DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103353/5001

MAY 29 2002

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

Dear Mr. Fellows:

Your request to supplement your biologics license application for Filgrastim to revise the Warnings and Precautions sections of the package insert to include updated information regarding adult respiratory distress syndrome and splenic rupture has been approved.

We acknowledge your written commitment to conduct post-marketing studies as described in your letter of May 28, 2002, and as outlined below:

1. To conduct a study of the use of Filgrastim in approximately 300 normal apheresis donors at 15 centers and prospectively collect data on clinical changes in the spleen. This study will be performed in normal donors 18 to 60 years old, inclusive, who meet the donor guidelines of the National Marrow Donor Program (NMDP). Donors will receive Filgrastim for at least four days prior to leukapheresis and on each day of leukapheresis. The study design will include a range of doses representing the current standard of practice. Spleen size will be measured by palpation during physical examination, and by ultrasound examination at baseline and every-other day through day 9 (e.g., days 3, 5, 7, and 9, +/- 1 day for each time point), and at day 15 in an initial cohort of 30 subjects. Splenic dimension will be measured and documented by a certified ultrasonographer. Both the ultrasonographers and the physicians performing the physical exams will be blinded to the others' findings. Hematology (CBC with differential) will be done daily on each day that Filgrastim is administered and each day an ultrasound examination is performed. After analysis of the first 30 subjects' data, the frequency and timing of palpation and ultrasound examinations for 270 donors will be established.

   The protocol synopsis will be submitted to CBER by August 2002; the final protocol will be submitted to CBER by November 2002; the study initiated by January 2003; the first subject enrolled by March 2003; subject enrollment completed by March 2005; the study completed (last patient exited) by April 2005; the final clinical study report with complete datasets in SAS transport files submitted to CBER by December 2005; and, revised labeling as appropriate submitted to CBER by February 2006.

2. To collect and analyze data on serious adverse events, using existing international registries, occurring in normal apheresis donors receiving Filgrastim at transplant centers and to submit these data and analyses annually for five years as a licensing

supplement. The PBSC donor database from the International Bone Marrow Transplant Registry (IBMTR) and the NMDP will be the major sources of data for the surveillance reports. You have estimated that data from greater than 1000 normal donors will be available for evaluation over a period of five years. Data for 2002 will be collected retrospectively; data for the following four years will be prospectively defined.

Data collection from the registries will be initiated by January 2003 and data collected annually through December 2006. An annual report with data summaries will be submitted to CBER three months following the completion of each year's data collection. Following completion of the five-year surveillance, you will perform analysis on all data collected and submit to CBER a combined final report with complete datasets in SAS transport files along with the appropriate SAS datasets by July 2007. Revised labeling, if necessary, will be submitted to CBER by July 2007.

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).

It is required 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 in accordance with 21 CFR 600.81. Postmarketing adverse experience reports and distribution reports should be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. All adverse experience reports should be prominently identified according to 21 CFR 600.80.

This information will be included in your biologics license application file.

Sincerely yours,

Patricia Keegan for Dr. Weiss

Karen D. Weiss, M.D.
Director
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research