CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125031/0

CHEMISTRY REVIEW(S)

Final Product Review of BLA-125031 (Amgen's Filgrastim-SD/01)

Date: December 7, 2001 (Final version January 28, 2002)
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Through: Amy Rosenberg, M.D., Director, DTP, OTRR
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To: BLA 125031 File

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Product: Filgrastim-SD/01 (Peg-Filgrastim; Peg-G-CSF)
Sponsor: Amgen, Inc.
Indication:

The focus of this review is the section of the Final Drug Product described in the CMC part of the BLA. Serge Beaucage, Ph.D., DTP, OTRR reviewed the section of the Drug Bulk Substance.

Table of Contents:

A. Overview of the product

Filgrastim-SD/01 is a sustained duration form of Filgrastim produced by covalent attachment of a 20 kd poly ethylene glycol (PEG) molecule to the amino-terminal methionine residue of the Filgrastim polypeptide chain. Filgrastim is human granulocyte colony stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is an internationally licensed product. Filgrastim Filtered Purified Bulk (FPB), manufactured as licensed, is the starting material for the manufacture of Filgrastim-SD/01. Filgrastim-SD/01 has been developed as a sustained duration version of Filgrastim. The sustained duration or increased plasma half-life of Filgrastim-SD/01 is achieved through PEG-modification of the Filgrastim molecule. Both Filgrastim-SD/01 and Filgrastim are indicated for

However, Filgrastim-SD/01 is administered once per cycle of chemotherapy, while Filgrastim is administered daily. Moreover, Filgrastim-SD/01 is administered SC at a single strength of 6 mg/adult patient, regardless the weight of the patient.

Filgrastim-SD/01 is manufactured

production of Filgrastim-SD/01 active substance, which is defined in this application as the Filgrastim-SD/01 Filtered Purified Bulk (Filgrastim-SD/01 FPB). Site of manufacture: Amgen, Thousand Oaks, CA (ATO). Production of Filgrastim-SD/01 at ATO includes of purified bulk.

he formulation of the Filgrastim-SD/01 FPB, followed by filling into syringes to produce Filgrastim-SD/01 Final Product. No more than of Filgrastim-SD/01 Filtered Purified Bulk (FPB) will be used to produce of Filgrastim-SD/01 Filtered Formulated Bulk (FFB). In addition of Filgrastim-SD/01 FPB would constitute less than of the total pooled volume required for Filgrastim-SD/01 FFB.
Site of manufacture: Amgen Bermuda Limited, Juncos, Puerto Rico (ABML).

abeling and final packaging of the Final Product, which is performed at 2 locations depending upon the final market for distribution.
Sites: ABML or Amgen European Logistics Center, BV, Breda, the Netherlands (ELC).

B. Composition of the Commercial and Medicinal Final Product

Filgrastim-SD/01 is manufactured as a solution for injection. The Filgrastim-SD/01 solution is formulated at a of solution. The final dosage form is a pre-filled syringe (PFS) for single use with a dose is 6 mg/06 ml. The excipients are acetate sorbitol polysorbate 20 , at pH 4.0. Table 2 shows the quantity per mL of the formulation ingredients and their function in the final product.

Table 2. Quantitative Composition of Filgrastim-SD/01 Final Product, 0.6 mL PFS

Ingredient	Quantity (Weight/mL)	Quantity per Unit[a]	Function
Filgrastim-SD/01	10.0 mg[b]	6.0 mg[b]	Active
Acetate (10 mM)	0.59 mg	0.35 mg	Buffer
Sodium (titrate)[c]			
Sorbitol	50 mg	30 mg	
Polysorbate 20	0.04 mg	0.02 mg	
Water for injection			Vehicle

[a] Based on deliverable volume of 0.6 mL. Target volume with

[b] Filgrastim-SD/01 mass is

[c]

Filgrastim-SD/01 degrades by a variety of reaction mechanisms. The major factor affecting these pathways and overall rates of and degradation of Filgrastim-SD/01 is A was selected

The final formulation is 10 mg/mL Filgrastim-SD/01, acetate, sorbitol 0.004% polysorbate 20 (wt%), at pH 4.0.

C. Manufacturing

Batch Definition
Commercial scale formulation may Currently only a formulation is manufactured.

Process Description
The formulation and filling of Filgrastim-SD/01 is conducted at ABML.
A detailed flowchart outlining the steps of the manufacturing process of syringes is provided in Figure 2.

Manufacturing Process Validation for Final Product
The formulation and filling processes have been validated to demonstrate that the product can be formulated with the appropriate concentration of Filgrastim-SD/01 in a that consistently contains the correct levels of excipients. The filling process has been validated to demonstrate that the product can be consistently filled to the correct volume. To validate the formulation and filling processes, lots and Filgrastim-SD/01 lots were manufactured. The formulation and formulated bulk lots manufactured for this validation are presented in Table 17 and Table 18. These are commercial lots manufactured in ABML facility in Puerto Rico. The results of this validation process for the 0.6 mL fill volume is provided in Table 19.

Appendix 1 addresses 9 questions to the sponsor regarding manufacturing. The sponsor was supposed to address these questions during the inspection of the facility in PR.

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Table 17. Validation Summary: Formulation

Table 19. Validation Summary: Final Product 10.0 mg/mL, 0.6 mL Fill Syringe

The data demonstrate that the product can be formulated with the appropriate concentration of Filgrastim-SD/01 .hat consistently contains the correct levels of excipients.

Syringe Fill Volume Validation

Syringe fill volume validation was performed to demonstrate that the , consistently operates within the pre-defined operating parameters to ensure target fill volume is achieved.

A total of syringe lots (commercial lots) were filled for this validation. A total of syringes the lot) per lot were sampled and tested for fill volume accuracy.

A summary of the syringe fill volume accuracy and volume of injection validation results are provided in Table 21 and Table 22, respectively.

Table 21. Syringe Fill Volume Accuracy Validation Summary

Table 22. Syringe Fill Volume (Fill Volume of Injection) Validation Summary

The data demonstrate that the syringe filling process consistently and reliably meets the established fill volume limits and the label claim.

, Syringe Inspection and Shipping conditions of Finished Product have been addressed during the inspection of Amgen's PR facility (see inspection report of Amin Pete, DPQC)

Reprocessing

Reworking

Rework is defined as re-manufacturing when a product specification fails. Commercial product will not be reworked.

D. Specifications for finished product

Specifications and Routine Tests

The commercial specifications for Filgrastim-SD/01 Finished Product and the analytical methods used for release testing are described by name and method number in Table 1. The testing was selected from a range of physicochemical and functional tests that were evaluated during the development process of Filgrastim-SD/01 and are used to confirm the quality of the drug substance by testing the identity, purity, and potency.

Table 1. Specifications for Filgrastim-SD/01 Finished Product

Parameter	Specification	Method
Identity		
Quantity		
. concentration		
Purity		
HPLC		
HPLC		
Excipients		
Polysorbate 20		
General product characteristics		
pH		
Volume in container		
Appearance		

[a] See Section 1.2.5.1

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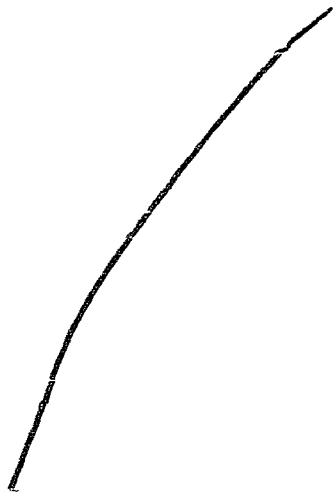

F. Stability of the Finished Product

The integrity and potency of Filgrastim-SD/01 Finished Product stored at [redacted] 12, [redacted] months was tested. Temperatures tested include the recommended storage temperature of 2^0 to 8^0C and [redacted]

Study Material

The ongoing Filgrastim-SD/01 Finished Product stability program currently includes [redacted] lots in [redacted] Syringes filled to a deliverable volume of 0.6 mL. In addition, [redacted] are included as supporting data. Filgrastim-SD/01 Finished Product in these alternative configurations is identical in formulation and behaves similarly to product in the commercial configuration (0.6 mL syringe). Therefore, these data are used in support of an expiry period of [redacted] for the 0.6 mL fill syringe.

A summary of lots included in the Filgrastim-SD/01 stability program and the latest time points for which data have been evaluated for these lots can be found in Table 1 (syringes) and Table 2 (vials). Stability data for product stored at 2° to 8°C are provided in Table 5 (syringes) and [redacted] are provided in Table 7 (syringes) [redacted] lots in table 1 ([redacted] are GMP commercial lots manufactured in Amgen's Puerto Rico facility and are primary stability lots.

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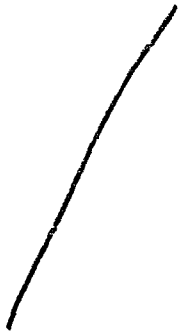

Stability of Filgrastin throughout the proposed expiration dating of Filgrastim-SD/01

Filgrastim is the biological active component of Filgrastim-SD/01. I asked Amgen, therefore, to provide data to support the proposed expiration dating of the product from synthesis of Filgrastim filtered purified bulk through the end of shelf life of Filgrastim-SD/01 finished product. On December 12, 2001 Amgen provided the following data: The expiry periods for the — in the manufacture of Filgrastin-SD/01 are:

- Filgrastim filtered purified bulk – — at $2^0 - 8^0$C
- Filgrastin-SD/01 filtered purified bulk - — at $2^0 - 8^0$C
- Filgrastin-SD/01 finished product – — , at $2^0 - 8^0$C

The maximum cumulative length of storage for Filgrastim is —.
Amgen provided stability data from — lots — , that exceeded the maximun cumulative length of storage of the material from the time of Filgrastim filtered purified bulk manufacture to the Filgrastim-SD/01 finished product (— respectively). The stability data show that the — lots met all acceptance criteria.

Conclusion and Proposed Shelf Life

Supportive data up to — from non-GMP are presented in the BLA. Taken together, the results of these analytical methods demonstrate the acceptable integrity and potency of Filgrastim-SD/01 Finished Product throughout the proposed expiry period of — when stored at 2^0 to 8^0C.

However, since real time stability data from commercial lots manufactured in PR under GMP are available for a period of 12 months only, the expiry period for Filgrastim-SD/01 is recommended for only 12 months at 2^0 to 8^0 C.

G. Immunogenicity

The first immunoassay developed was an RIA that used immobilized r-metHuG-CSF, followed by addition of serum samples, followed by ^{125}I-labeled protein A to detect antibodies. While useful to detect antibodies from different species, protein A is limited in its ability to detect all classes of human immunoglobulins. Specifically, protein A demonstrates very limited binding to IgM, IgA, and IgE. The second-generation assay was an ELISA that used immobilized r-metHuG-CSF followed by serum sample addition,and enzyme-labeled anti-human IgG. This assay was broader than the RIA, in that it was able to detect all Ig classes.

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Results

For the phase 1 and certain phase 2 studies (970144, 970230, 980147, and 980230) only the RIA and EIA were available. The [redacted] assay was used in the later phase 2 and the pivotal studies (990117, 990118, 980226, and 990749). Although the Integrated Summary of Safety presents results from all 8 studies, it should be noted that 3 different screening methodologies are represented. However, the same cell-based bioassay to detect neutralizing antibodies was used throughout. Table 8-97 summarizes the incidence of antibodies in patients receiving SD/01 or Filgrastim.

Table 8-97. Incidence of Antibodies to Filgrastim and Filgrastim-SD/01

	Filgrastim	Filgrastim-SD/01
	5 µg/kg/day	All
Number of subjects screened[a]	340	534
Subjects with nonreactive samples	329	488
Subjects with ≥ 1 confirmed reactive samples	11/340 (3%)	46/534 (9%)
RIA and/or EIA	8/61 (13%)	46/251 (18%)
[redacted]	3/279 (1%)	0/283 (0%)
Reactive samples subjected to [redacted] immunoassay	11	46
Generated neutralizing antibodies	0 (0%)	0 (0%)

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[a] Includes results from RIA, EIA, and [redacted] assays

Sera of 534 patients who received Filgrastim-SD/01 were screened for antibodies. Of those, 251 were screened against Filgrastim in the RIA and EIA assays. A total of 46 patients were found seropositive to Filgrastim (32 patients in the RIA assay, 2 patients in the EIR assay and 12 patients in both RIA and EIA assays). The 46 sera that turned out to be reactive in the RIA and/or EIA were not verified to be positive due to human anti Filgrastim antibody. However, the 46 positive sera were tested for neutralizing antibodies in the bioassay against Pegfilgrastim and Filgrastim. All sera were negative against both drugs. Additional sera from 283 patients were screened for antibodies against Filgrastim-SD/01 and Filgrastim in the [redacted] assay. All sera were negative. The 3 sera which were positive in the [redacted] when assayed with Filgrastim were negative when assayed with Pegfilgrastim.

In summary, 3 different assays were used in the screening process for detection of binding antibodies against either Filgrastim or SD/01: the EIA assay (the most sensitive assay with a detection level of [redacted], followed by the [redacted] assay ([redacted],

followed by the RIA (—).

The specificity of the binding antibodies which were detected in sera from 46 patients (using the RIA and/or EIA) was not confirmed by competition with SD/01 or Filgrastim. All 46 sera were negative in the neutralizing bioassay (detection level — for G-CSF and — for SD/01). Although all the assays have been properly validated the incidence of antibody development in patients receiving SD/01 has not been adequately determined. The time interval between post treatment and blood drawn for antibody screening is unclear. Thistime interval is important for the following reasons: 1) The patients are treated with chemotherapy, which can delay immune responses, and 2) SD/01, which is a sustained duration form of Filgrastim and has a lower serum clearance than Filgrastim, if present in the serum when blood is drawn, can bind to antibodies and mask their presence in the screening assays.

Additional comments (as a result of discussion with Amy and Wendy):

1. The specificity of the early screening assays (RIA and EIA) was not determined. 46 sera were seropositive to Filgrastim. The specificity of the seropositive was not confirmed by competing with Filgrastim and/or Pegfilgrastim with the binding of the sera to the immobilized Filgrastim.
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Memorandum

Date: May 14, 2001

From: Serge L. Beaucage, Ph. D., DTP, CBER 1-26-02

Subject: Amgen BL 125031/0
Product: PEGylated Granulocyte Colony-Stimulating Factor (Filgrastim-SD/01)
Manufacturer: Amgen Inc.
Proposed use:

Through: Barry Cherney, Ph. D., Deputy Director, DTP, CBER 1-31-02
Dov Pluznik, Ph.D., DTP, CBER

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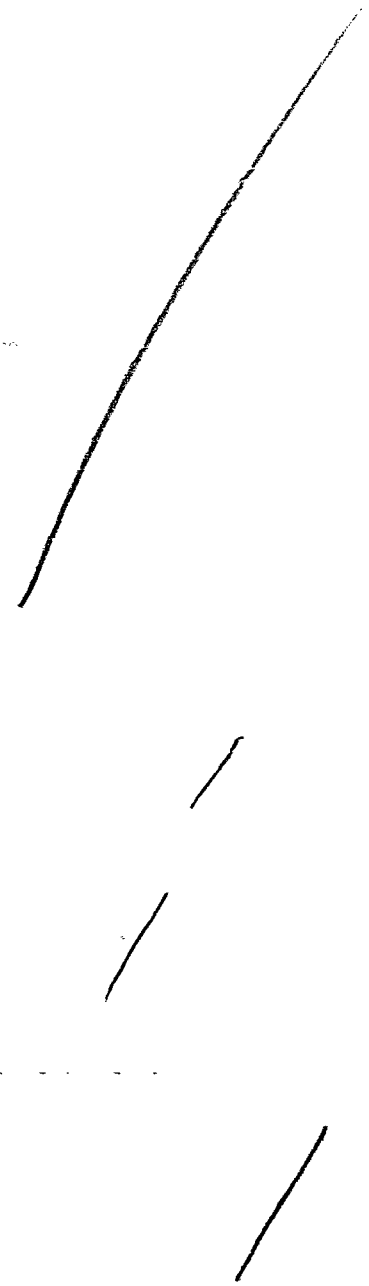
2. Characterization

Filgrastim-SD/01 (SD/01) contains a single PEG molecule of approximately 20 kDa covalently attached to the N-terminal methionine residue of Filgrastim. The reaction used to attach the PEG molecule to the Filgrastim is , and is shown in Figure 1.



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