Our STN: BL 125031/0

Jeffrey N. Fellows
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Fellows:

Your biologics license application for Pegfilgrastim is approved effective this date. Amgen, Incorporated, Thousand Oaks, California, is hereby authorized to introduce or deliver for introduction into interstate commerce, Pegfilgrastim under Department of Health and Human Services U.S. License No. 1080.

Pegfilgrastim 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. Under this authorization, you are approved to manufacture Pegfilgrastim filtered purified bulk at your facility in Thousand Oaks, California. Final formulation will be performed at Amgen (Bermuda) Manufacturing Limited, Juncos, Puerto Rico. In accordance with approved labeling, your product will bear the proprietary name Neulasta™, and will be marketed in 0.6 mL pre-filled, single-use syringes containing 6 mg Pegfilgrastim, based on protein weight.

The dating period for Pegfilgrastim final drug product shall be 12 months from the date of manufacture when stored at 2-8° C. The date of manufacture shall be defined as the date of final sterile filtration of the final formulated product. The bulk drug substance may be stored for up to [redacted] Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Pegfilgrastim to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

Any changes in the manufacturing, testing, packaging or labeling of Pegfilgrastim, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 601.27. On the basis of your commitment described in item 3 below, we are deferring the submission of your pediatric studies, under 21 CFR 601.27(b), until February 2006.

We acknowledge your written commitments to provide additional information on ongoing studies and to conduct post-marketing studies as described in your letters of January 24 and 27, 2002, and as outlined below:

1. To develop and fully validate a — assay with a sensitivity of — or better for detection of anti-Pegfilgrastim antibodies in human serum by July 2002.

   a. You will use — from — for testing the sensitivity of the — assay.

   b. You will use multiple human serum samples that previously tested antibody-positive to Filgrastim or Pegfilgrastim as part of the — assay validation.

   c. If you are unable to achieve a sensitivity of at least — using the — assay by July 2002, you commit to meet with the Agency to discuss a schedule to develop and validate an ELISA to detect anti-Filgrastim and anti-Pegfilgrastim antibodies with a sensitivity of at least —.

   d. You will obtain serum samples from 500 individual patients enrolled in your Phase 3 protocol #20010144 entitled "A Double-blind, Placebo-Controlled, Multicenter, Randomized Study Evaluating the Prophylactic Use of Pegfilgrastim on the Incidence of Febrile Neutropenia in Subjects with Advanced Breast Cancer Treated with Single Agent Doxetaxel", who have received Pegfilgrastim. Sampling times should take into account the time required to mount an antibody response and ongoing chemotherapy. These samples will be analyzed with the new, validated immunogenicity assay.

2. To obtain data to support the proposed — resin re-use of the — column used in the purification of Pegfilgrastim bulk. Validation studies were initiated in January 2002, will be completed by June 2003, and validation data will be submitted to FDA by December 2003.

3. To submit results from an ongoing study to evaluate the pharmacokinetics (PK), safety and efficacy of Pegfilgrastim in pediatric patients. The protocol for study 990130

entitled "A Single Dose Per Cycle Filgrastim-SD/01 as an Adjunct to VadriaC/IE Chemotherapy in Pediatric Sarcoma Patients" was submitted to BB-IND --- on August 9, 1999 and the study was initiated in April 2000. Patient accrual will be completed by December 2004, the study completed (last patient exited) by September 2005, and the final clinical study report, with revised labeling if applicable, will be submitted to FDA by February 2006.

Upon completion of the study and prior to finalization of the study report, you commit to discuss with the Agency the appropriateness of an --- to make Pegfilgrastim --- and approval of an indication for pediatric use.

4. To develop a pediatric dosage form based upon the data obtained from the pediatric study 990130 described in item 3. Formulation development will be completed by March 2006, six-month stability studies will be completed by September 2006, and a supplement with revised labeling will be submitted to FDA by November 2006.

5. To submit data from an ongoing study to assess the PK and safety of retreatment with Pegfilgrastim. A retreatment study, SD/01 990736, entitled "A Study of Retreatment with Filgrastim-SD/01 in Subjects Receiving Myelosuppressive Chemotherapy" was submitted to BB-IND - on August 19, 1999 and the study was initiated in February 2000. An amendment to modify eligibility criteria will be submitted by April 2002, patient accrual will be completed by June 2004, the study completed (last patient exited) by October 2004, and a clinical study report, with revised labeling if applicable, submitted to FDA by May 2005.

6. To conduct a surveillance study of patients with sickle cell disease who received treatment with Pegfilgrastim or Filgrastim. This study will be designed to capture demographics and safety data to evaluate the safety profile of these cytokines in this patient population. A protocol will be submitted to FDA by September 2002, the study initiated by December 2002, and data submitted to FDA annually for five years, or until such time as Amgen, Incorporated, the FDA, and an expert panel composed of recognized experts in the field of hemoglobinopathies reach consensus that adequate data has been accrued to assess the safety of Pegfilgrastim or Filgrastim in patients with sickle cell disease.

7. To evaluate the PK of Pegfilgrastim in patients with renal impairment. You will conduct an open-label, single-dose PK study of 6.0 mg subcutaneous Pegfilgrastim. The protocol will be submitted by April 2002, the study initiated by May 2002, patient accrual completed by November 2002, the study completed (last patient exited) by November 2002, and the final clinical study report, with revised labeling if applicable, will be submitted to FDA by August 2003.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports

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should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

/S/

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure