:** McMullen, Rachel  
**Subject:** RE: BLA 125031-S175, Neulasta Delivery Device - Advice Information Request

Hello Rachel,

Amgen's responses to the FDA review team's request for information are attached. Please note that

the Toxicology report was just submitted with a previous response sent earlier today. If you are not able to find that report or if you would like for Amgen to re-send a copy, we will be happy to do so.

A formal amendment via the CDER gateway will be submitted.

Please let me know if there is additional information that is needed or if there are any additional questions.

Also, if you could confirm receipt of this email, it is appreciated

Kind Regards,  
Ray

Ray Silkaitis  
Amgen Inc.  
Device Regulatory  
Desk: 805-447-6865

(b) (6)

---

**From:** McMullen, Rachel [<mailto:Rachel.Mcmullen@fda.hhs.gov>]  
**Sent:** Friday, October 17, 2014 11:55 AM  
**To:** Silkaitis, Ray  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Importance:** High

Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. The (b) (4) of the Amgen Neulasta Delivery Device has introduced a new material, which is (b) (4), (b) (4). (b) (4) However, biocompatibility testing based on the (b) (4) has not been provided. In the Response to FDA Information Request of 03 October 2014, you state that the (b) (4) was evaluated following ISO 10993-17:2002, assuming 100% of each component would be released and have patient contact. You claim that under this maximum exposure assumption, the assessment showed negligible patient risk and acceptability of the (b) (4). However the risk assessment document cannot be located. Please provide a detailed risk assessment for the (b) (4), including toxicology evaluation of all three chemicals contained in the (b) (4). In your risk assessment report, please

include all calculations, such as the calculations for the MOS, the body weight for various user populations (adults, pediatrics), the reference doses/LOAELs/NOAELs, the limit of detections (LODs), the limit of quantifications (LOQs), the exposure assessment, and etc.

2. In response to the deficiency regarding the two *in vitro* genotoxicity testing where non-polar test extracts were not tested, you state “*Genotoxicity testing is more relevant with polar extracts than with non-polar extracts with the Neulasta drug product because drug product is an aqueous formulation*”. You further state that DMSO was justified as a second *in vitro* extraction medium in addition to water. To determine if your testing and justification provided is adequate, please address the following:

- To support that your devices will only have indirect contact via a polar solution, please clearly describe the formulation and composition of the intended drug solution.
- Please clarify if the DMSO extracts were tested at the neat levels (without being diluted). This information was not provided in your test reports submitted.

Please respond to the request no later than **1pm EST on Wednesday, October 20, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/22/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Friday, October 17, 2014 2:54:00 PM  
**Importance:** High

---

Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. (b) (4) of the Amgen Neulasta Delivery Device has introduced a new material, which is (b) (4).  
(b) (4) -  
(b) (4) However, biocompatibility testing based on the (b) (4) has not been provided. In the Response to FDA Information Request of 03 October 2014, you state that the (b) (4) was evaluated following ISO 10993-17:2002, assuming 100% of each component would be released and have patient contact. You claim that under this maximum exposure assumption, the assessment showed negligible patient risk and acceptability of the (b) (4). However the risk assessment document cannot be located. Please provide a detailed risk assessment for the (b) (4), including toxicology evaluation of all three chemicals contained in the (b) (4). In your risk assessment report, please include all calculations, such as the calculations for the MOS, the body weight for various user populations (adults, pediatrics), the reference doses/LOAELs/NOAELs, the limit of detections (LODs), the limit of quantifications (LOQs), the exposure assessment, and etc.
2. In response to the deficiency regarding the two *in vitro* genotoxicity testing where non-polar test extracts were not tested, you state "*Genotoxicity testing is more relevant with polar extracts than with non-polar extracts with the Neulasta drug product because drug product is an aqueous formulation*". You further state that DMSO was justified as a second *in vitro* extraction medium in addition to water. To determine if your testing and justification provided is adequate, please address the following:
  - To support that your devices will only have indirect contact via a polar solution, please clearly describe the formulation and composition of the intended drug solution.
  - Please clarify if the DMSO extracts were tested at the neat levels (without being diluted). This information was not provided in your test reports

submitted.

Please respond to the request no later than **1pm EST on Wednesday, October 20, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/17/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Thursday, October 16, 2014 4:23:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. Your response refers to a risk assessment report. However, the file does not contain the report. Please provide the report referred to as "ToxServices Report: Toxicological Assessment of [REDACTED] (b) (4) (referenced in Doc # INSPR020 Toxicological Review and Gap Analysis).
2. Also, throughout the biocompatibility documentation, there are references to the device 510(k) submission(s). However, the BLA does not contain the LoA for the device submissions. Please submit the LoA authorizing cross-reference to the applicable device 510(k)s.

Please respond to the request no later than **3pm EST on Friday, October 17, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/16/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Wednesday, October 15, 2014 4:13:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

***FDA comments to the response (e-mail) submitted on October 09, 2014:***

- 1. In your response to question 2, two different lot numbers for Neulasta PFS drug product are included: Neulasta PFS drug product, lot number 1011223 is used for post transportation CCI testing and PFS lot number 0010092754 is used for CCI test method validation by [REDACTED] (b) (4). Please clarify the discrepancy and confirm the correct lot number.*
- 2. What are the controls in place to prevent the inclusion of the approved Neulasta prefilled syringe containing 0.6mL drug product in place of Device PFS containing 0.64mL drug product in the delivery device kit.*

Please respond to the request no later than **1pm EST on Wednesday, October 20, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/15/2014

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

## Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

**When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes.** For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

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## APPLICATION INFORMATION

PDUFA Action Date: **October 27, 2014**  
Applicant Name: **Amgen Inc.**  
U.S. License #: **# 1080**  
STN(s): **STN 125031/175**  
Product(s): **Neulasta® (pegfilgrastim)**  
Summary: **Request for approval of a new combination product presentation**

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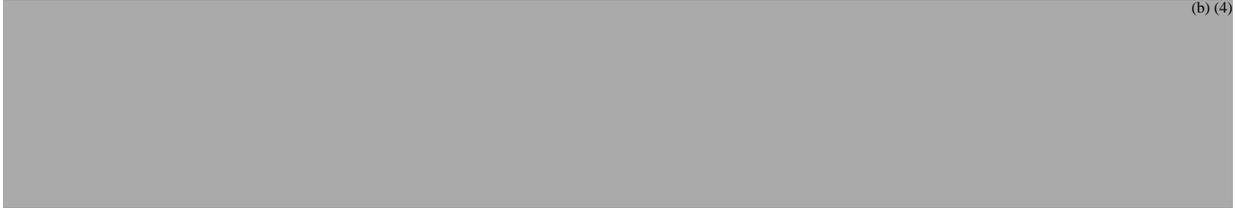
## FACILITY INFORMATION

Firm Name: **Amgen Inc.**  
Address: **Thousand Oaks, CA**  
FEI: **2026154**  
Short summary of manufacturing activities performed: **Drug substance manufacturing (fermentation, purification, PEGylation, bulk filtration); release and stability testing for both drug substance and drug product**

Firm Name: **Amgen Manufacturing, Limited**  
Address: **P.O. Box 4060, Road 31 km 24.6, Juncos, Puerto Rico**  
FEI: **1000110364**

Short summary of manufacturing activities performed: **Drug substance manufacturing (fermentation, purification, PEGylation, bulk filtration, release testing, stability testing).**

**Drug product manufacturing (formulation, sterile filtration, fill and finish, packaging/labeling, release testing, stability testing)**



Firm Name: **Insulet Corporation**

Address: **Oak Park Drive, Bedford, MA 01730**

FEI:

Short summary of manufacturing activities performed: **Device design and manufacture**



**OVERALL RECOMMENDATION**

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/s/  
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RACHEL S MCMULLEN  
10/09/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Wednesday, October 08, 2014 5:51:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. The response provided on October 6, 2014 regarding the final testing of the combination product kit stated that, (b) (4)  
(b) (4)  
(b) (4). As per 21 CFR 610.14, the contents of the final container, which is the kit, must be tested for identity. Please add an identity test for the kit in order to release the kit for market. The identity test does not necessarily have to be the same as performed for release of the pre-filled syringe, but the test should be adequate to identify the product in the kit and to distinguish it from any other product being processed in the same facility.
2. Section 3.2.P.2.6 states that ethylene oxide (EtO) is known to (b) (4)  
(b) (4) and that Amgen conducted studies to determine the level at which EtO will not affect product quality. The EtO study to justify the (b) (4) for residual EtO was not provided in the submission. Please provide the EtO study report in order to evaluate the acceptability of the residual EtO specification for the device.

Please respond to the request no later than **4pm EST on Wednesday, October 15, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/08/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Monday, October 06, 2014 8:25:00 AM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. You claim that the Neulasta Delivery Device proposed is non-pyrogenic. However, in sBLA 125031, you have only provided the LAL bacterial endotoxin testing, while the material mediated pyrogenicity testing (the rabbit pyrogen test) is not provided. Since the LAL test only assesses the endotoxins from Gram negative bacteria, and does not provide the necessary information with regards to the pyrogens from other microorganisms or materials, FDA considers that the rabbit pyrogen test is necessary to ensure that the device proposed does not contain any material mediated pyrogens that will contaminate the intended drug. Please provide a rabbit pyrogen test report, based on neat test extracts of the final finished subject device. We recommend that you follow the FDA Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers (June 2012) and ISO 10993 Biological evaluation of medical device, Part 11 Tests for systemic toxicity, for the test.
2. You state that the EtO residual testing did not meet the acceptance criteria for the initial 14 or 21 days following the sterilization. Please address the safety concerns related, describe your recommended risk mitigation procedure, and address the need for any information to be added into labeling regarding this issue.

Please respond to the request no later than **4pm EST on Thursday, October 9, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/06/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Friday, October 03, 2014 2:13:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

***FDA comments to the response submitted on September 26, 2014:***

*The amendment submitted on September 26, 2014 did not include the post-transportation CCI testing information for Neulasta PFS DP lot in work-in-progress (WIP) packaging. This CCI testing information was provided in the email dated September 24, 2014 as a response to the question # 2 of the IR dated September 19, 2014. Please amend the BLA with the CCI testing information.*

- 1. Submit the report, RPT-001425 "Amgen's Transport Validation Life Cycle Planning Operational Qualification Test Sequence".*
- 2. Please provide the following information regarding the CCI test:*
  - a. critical parameters (pressure and time of exposure of samples to the dye)*
  - b. drug product lots used for CCI qualification*
  - c. preparation of positive (with the size of the needle, diameter of the microtubes used) and negative controls*
  - d. clarify if a visual positive control was included*
  - e. sensitivity of the method (LOD) as a function of breach size*
  - f. describe in detail how the LOD of the test was calculated*

Please respond to the request no later than **4pm EST on Thursday, October 9, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs

Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/03/2014

**From:** McMullen, Rachel  
**To:** "Silkaitis, Ray"  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Friday, October 03, 2014 2:00:00 PM  
**Importance:** High

---

Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

**Information Request for STN 125031/175 Neulasta Delivery Device PAS:**

1. In sBLA 125031, you state that the Amgen Neulasta Delivery Device proposed is based on Insulet Eros OmniPod. You further state that the patient contacting components of both devices are composed of the same materials, dimensions and are built using the same manufacturing processes (b) (4). (b) (4). To evaluate the biocompatibility of the (b) (4), please address the following:

- a) (b) (4). Please identify the CAS number, composition, health problems associated with the (b) (4), and toxicological data (reference doses, LD50, NOAEL, and LOAEL). This information may be contained in the Material Safety Data Sheet (MSDS) or Technical Specification Sheet.
- b) In sBLA 125031, you have provided the biocompatibility testing based on the Eros OmniPod including the (b) (4). You claim that based on your risk assessment of the (b) (4), the Eros OmniPod and the Amgen Neulasta Delivery Device are toxicologically equivalent. Please be advised that FDA considers (b) (4). Risk assessment based on raw materials may have limitations and may not represent the final finished subject device. Therefore we consider that biocompatibility testing based on the (b) (4) is inadequate to address the safety concerns related to the clinical use of the (b) (4). Please provide revised biocompatibility testing reports using the final finished (b) (4) based on the device's exposure type and duration.

2. In sBLA 125031, you have provided two *in vitro* and one *in vivo* genotoxicity testing for the Eros Pod Fluid Path Assembly. However the two *in vitro* genotoxicity testing (the Ames Reverse Mutation assay and Mouse Lymphoma Gene Mutation assay) was

based solely on polar test extracts (0.9% NaCl and DMSO extracts), while non-polar device extracts were not tested. Since both polar and non-polar residues can be extracted and leached from the device during its use, we believe that testing of both polar and non-polar device extracts is necessary. Please provide revised study report for the two *in vitro* genotoxicity testing, using both polar and non-polar extracts.

Please respond to the request no later than **4pm EST on Wednesday, October 8, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/03/2014

**From:** McMullen, Rachel  
**To:** ["Silkaitis, Ray"](#)  
**Subject:** BLA 125031-S175, Neulasta Delivery Device - Advice Information Request  
**Date:** Thursday, October 02, 2014 2:22:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

**Information Request for STN 125031/175 Neulasta Delivery Device PAS:**



**Electrical Equipment and Separation Distances**

- Identify specific examples of electrical equipment to avoid.
- If exposure is likely, such as microwaves or other common appliances, provide separation distances.

Please respond to the request no later than **8am on Friday, October 3, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Please also provide a  <sup>(b) (4)</sup>, by **Monday, October 6, 2014.**

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
10/03/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device - Advice/Information Request  
**Date:** Friday, September 26, 2014 5:29:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information. Please note there are 38 questions in total.

**Information Request for STN 125031/175 Neulasta Delivery Device PAS:**

1. The Description of Manufacturing Process and Process Controls section, 3.2.P.3.3, states that the (b) (4). It was not clear from the submission if the kit components will be pulled for testing following kit assembly or prior to assembly. Please clarify *a)* when quality testing is performed on the product in pre-filled syringes and *b)* whether identity testing is performed on the product in the final kit (as required by 21 CFR 610.14).
2. The submission did not provide the batch sizes for the PFS to be co-packaged with the device and for the intended commercial kit. Please provide the intended commercial batch sizes.
3. The DP lot numbers shown in the in-use stability study (data shown in section 3.2.P.8.3) do not correspond to the DP lot numbers in the batch analysis table. Please clarify this difference in lot numbers and whether the DP lots shown in batch analysis table were used for the in-use stability study.
4. The submission references the subcutaneous delivery cannula as a (b) (4). The report, RPT-043456, notes that this is a (b) (4). We also note that several software versions have implemented changes to address occlusion detection and false occlusions (e.g., SW versions 10.2, 10.3, 12.0, 15.0, and 16.0). The issues precipitating the continual updating of occlusion related requirements and (b) (4) Please address the following issues:
  - a. Describe the reasons for the software and (b) (4), including references to applicable study reports and provide evidence verifying and validating the effectiveness of the cumulative modifications in order to demonstrate that the final design effectively mitigates occlusions.
  - b. Given the implementation of these changes, identify the expected rate of occurrence of occlusions and reference the source of your assessment.
5. The pulse rate specified in software for drug delivery was originally specified at (b) (4). In software version 7.0, the pulse rate was changed to (b) (4). Software version 10.2 changed the delivery pulse rate to (b) (4). Please describe the impact the pulse rate has on the drug delivery and describe the reasoning for the (b) (4).

(b) (4) pulse rate delivery time.

6. A number of the design verification reports identified manufacturing related defects (e.g., misassembled / improperly installed components, short circuited components, tolerance stack-ups, etc.). Please describe how these device manufacturing issues identified throughout design verification studies have been dispositioned and mitigated for the commercial product.
7. Many test reports are several years old. Please identify what, if any, modifications are implemented into the commercial version compared to the samples that were tested, and provide an assessment concluding that the changes would not impact the test results, or provide new testing as needed.
8. The requirements traceability document references test protocol and report, TP/TR14-017, as demonstrating satisfaction of requirement # RS-002048-1,. "The device shall deliver a minimum volume of 0.6mL." Section 6.1.3.3 references test protocol TP14-026. This test protocol and associated report is not include in BLA 125031 and is not referenced in the design requirements traceability. Provide the protocol and report, TP/TR14-026 and update the traceability matrix, as needed.
9. It is unclear when the priming of the cannula with Neulasta occurs. Describe when cannula priming occurs and controls in place to prevent unintended Neulasta delivery during priming, if applicable.
10. We have completed a review of the Mechanical Vibration and Shock testing. Please address the following issues identified in our review:
  - a. Section 6.1.6 of TP14-017 states the following "...and in accordance with the values stated in **Error! Reference source not found.**" There are also other locations throughout this document with the same error. Please provide an updated protocol document with the errors corrected.
  - b. The ISO 11608 standard referenced for vibration and shock testing references another standard for test methods, IEC 60068-2-64 and IEC 60068-2-27, respectively. Please explain how the test methodology is applicable to the conditions to which Neulasta Delivery Device will be subjected.
  - c. Test report, TR14-017, reports results for visual inspection per ISO 11608 Section 11, but does not specify which part of the ISO 11608 series is referenced. Please update the report to identify which part the ISO 11608 is series is being referenced and provide the report.
11. The submission describes design requirements for delivery of 0.6mL in (b) (4) (b) (4) (PDD, ID#3) and delivery of a minimum volume of 0.6mL (PDD, #1). The test reports for Delivery Time (TR12-075) and Hold Up Volume (TR12-154) conclude that delivery of 0.6mL occurs in (b) (4) and that a minimum volume of 0.6mL is delivered. The variability of the expected value, 0.6mL delivered, is not directly addressed by either report. Provide data demonstrating that the expected value of 0.6mL Neulasta is reliably delivered.

12. As described in labeling, design requirements and design verification testing documents, the Neulasta Delivery Device is designed to deliver 0.6 mL of Neulasta (b) (4). (b) (4) There does not appear to be a corresponding requirement to constrain the device from delivering Neulasta too quickly (e.g., flow rate must be x.y mL/min or delivery shall not complete prior to x minutes).. Identify a complete set of requirements needed to assure that a safe and effective dose of Neulasta is delivered and provide the relevant evidence to assure reliable implementation of the requirement.
13. The Delivery Time design verification report, TR12-075, Rev B, Dated April 2013, is intended to demonstrate that the delivery device meets the design requirement for delivery of 0.60mL in (b) (4). The description of device samples is described as 59 Neutime Devices. The relationship between the test samples and the proposed commercialized device is unclear. Provide a description of any differences between test samples used for Delivery Time evaluation and the proposed commercial device and include explanation for how each difference would not impact Delivery Time performance. Also, verify that Delivery Time and other associated delivery accuracy tests were conducted with Neulasta.
14. Multiple test reports describe removal or addition of a (b) (4). The submission does not describe the function of this component and the reports do not explain why the component should be removed or added and does not explain how its removal / addition could impact the results of various tests. Provide a description of the component's function and provide an explanation for why it is removed / added to certain tests and its impact on results.
15. The ESD & RF Immunity test protocol, TP14-025, specifies contact and air discharge requirements for ESD, as required by ISO 11608-1. Please explain how these requirements are valid for a body-worn device versus the hand-held injector covered by ISO 11608.
16. Based on the data provided in ESD & RF Immunity Test Report, TR14-025, the device failures occurred when exposed to air discharge of (b) (4). Identify the failure rate of devices exposed to (b) (4) and provide explanation for acceptability of the failure rate.
17. Several device requirements reference TP/TR12-026, which is software verification document, and TP/TR 12-002, which is hardware verification document, as verification of implementation. Both documents are large and the satisfaction of the requirements is not explicitly clear from a review of these documents. Please specify where in these documents the requirements RS-002048-2, RS-002048-8, RS-002048-11, RS-002048-15, RS-002048-21, RS-002048-27, and RS-002048-30 were verified. Also verify that the hardware and software evaluated in TP/TR12-026 and TP/TR12-002 are representative of the proposed commercial combination product.
18. The Device Battery Life and LED Indicator protocol, TP12-092, requires analysis and development of aging test to evaluate battery performance after storage on the shelf and assembled in device shelf life. The protocol does not include the analysis, accelerated test method, and methods validation to support the results of TR12-092. The analysis does appear to be included in TP13-109. Please clarify if the analysis referenced in TP12-092 is found in TP13-109. Additionally, the attachment 1 analysis from TP13-109 states the shelf life requirements were assumed at room temperature even though the

device is stored at 2-8C for 3 years. Please explain why the room temperature assumption is valid, rather than worse case low temperature that reflects the actual storage condition. Please revise the analysis and repeat the test as needed. Please also provide information supporting the validity of the accelerated test method used in TP13-109.

19. The device design traceability matrix, RPT-043057 Ver 1.0, states that TP/TR12-080 is the protocol and report verifying implementation of RS-002048-14. This requirement states that the device shall power up at less than 0.60ml fill into the device. A review of TP/TR12-080 demonstrates that the testing addresses occlusion and delivery pressure. No mention of device activation is included within the purpose of the protocol or acceptability criteria, or the results of the testing. Further, the trace matrix references TP/TR12-080, Rev A, while only Rev B has been submitted to the BLA. Please address the following:
  - a. Describe how the device activation function operates.
  - b. Identify the acceptable success criteria and provide an explanation needed to support the adequacy of the criteria.
  - c. Identify the correct protocol and report verifying implementation of this requirement or update the referenced protocol and report to explicitly address RS-002048-14.
20. The design requirement RS-002048-15 states that the device shall alarm if it detects a failure to complete delivery of (b) (4). The reference design verification tests include software verification (TP/TR 12-026, Rev A-G) and occlusion / delivery pressure testing (TP/TR12-080, Rev B. It is not certain from the information provided that the only failure modes leading to failure to achieve the requirement stem from software, occlusions and delivery pressure. Please identify the causes leading to the failure state and reference additional controls and verification tests, as appropriate.
21. Design requirement RS-002048-54 states that *“the device shall perform automated functions (RS-002048-24, RS-002048-25, RS-002048-30) and drug delivery (RS-002048-1) with (b) (4) at a confidence level of ≥95% under a constant backpressure of (b) (4) while design requirement RS-002048-16.1 states that the “Device when applied and cannula fully inserted, should deliver the drug into a peak back pressure of at least (b) (4) even when tip of the cannula is occluded.”* There is an apparent discrepancy between these two requirements. Please update the requirements document submitted to the BLA to address the discrepancy and provide an explanation supporting the validity of the final requirement selected.
22. The traceability matrix, RPT-043057, references numerous protocol and reports provided by Insulet Corp. The test protocols and reports reference Insulet design specifications. It is uncertain the design specifications referenced in the test protocols and reports align with the design requirements specifications referenced in the Neulasta Delivery Device Traceability Matrix RPT-043057. Verify that the referenced specifications being verified in the test protocols / reports align with the requirements specifications referenced in RPT-043057.

23. The device requirement RS-002048-17 states that the device shall deliver the original volume of the reservoir (b) (4). The NDD Traceability Matrix cites TP/TR12-090 as evidence of requirements verification. However, our review of the test protocol and report shows that the testing did not verify that the device delivers the original volume of the reservoir (b) (4) as specified. Rather, the test verified zero observed leaks from the (b) (4). Please provide evidence to support verification of the requirement RS-002048-17 in the proposed commercial device constituent.
24. Device requirement RS-002048-18 states that the device shall contain (b) (4) when filled with  $\geq 0.64$ ml of fluid from a bubble free source. The protocol and test report (TP/TR 12-122) do not appear to be sufficient verification of the requirement because the test method does not appear to evaluate the actual use of the combination product and any air that is observed is removed prior to measurement. Please provide an explanation supporting the requirement, including analysis of how air impacts the safe and effective use of the system (e.g. harm from air infusion, or impact of air on device performance). Also, provide an explanation for how the TP/TR12-122 demonstrate verification of the requirement or provide additional evidence.
25. Requirements specifications RS-002048-23, RS-002048-26, and RS-002048-61 cite PTC 019382 and RPT 050399 as evidence of verification. We are unable to locate these documents within the BLA. Please provide the documents.
26. Requirement, RS-002048-26 states that the device shall have a reservoir inspection window with EMPTY and Full graduations. The reports, TP/TR12-138, verify the existence of the inspection window with EMPTY, FULL, and (b) (4). However, there does not appear to be a report verifying the acceptable accuracy of the graduations. Described the functionality of this mechanism and provide evidence demonstrating the accuracy of the reservoir inspection window is acceptable and update the design control documents (e.g., requirements specifications, traceability matrix, etc.) as necessary to address graduation accuracy.
27. Test protocol and report, TP/TR12-136, reference a Pink Slide Insert that denotes an unfired device. Verify if this component exists in the proposed commercial version of the Neulasta Delivery Device.
28. Requirement, RS-002048-27, states that the device shall be single use only. The cited verification report is TP/TR 12-026, Rev A-G, which is a software verification report. Please describe how the single-use only requirement is addressed through software and not through other means (e.g., mechanical / hardware requirements).
29. Requirement, RS-002048-100, states that the device (b) (4). The cited verification reports, TP/TR12-135, addresses leaking only during the filling process, and TP/TR13-098, addresses leaking of packaging following device shipping. Please provide evidence demonstrating satisfaction of the requirement during (b) (4). Update the traceability matrix, as necessary, to cite additional evidence.
30. We have completed a review of the Neulasta Delivery Device shelf life study provided in TP/TR13-133. There are several issues identified in our review that need to be

addressed, including the Severity A Failure Rate, missing data from the 36-month accelerated aging arm of the study, ongoing corrective action investigations (e.g., CAPA-2014-00007), and no protocol to address on-going real-time studies. Please provide the following:

- a. Several device functionality studies conducted under TP13-133 reported Severity A failures. The conclusion stated in the report TR13-133 indicate that the failures are not related to the shelf life testing. For example, mechanical tolerance stack-up is cited as one cause. However, other failures did not include a conclusion supporting the relationship of the failure to the shelf life. Provide an explanation supporting your conclusions that the Severity A failures are not related to shelf life.
  - b. Provide the 36 month accelerated aging results.
  - c. Design changes to address mechanical stack-up are referenced in the report. Describe any impact of this change on device performance and your conclusion that it does not require re-verification of device performance studies.
  - d. The report cites CAPA-2014-00007. Provide additional information regarding the status of this investigation and its impact on the device constituent.
  - e. Provide a protocol to address the use of real-time shelf life data, including defined acceptability criteria and action points. The protocol should also include acceptability criteria for the battery.
  - f. Define Severity A and Severity B failures.
31. The sterilization residuals are identified in parts per million. The relevant standard, ISO 10993-7, allowable limits for ethylene oxide residuals is less than 4 mg of EO and less than 9 mg of ECH in 24 hour period. Provide the information supporting conformance to these limits.
32. You have provided your Software Traceability Analysis (TA) in your submission. However, it appears that you have not included identified hazards in your hazard analysis. Therefore, the Agency is not certain if all identified hazards are properly mitigated. Please revise your software TA to include all identified hazards.
33. The description of NDD software states that failures occurring during the 27 hour waiting period cause visible and audible alarms. Please describe which failure states are being monitored by software, timing interval of software self-tests, identify the test report location where these self-tests are verified, and verify that the testing was conducted on production software loaded onto the device.
34. The description of NDD firmware states that the radio frequency communicator functions are active until the NDD is activated by filling with Neulasta. Please describe the purpose for leaving the RF functions active until its point of use.
35. The submission contains a document titled, "Neulasta Delivery Device, Device Requirements Document" in BLA 125031, Sequence 186, Section 3.2.R. Document

Number RS-002048, Version 12.0, dated March 28, 2014. The document captures the configuration of the Neulasta Delivery Device expected for commercial launch and is intended to translate user needs, risk controls, and applicable human factors input into device requirements for a drug delivery device for Neulasta. Requirements are segregated into three categories: Critical, Key, and Desired. There are several Key Characteristics that appear to qualify as Critical Characteristics, which include:

- a. RS-002048-16: The device shall be capable of a peak delivery pressure of (b) (4)
- b. RS-002048-16.1: Device when applied and cannula fully inserted, should deliver the drug into a peak back pressure of at (b) (4) even when tip of the cannula is occluded.
- c. RS-002048-18: The device shall contain (b) (4) of air when filled with  $\geq 0.64$ ml of fluid from a bubble free source
- d. RS-002048-32: The device, as worn shall be waterproof in conformance with IPX8: Submersed in 8ft of water for one hour.
- e. RS-002048-61: The device shall have a cannula and needle inspection window

Please recode these design requirements as Critical Characteristics.

36. Please describe how the cannula insertion needle is prevented from moving or being accessed following retraction.
37. Identify requirements implemented to achieve the single use of the NDD and provide any data necessary to verify effectiveness.
38. The submission does not appear to contain the necessary information to evaluate the use of the Neulasta 0.64mL PFS for injection into the Neulasta Delivery Device. Please provide information and test reports to address the following:
  - a. Reliability of the PFS needle safety guard.
  - b. Injection force requirements specifications to fill the NDD.
  - c. Evidence demonstrating that risk of PFS needle bending or breakage during NDD filling process is adequately mitigated.

Please respond to the request by **COB Friday, October 3, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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/s/  
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RACHEL S MCMULLEN  
09/26/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray \(rsilkait@amgen.com\)](mailto:rsilkait@amgen.com)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device - Advice/Information Request  
**Date:** Friday, September 19, 2014 4:28:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

1. Please clarify if the approved commercial Neulasta PFS shipping validation studies covered the distance for the new route, from AML to the (b) (4) (b) (4).
2. Please provide shipper transportation test results performed for the final kit per ASTM D4169 including the number of units tested for each of the attributes and clarify if CCI of the PFS was tested after this simulated transportation test.
3. Identification of the site responsible for the final combination product and the name of the firm that owns all device specifications.
4. Summarize what supplier controls /agreements are established with all of its suppliers including the firm who owns responsibility for each device component
5. Summarize the supplier controls established by the firm to demonstrate is has validated and reviewed the Sterilization site through its supplier agreements.

Please respond to the request by **COB Wednesday, September 24, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
09/19/2014

**From:** McMullen, Rachel  
**To:** "[Silkaitis, Ray](#)"  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device - Advice/Information Request  
**Date:** Tuesday, September 16, 2014 10:34:00 AM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the review team is requesting the following information.

Please provide the design requirements specifications and traceability documents for the Neulasta Delivery Device. In your submission, documents titled "design input requirements" and "design outputs" only provide the SOP for creating the design documents.

Please respond to the request by **COB Thursday, September 18, 2014** via email, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
09/16/2014

**From:** McMullen, Rachel  
**To:** [Silkaitis, Ray](#)  
**Subject:** BLA 125031/S-175, Neulasta Delivery Device - Advice/Information Request  
**Date:** Friday, September 12, 2014 3:41:00 PM  
**Importance:** High

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Dear Mr. Silkaitis,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the reviewers have identified the following deficiencies during their review. Please respond to the deficiencies by the date provided.

The following deficiencies have been identified in the review of the STN 125031/175

1. The extractables and leachables studies conducted on the delivery device resulted in identification of various organic compounds for which Amgen performed a toxicological risk assessment. Based on the risk assessment, the delivery device was concluded to have a similar safety and efficacy profile as the currently marketed Neulasta product. The toxicological risk assessment for the extractables and leachables report was not provided in the supplement. Please provide the risk assessment report. Be sure to include in tabular format the levels of the extractables and leachables found, the known toxicity profile for each, and the expected patient exposure on a dose basis in order to support the conclusion that the delivery device is as safe and efficacious for use as the currently marketed Neulasta product.
2. The Neulasta delivery device dynamic characterization study examined the impact of vibration on stability of the product in the device. In order to evaluate the adequacy of the study, please provide a justification for the study conditions (b) (4)  
(b) (4)  
*i.e.* explain how the study conditions are relevant to the proposed real-life use. In addition, please provide raw data from the dynamic characterization study.
3. A shipping validation study for the device pre-filled syringe (PFS) to the kit manufacturing site was not conducted. The justification for not conducting the shipping validation study was that the shipping conditions for the device PFS is the same as the licensed PFS Neulasta product. However, it is not clear from the submission how the device PFS shipping route compares to the conditions studied in support of the original licensure application for Neulasta PFS. Please provide an explanation and any data to support the use of the Neulasta PFS shipping validation study for the device PFS.
4. A shipping validation study for the Neulasta delivery device kit was conducted. However, the study report was not provided for review. Please provide the kit shipping validation study report.
5. The batch analysis section Table 1 lists drug product lots manufactured as a kit component with the delivery device. Drug product lot # 0010101740 is listed as being filled at ATO (Amgen Thousand Oaks, CA) rather than AML, (Amgen Juncos, PR). The submission states that AML is the site of Neulasta PFS fill for both the manually applied product and the product co-packaged with the delivery device. Please provide a clarification of where the future manufacturing site will be for the device PFS and why the drug product lot # 0010101740 was made at ATO.

Please submit your response by **noon on Friday, September 19, 2014** via e-mail, so the review can proceed. Following that, please submit the information formally to the BLA.

Kindly confirm receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993

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RACHEL S MCMULLEN  
09/12/2014

**MANDATORY:** Send a copy of the consult request form to the Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_

Assigned to: \_\_\_\_\_

Date Assigned: \_\_\_\_\_

Assigned by: \_\_\_\_\_

Completed date: \_\_\_\_\_

Reviewer Initials: \_\_\_\_\_

Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center: CDRH  
Division: GHDBP  
Mail Code: HF  
Consulting Reviewer Name: Alan Stevens  
Building/Room #:  
Phone #:  
Fax #:  
Email Address:  
RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER  
Division: Hematology Products  
Mail Code: HF 161  
Requesting Reviewer Name: Pat Dinndorf  
Building/Room #:  
Phone#: 240-402-4574  
Fax #:  
Email Address: rachel.mcmullen@fda.hhs.gov  
RPM/CSO Name and Mail Code: Rachel McMullen  
Requesting Reviewer's Concurring Supervisor's Name: Al Deisseroth

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: 9/3/2014

**Requested Completion Date:** 10/1/2014

Submission/Application Number: sBLA 125031  
(Not Barcode Number)

Submission Type: \_\_\_\_\_  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: 6/27/2014

Official Submission Due Date: 10/20/2014

Name of Product: Neulasta® (pegfilgrastim)

Name of Firm: Amgen, Inc.

**Intended Use:** This submission proposes to have the pegfilgrastim co-packaged with a drug delivery device (pre-filled syringe) designed to facilitate the administration of Neulasta® (pegfilgrastim) according to the approved dosing schedule and route of administration for which pegfilgrastim is currently approved.  
This will be reviewed under a 4 month clock with a PDUFA date of 10/27/14.

**Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):**

The Division is requesting review of the patient IFU for the delivery device.

The link below provides the applicant's data to support the proposal for the combination product (pre-filled syringe):  
\\cdsesub1\bla\cCTD\_Submissions\STN125031\0186\m3\32-body-data

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

Amgen had a meeting with the Agency on November 7, 2011 where there was discussion of the development/registration plans for the use of the combination device. A copy of the preliminary meeting minutes is attached for reference.  
The primary clinical study supporting the pegfilgrastim delivery device is a bio-equivalence study to be reviewed primarily by clinical pharmacology.  
The sponsor has also proposed partial labeling for the device. The draft container label components are in Module 1

The Division is requesting CDRH's review of the patient IFU for the delivery device.

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RACHEL S MCMULLEN  
09/04/2014

From: McMullen Rachel  
To: [Kraft, Donna](#)  
Subject: BLA 125031 Neulasta - Please submit Form FDA 3674  
Date: Wednesday, August 06, 2014 3:15:00 PM  
Importance: High

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Good afternoon Donna,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), we note that Form FDA 3674, "Certification of Compliance, was not included in the submission

-

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendmentsToTheFDCA/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>

Additional information regarding Title VIII of FDAAA is available at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html> Additional information for registering your clinical trials is available at the Protocol Registration System website

<http://prinfo.clinicaltrials.gov/>

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 125031/175** submitted on June 27, 2014 and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993  
[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
08/06/2014

From: McMullen, Rachel  
To: "Kraft, Donna"  
Subject: BLA 125031 Neulasta - Advice/Information Request  
Date: Friday, August 01, 2014 3:58:00 PM  
Importance: High

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Dear Ms. Kraft,

In reference to your Supplemental Biologics License Application 125031/S-175 for Neulasta® (pegfilgrastim), the reviewers have identified the following deficiencies during their preliminary review. Please respond to the deficiencies by the date provided.

*The following deficiencies have been identified in the review of the STN 125031/175*

1. Please update the Table 1, 'List of Device Manufacturers and Testers' in Section 3.2.P.3.1 – Manufacturer(s) of Neulasta Delivery Device with FEI numbers of the manufacturing sites.
2. Regarding the Pegfilgrastim microbial challenge testing,
  - a. Please justify the use of (b) (4) as a control media. The initial viable concentration of the inocula of test organisms are generally estimated using TSA/SDA.
  - b. You state that inoculated samples were compared to their respective controls for evaluating the microbial growth. Please clarify if the growth of the inoculated samples are compared to that of the control media and if the answer is yes, provide the growth of the test organisms in the control medium at various time points.
  - c. You mention that the test organisms were inoculated to Pegfilgrastim samples to achieve a concentration of (b) (4). According to test result data, for example, the colony counts for *Pseudomonas aeruginosa* at 0 time point were (b) (4) (b) (4) for control and (b) (4) (b) (4) for test sample. Please clarify the discrepancy and

*provide the inoculum level used for this study.*  
*d. Please provide the protocol used to execute this study.*

Please submit your response by COB Tuesday, August 12, 2014 via e-mail, so the review can proceed.

Kindly acknowledge receipt of this email.

Thank you,

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Avenue | Silver Spring, MD 20993  
[Rachel.McMullen@fda.hhs.gov](mailto:Rachel.McMullen@fda.hhs.gov) | 240-402-4574

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RACHEL S MCMULLEN  
08/01/2014

**MANDATORY:** Send a copy of the consult request form to the Office of Combination Products as follows:  
--Originating Center: When the consult request is initiated.  
--Consulting Center: When the consult is completed.  
Email: combination@fda.gov or FAX: 301-427-1935

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_  
Assigned to: \_\_\_\_\_  
Date Assigned: \_\_\_\_\_  
Assigned by: \_\_\_\_\_  
Completed date: \_\_\_\_\_  
Reviewer Initials: \_\_\_\_\_  
Supervisory Concurrence: \_\_\_\_\_

### Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center:   
Division: Office of Compliance  
Mail Code: HF  
Consulting Reviewer Name:  
Building/Room #:  
Phone #:  
Fax #:  
Email Address:  
RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER  
Division: Hematology Products (On Behalf of BMAB reviewer)  
Mail Code: HF161  
Requesting Reviewer Name: Lakshmi Narasimhan (BMAB)  
Building/Room #:  
Phone#: 240-402-4574  
Fax #:  
Email Address: rachel.mcmullen@fda.hhs.gov  
RPM/CSO Name and Mail Code: Rachel McMullen  
Requesting Reviewer's Concurring Supervisor's Name: Pat Hughes (BMAB)

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: 7/31/2014

**Requested Completion Date:** 8/15/2014 per BMAB request

Submission/Application Number: sBLA 125031  
(Not Barcode Number)

Submission Type: sBLA  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: 6/27/2014

Official Submission Due Date: 10/20/2014

Name of Product:  Name of Firm:

Intended Use:

**Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):**

The Division is requesting initial input regarding filing before the August 26, 2014 filing date.  
The link below provides the applicant's data to support the proposal for the combination product (pre-filled syringe):  
[\\cdsesub1\bla\CTD\\_Submissions\STN125031\0186\m3\32-body-data](#)

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

Amgen had a meeting with the Agency on November 7, 2011 where there was discussion of the development/registration plans for the use of the combination device. A copy of the preliminary meeting minutes is attached for reference.

BMAB contacted the Division of Hematology Products to request CDRH Office of Compliance's assessment of the suitability of the new combination product presentation (pegfilgrastim in pre-filled syringe co-packaged with a drug delivery device) and the need for inspection of the following sites. BMAB would like CDRH to provide the scope of the inspection if an inspection is necessary. The list of inspection sites is attached.

Reference ID: 3603668

**From:** [Narasimhan, Lakshmi](#)  
**To:** [McMullen, Rachel](#)  
**Cc:** [Hughes, Patricia](#)  
**Subject:** FW: CDRH/OC consult request for PAS STN125031/175 Neulasta (Pegfilgrastim)  
**Date:** Thursday, July 31, 2014 10:50:05 AM

---

Hi Rachel,

Since the PDUFA Date for this submission is October 27, 2014, could you please request for a response from CDRH by 15 Aug 2014.

Thanks,

Lakshmi

---

**From:** Narasimhan, Lakshmi  
**Sent:** Thursday, July 31, 2014 9:53 AM  
**To:** McMullen, Rachel  
**Cc:** Hughes, Patricia  
**Subject:** CDRH/OC consult request for PAS STN125031/175 Neulasta (Pegfilgrastim)

Hi Rachel,

BMAB would like to request a consult to CDRH/OC for PAS STN125031/175 (Pegfilgrastim) to assess the suitability of the new combination product presentation (pegfilgrastim in pre-filled syringe co-packaged with a drug delivery device) and the need for inspection of the following sites. We would like CDRH to provide the scope of the inspection if an inspection is necessary.

(b) (4)



Short summary of manufacturing activities performed: (b) (4)

(b) (4)

Firm Name: Insulet Corporation

Address: Oak Park Drive, Bedford, MA 01730

FEI:

Short summary of manufacturing activities performed: Device design and manufacture

(b) (4)





Thanks,

Lakshmi

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/s/  
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RACHEL S MCMULLEN  
08/01/2014

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

## Instructions:

The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS “Communication Group” is “BLA Administrative Form” and the “Communication Name” is “FRM-BLAADMIN-61 – Establishment Evaluation Request Form.”

TB-EERs should be submitted:

- 1) within 10 business days of the application filing date (initial TB-EER)
- 2) 15-30 days prior to the planned action date (final TB-EER)

**When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes.** For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

---

## APPLICATION INFORMATION

PDUFA Action Date: **October 27, 2014**  
Applicant Name: **Amgen Inc.**  
U.S. License #: **# 1080**  
STN(s): **STN 125031/175**  
Product(s): **Neulasta® (pegfilgrastim)**  
Summary: **Request for approval of a new combination product presentation**

---

## FACILITY INFORMATION

Firm Name: **Amgen Inc.**  
Address: **Thousand Oaks, CA**  
FEI: **2026154**  
Short summary of manufacturing activities performed: **Drug substance manufacturing (fermentation, purification, PEGylation, bulk filtration); release and stability testing for both drug substance and drug product**

Firm Name: **Amgen Manufacturing, Limited**  
Address: **P.O. Box 4060, Road 31 km 24.6, Juncos, Puerto Rico**  
FEI: **1000110364**

Short summary of manufacturing activities performed: **Drug substance manufacturing (fermentation, purification, PEGylation, bulk filtration, release testing, stability testing).**

**Drug product manufacturing (formulation, sterile filtration, fill and finish, packaging/labeling, release testing, stability testing)**



Firm Name: **Insulet Corporation**

Address: **Oak Park Drive, Bedford, MA 01730**

FEI:

Short summary of manufacturing activities performed: **Device design and manufacture**



## OVERALL RECOMMENDATION

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/s/  
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LAKSHMI RANI NARASIMHAN  
07/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>			
TO: <b>CDER-DMPP-PatientLabelingTeam</b>			FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Rachel McMullen, Division of Hematology Products, (240)-402-4574</b>		
REQUEST DATE: <b>July 22, 2014</b>		NDA/BLA NO.: <b>sBLA 125031/S-175</b>	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)		
NAME OF DRUG: <b>Neulasta® (pegfilgrastim)</b>	PRIORITY CONSIDERATION: <b>Priority</b>	CLASSIFICATION OF DRUG: <b>Biologic-Device Combination Product</b>	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) <b>October 1, 2014</b>		
SPONSOR: <b>Amgen, Inc.</b>			PDUFA Date: <b>October 27, 2014 (4 month Goal Date)</b>		
<b>TYPE OF LABEL TO REVIEW</b>					
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input checked="" type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b> <a href="\\cdsesub1\bla\CTD_Submissions\STN125031\0186\m1">\\cdsesub1\bla\CTD_Submissions\STN125031\0186\m1</a> (Section 1.14) The sponsor has also proposed partial labeling for the device. The draft container label components are in Module 1.					
<b>Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.</b>					
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Amgen had a meeting with the Agency on November 7, 2011 where there was discussion of the development/registration plans for the use of the combination device. A copy of the preliminary meeting minutes may be referenced here: <a href="\\cdsesub5\EVSPROD\BLA125031\0186\m1\us\correspondence-mtgs.pdf">\\cdsesub5\EVSPROD\BLA125031\0186\m1\us\correspondence-mtgs.pdf</a> This submission is a CMC prior approval supplement, proposing pegfilgrastim as a combination product in a pre-filled syringe. The primary clinical study supporting the pegfilgrastim delivery device is a bio-equivalence study to be reviewed primarily by clinical pharmacology. This will be reviewed under a 4 month clock with a PDUFA date of 10/27/14. The Division is requesting review of the patient package insert and the new instructions for use. <u>The Division is requesting initial input regarding filing before the August 26, 2014 filing date.</u> Link to the labels: <a href="\\cdsesub1\bla\CTD_Submissions\STN125031\0186\m1">\\cdsesub1\bla\CTD_Submissions\STN125031\0186\m1</a> Filing/Planning Meeting: <b>August 26, 2014</b> Mid-Cycle Meeting: TBD Labeling Meetings: TBD Wrap-Up Meeting: <b>October 20, 2014</b>					
SIGNATURE OF REQUESTER <b>Rachel McMullen</b>					
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS		

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/s/  
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RACHEL S MCMULLEN

07/22/2014

Review of the patient package insert and the new instructions for use is requested

# REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO:  <b>CDER-OPDP-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Rachel McMullen, Division of Hematology Products, (240)-402-4574</b>	
REQUEST DATE <b>July 22, 2014</b>	IND NO.	NDA/BLA NO. <b>sBLA 125031/S-175</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG <b>Neulasta® (pegfilgrastim)</b>		PRIORITY CONSIDERATION <b>Priority</b>	CLASSIFICATION OF DRUG <b>Biologic-Device Combination Product</b>  DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)  <b>October 1, 2014</b>
NAME OF FIRM: <b>Amgen, Inc.</b>		PDUFA Date: <b>October 27, 2014 (4 month Goal Date)</b>	

## TYPE OF LABEL TO REVIEW

<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION  <b>For OSE USE ONLY</b> <input type="checkbox"/> REMS
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**EDR link to submission:** [\cdsesub1\bla\CTD Submissions\STN125031\0186\m1](#) (Section 1.14)

The sponsor has also proposed partial labeling for the device. The draft container label components are in Module 1.

**Please Note:** There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, “substantially complete” labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

**OSE/DRISK ONLY:** For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

**COMMENTS/SPECIAL INSTRUCTIONS:**  
 Amgen had a meeting with the Agency on November 7, 2011 where there was discussion of the development/registration plans for the use of the combination device. A copy of the preliminary meeting minutes may be referenced here: [\cdsesub5\EVSPROD\BLA125031\0186\m1\us\correspondence-mtgs.pdf](#)

This submission is a CMC prior approval supplement, proposing pegfilgrastim as a combination product in a pre-filled syringe. The primary clinical study supporting the pegfilgrastim delivery device is a bio-equivalence study to be reviewed primarily by clinical pharmacology. This will be reviewed under a 4 month clock with a PDUFA date of 10/27/14.

The Division is requesting OPDP's review of the patient package insert and the new instructions for use. The Division is requesting initial input regarding filing before the August 26, 2014 filing date.

Link to the labels: [\cdsesub1\bla\CTD Submissions\STN125031\0186\m1](#)

Filing/Planning Meeting: **August 26, 2014**  
 Mid-Cycle Meeting: TBD  
 Labeling Meetings: TBD  
 Wrap-Up Meeting: **October 20, 2014**

SIGNATURE OF REQUESTER <b>Rachel McMullen</b>	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND

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/s/  
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RACHEL S MCMULLEN

07/22/2014

The Division is requesting review of the patient package insert and the new instructions for use.

**MANDATORY:** Send a copy of the consult request form to the Office of Combination Products as follows:  
--Originating Center: When the consult request is initiated.  
--Consulting Center: When the consult is completed.  
Email: combination@fda.gov or FAX: 301-427-1935

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_  
Assigned to: \_\_\_\_\_  
Date Assigned: \_\_\_\_\_  
Assigned by: \_\_\_\_\_  
  
Completed date: \_\_\_\_\_  
Reviewer Initials: \_\_\_\_\_  
Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center:   
Division: Human Factors  
Mail Code: HF  
Consulting Reviewer Name: Quynh Nguyen  
Building/Room #:  
Phone #:  
Fax #:  
Email Address:  
RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER  
Division: Hematology Products  
Mail Code: HF161  
Requesting Reviewer Name: Pat Dinndorf  
Building/Room #:  
Phone#: 240-402-4574  
Fax #:  
Email Address: rachel.mcmullen@fda.hhs.gov  
RPM/CSO Name and Mail Code: Rachel McMullen  
Requesting Reviewer's Concurring Supervisor's Name: Al Deisseroth

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: 7/18/2014

**Requested Completion Date:** 10/1/2014

Submission/Application Number: sBLA 125031  
(Not Barcode Number)

Submission Type: sBLA  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: 6/27/2014

Official Submission Due Date: 10/20/2014

Name of Product:

Name of Firm:

Intended Use:

**Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):**

The Division is requesting initial input of this submission ahead of the August 26, 2014 filing date.  
The link below provides the reference to the applicant's bio-equivalence study:  
[\\cdsesub1\bla\CTD\\_Submissions\STN125031\0186\m3\32-body-data\32p-drug-prod\neulasta-subcutaneous-injection\32p7-cont-closure-sys](\\cdsesub1\bla\CTD_Submissions\STN125031\0186\m3\32-body-data\32p-drug-prod\neulasta-subcutaneous-injection\32p7-cont-closure-sys)

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

Amgen had a meeting with the Agency on November 7, 2011 where there was discussion of the development/registration plans for the use of the combination device. A copy of the preliminary meeting minutes is attached for reference.

The primary clinical study supporting the pegfilgrastim delivery device is a bio-equivalence study to be reviewed primarily by clinical pharmacology.

The Division is requesting CDRH's review of the human factor's engineering study.

Reference ID: 3596405

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE/DMEPA</b> <b>OSE RPM: Kevin Wright</b>		FROM: Rachel McMullen, Division of Hematology Products, (240)-402-4574		
DATE July 18, 2014	IND NO.	NDA/BLA NO. sBLA 125031/S-175	TYPE OF DOCUMENT Manufacturing Supplement	DATE OF DOCUMENT: June 27, 2014
NAME OF DRUG: <b>Neulasta®</b> (pegfilgrastim)	PRIORITY CONSIDERATION <b>Priority</b>	CLASSIFICATION OF DRUG Biologic-Device Combination Product	DESIRED COMPLETION DATE: <b>October 1, 2014</b> <b>4 month PDUFA Goal Date: October 27, 2014</b>	
NAME OF FIRM: <b>Amgen, Inc.</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input checked="" type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>HF Study and Draft Container Label</b>				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  Amgen had a meeting with the Agency on November 7, 2011 where there was discussion of the development/registration plans for the use of the combination device. A copy of the preliminary meeting minutes is attached for reference.  This submission is a CMC prior approval supplement, proposing pegfilgrastim as a combination product in a pre-filled syringe. The primary clinical study supporting the pegfilgrastim delivery device is a bio-equivalence study to be reviewed primarily by clinical pharmacology.  The link below provides the reference to the applicant's bio-equivalence study: <a href="\\cdsesub1\blaleCTD_Submissions\STN125031\0186\m3\32-body-data\32p-drug-prod\neulasta-subcutaneous-injection\32p7-cont-closure-sys">\\cdsesub1\blaleCTD_Submissions\STN125031\0186\m3\32-body-data\32p-drug-prod\neulasta-subcutaneous-injection\32p7-cont-closure-sys</a>  The Division is requesting DMEPPA's review of the human factors engineering study and draft container labeling for the Neulasta delivery device. Please note we have also consulted CDRH for the Human factors study. The Human Factors Study can be found in Module 3 under 3.2.P.7  The sponsor has also proposed partial labeling for the device. The draft container label components are in Module 1. <a href="\\cdsesub1\blaleCTD_Submissions\STN125031\0186\m1">\\cdsesub1\blaleCTD_Submissions\STN125031\0186\m1</a>				

SIGNATURE OF REQUESTER <b>Rachel McMullen</b>	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/  
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RACHEL S MCMULLEN  
07/21/2014



BLA 125031/S-175

**PRIOR APPROVAL SUPPLEMENT -  
ACKNOWLEDGEMENT & FILING**

Amgen Inc.  
Attention: Donna L. Kraft  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
M/S 17-2-A  
Thousand Oaks, CA 91320

Dear Ms. Kraft

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

**BLA SUPPLEMENT NUMBER:** 125031/S-175

**PRODUCT NAME:** Neulasta<sup>®</sup> (pegfilgrastim)

**DATE OF SUBMISSION:** June 27, 2014

**DATE OF RECEIPT:** June 27, 2014

This supplemental application proposes the following change(s): a combination product comprising a pegfilgrastim prefilled syringe co-packaged with a drug delivery device designed to facilitate the administration of Neulasta<sup>®</sup> (pegfilgrastim) according to the approved dosing schedule and route of administration for which pegfilgrastim is currently approved.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 26, 2014 in accordance with 21 CFR 601.2(a).

If the application is filed, the user fee goal date will be October 27, 2014.

**CONTENT OF LABELING**

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, call me at (240) 402-4574.

Sincerely,

*{See appended electronic signature page}*

Rachel McMullen, MPH  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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RACHEL S MCMULLEN  
07/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

PIND 7110

## MEETING MINUTES

Amgen, Inc  
Attention: Monica Sandberg, Ph.D.  
Manager, Regulatory Affairs  
1 Amgen Center Drive MS 17-2-B  
Thousand Oaks, CA 91320

Dear Dr. Sandberg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pegfilgrastim.

We also refer to the teleconference between representatives of your firm and the FDA scheduled for November 7, 2011. The purpose of the meeting was to the development and registrational plans for the use of pegfilgrastim drug product in combination with the pegfilgrastim delivery device.

The preliminary minutes were sent on Thursday, November 3, 2011, via electronic (email) communication. Your firm reviewed our comments to the questions posed in the October 6, 2011, briefing package and has elected to cancel the November 7, 2011, meeting and address our comments in a separate amendment to the IND. I have included a copy of the minutes provided to you on November 3, 2011.

If you have any questions, call me at (301) 796-0704.

Sincerely,

*{See appended electronic signature page}*

Gina M. Davis, M.T.  
Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** C  
**Meeting Category:** IND  
**Meeting Date and Time:** November 7, 2011 from 12:00 PM – 1:00 PM  
**Application Number:** 7110  
**Product Name:** Neulasta (Pegfilgrastim)  
**Indication:** To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia  
**Sponsor/Applicant Name:** Amgen, Inc.  
**Meeting Chair:** Emily Shacter  
**Meeting Recorder:** Gina Davis

**FDA TENTATIVE ATTENDEES**  
**Office of Hematology and Oncology Products**  
**Division of Oncology Products 2**

Patricia Keegan  
Gina Davis

**Office of Clinical Pharmacology**  
**Division of Clinical Pharmacy V**

Hong Zhao  
Ruby Leong

**Center for Devices and Radiological Health**  
**Office of Device Evaluation**  
**Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices**

Jacqueline Ryan  
Nikhil Thakur

**Office of Biotechnology Products**  
**Division of Therapeutic Proteins**

Emily Shacter  
Kathy Lee  
Dov Pluznik

**SPONSOR ATTENDEES****Amgen, Inc.**

Alex Cairns, Bs	Senior Engineer, Drug Delivery
Mei Ling Chang-Lok, Ph.D.	Director, Global Regulatory Affairs
Lyndah Dreiling, M.D, MBA	Executive Director, Global Clinical Development
Steven Galson, M.D., MPH	Vice President, Global Regulatory Affairs
Jay Gerondale, M.S.	Director, Device Quality
Gisila Guzman, Ph.D.	Director, Product Quality
Kristi Kistner, B.S.	Director, Global Regulatory Affairs
Tony Mire-Sluis, Ph.D.	Vice President, Corporate, Products and Device
Quality	
Mallik Paranandi, Ph.D.	Director, Process Development
Monica Sandberg, Ph.D.	Manager, Global Regulatory Affairs
Bing-Bing Yang, Ph.D.	Director, Pharmacokinetic and Drug Metabolism
Hong Xia Zheng, M.D., Ph.D.	Director, Medical Sciences/Early Development

**Insulet**

Michael Doyle, B.S.	Senior Manager, Regulatory Affairs
Kevin Schmid, MBA	Vice President, Business Development

**1.0 OBJECTIVE**

- To obtain feedback on the proposed development program to obtain licensure of the pegfilgrastim combination product

**2.0 BACKGROUND**

Neulasta® (pegfilgrastim) has been approved in the United States (US) since 2002 to decrease the incidence of infection, as manifested by febrile neutropenia (FN), in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of FN.

The active ingredient in Neulasta is pegfilgrastim, a covalent conjugate of filgrastim and polyethylene glycol (PEG) with an approximate average molecular weight of 39 kDa. Filgrastim is obtained from the bacterial fermentation of a strain of Escherichia coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim, a 20 kDa PEG molecule is covalently bound to the N-terminal methionyl residue of filgrastim.

The pegfilgrastim drug product is formulated at a single strength of 10 mg protein/mL in a buffer solution containing (b) (4) sorbitol, (b) (4) sodium acetate, (b) (4) polysorbate20, pH 4.0 and supplied in a prefilled syringe containing 0.6 mL deliverable volume. The

recommended dosage of pegfilgrastim is a single subcutaneous (SC) injection of 6 mg administered once per chemotherapy cycle in adults 27 hours after administration of chemotherapy.

Amgen, in collaboration with Insulet Corporation, is developing a delivery device that will automatically administer pegfilgrastim 27 hours after chemotherapy, thereby reducing improper same-day dosing, eliminating the need for the return visit to the health care provider, and facilitating the administration of pegfilgrastim according to the approved dosing recommendation.

The pegfilgrastim combination product will consist of the pegfilgrastim delivery device in a sterile blister that is co-packaged with a specifically designated prefilled syringe containing pegfilgrastim, an adhesive remover, and the patient and HCP instructions for use.

Amgen states that the pegfilgrastim delivery device is a small and light weight, durable, battery-powered, sterile, single-use, disposable, water-resistant, electromechanical drug delivery system that is applied directly to the patient's skin using a self-adhesive backing.

The proposed pegfilgrastim drug delivery system is directly attached to the patient's skin using a self-adhesive backing. The pegfilgrastim delivery device will be prepared by the health care provider and applied to the patient the same day as chemotherapy administration. It will be pre-programmed to deliver a 6 mg SC dose of pegfilgrastim 27 hours after activation of the device.

The health care provider will fill the Drug Reservoir through the identified fill port in the pegfilgrastim delivery device using the provided pegfilgrastim prefilled syringe, automatically activating the device, and will apply the device to the patient's abdomen. Three minutes after filling, the soft cannula is automatically inserted into the patient SC tissue and subsequently the insertion needle retracts. The patient will depart the health care provider's office and the device will automatically deliver pegfilgrastim 27 hours later through the cannula.

Amgen states that the full pegfilgrastim dose is delivered slowly (b) (4) Both audible and visual signals notify the patient of pre-delivery and confirm successful delivery of the dose. Additionally the device has a (b) (4) (b) (4) (b) (4) (b) (4) Once the patient confirms delivery of pegfilgrastim, the patient will remove the device and the cannula, and dispose of it as instructed by the HCP and patient instructions.

Amgen intends to submit a supplemental biologic license application (sBLA) in 2013 for approval of the pegfilgrastim combination product to the Center for Drugs Evaluation and Research (CDER).

To register this combination product, Amgen plans to confirm/validate that the product quality is not compromised and that the same amount of product is delivered with the device compared with the currently available prefilled syringe which includes the following:

- To confirm the performance of the delivery device by design verification and design validation
- To confirm product quality through a comprehensive product quality evaluation plan that includes drug/device product compatibility and analytical comparability (release, characterization, and stability testing)
- To confirm comparability of pegfilgrastim delivery by the device relative to the prefilled syringe by conducting a pharmacokinetics (PK) comparability study in 212 healthy subjects (n=106 per arm).

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## General Comments

As a result of the re-organization of September 11, 2011, the responsible organization within the Center for Drug Evaluation and Research (CDER) for IND 7110 and BL STN 125031, is now the Division of Hematology Product (DHP). Your new regulatory contact for IND 7110 is Lara Akinsanya, who can be reached at 301-796-9634.

## Sponsor Submitted Questions and FDA Responses:

### Pegfilgrastim Delivery Device

The performance of the pegfilgrastim delivery device will be confirmed through appropriate design verification and design validation testing, which will include Human Factors Engineering (HFE) / Usability Engineering (UE) and clinical use studies. A description of the design verification and design validation testing plans is provided in Section 9 of this briefing document.

The expected outcome of the design verification and design validation testing plans is that the pegfilgrastim delivery device will be confirmed to be safe and effective for the intended use.

1. Does the Agency agree with the design verification and design validation testing plans as described?

**FDA Response:** FDA agrees with the proposed design verification and validation testing plans as presented. FDA reserves the right to add additional comments regarding Amgen's Human Factors Usability proposal and clinical use studies.

2. Amgen intends to submit the Human Factors Master Validation Plan for FDA review by 18 November 2011. As FDA is reviewing the overview of the plan during this Type C meeting, Amgen would like to request CDER and the Center for Devices and Radiologic Health (CDRH) provide input on the Human Factors Master Validation Plan within 30 days of submission, ie, by 19 December 2011, and engage in additional meetings and discussions as necessary to establish a mutually agreeable protocol.

Does the Agency agree to this review time period and process?

**FDA Response:** The review time period may depend on the complexity of Amgen's protocol. Generally, FDA is able to complete the initial review within forty-five days. CDRH is willing to engage in additional meetings and discussions to establish a mutually agreeable protocol. Please ensure that information amendments or requests for meetings regarding this combination product are submitted as amendments to IND 7110.

#### Chemistry, Manufacturing and Controls

3. A comprehensive product quality evaluation is planned that includes drug/device product compatibility and analytical comparability (release, characterization, and stability testing) as described in Section 11.

Does the Agency agree with the product quality test plan?

**FDA Response:** In general the proposal is acceptable. Amgen should address the following comments:

- a. In addition to the stability testing, please perform extractable/ leachable studies on the delivery device. The leachables testing should be performed in the presence of the DP under conditions of use of the device (e.g., time and temperature).
  - b. Please clarify which container closure will be utilized for the microbial challenge study and the purpose of this study.
4. A prefilled syringe with a slightly higher fill volume than currently manufactured will be supplied for use with the delivery device in order to ensure that patients receive the appropriate (6-mg) dose of pegfilgrastim in accordance with the current Neulasta® USPI (June 2011).

Amgen plans to apply the same expiry dating of the currently approved prefilled syringe to the delivery device prefilled syringe proposed for the pegfilgrastim combination product based on the proposed comparability assessment and an evaluation of stability data against historical results as described in Section 11.

Does the Agency agree with this plan?

**FDA Response:** No, the volume of the prefilled syringe should not exceed the volume required to fill the device Drug Reservoir to enable the device to deliver the 6 mg dose to the patient. Amgen should provide a plan to ensure that the device consistently delivers 6 mg of the drug product. Please ensure that if both presentations (the syringe and the pegfilgrastim combination product) are marketed concurrently, a description of the plans to mitigate the risk of medication errors is provided in the supplement seeking approval of this combination product in the event that the device and syringe are separated.

### Clinical Pharmacology

5. Amgen does not expect the bioavailability of pegfilgrastim to be affected by SC administration via the pegfilgrastim delivery device because no changes have been made to the pegfilgrastim formulation, protein concentration, or dose. To confirm this expectation, Amgen is planning to conduct Study 20101153, which will enroll healthy subjects to assess the PK comparability of a single SC dose of pegfilgrastim delivered manually from a prefilled syringe versus delivery by the pegfilgrastim delivery device. A synopsis of the proposed Study 20101153 is provided in Appendix A.

The expected outcome of Study 20101153 is that the PK of pegfilgrastim delivered via the pegfilgrastim delivery device will be comparable to that of pegfilgrastim administered manually from the currently approved prefilled syringe.

Does the Agency agree with the design of the proposed comparability Study 20101153, in particular with the sample size, study endpoints, comparability criterion, and the abdomen as the single reference site of administration to be representative of all indicated sites?

**FDA Response:** The sample size and comparability criterion (90% CI: 80-125%) for assessment of PK comparability is acceptable. However, FDA recommends that both AUC and  $C_{max}$  be included as PK endpoints to demonstrate comparability between pegfilgrastim administered by the two delivery methods. Selection of the abdomen (one of the approved labeling recommended sites) as the injection site for this comparability study is acceptable.

### Multidisciplinary

6. Amgen believes that the proposed development program for the pegfilgrastim combination product is sufficient to provide evidence of comparability between pegfilgrastim delivered with the pegfilgrastim delivery device and pegfilgrastim delivered manually from the currently approved prefilled syringe.

Does the Agency agree that the proposed development program is adequate for licensure of the pegfilgrastim combination product?

**FDA Response:** In general, the development program, consisting of plans for physicochemical comparability and compatibility comparisons of the proposed to the current presentations, a pharmacokinetic comparability study and human factor studies in human subjects, and appropriate characterization of the new device alone and for its intended use with Neulasta appears adequate. The acceptability of the data obtained in this development program will be determined during the review issue of the BLA supplement.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GINA M DAVIS  
11/08/2011