DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125268/0

AUG 22 2008

Amgen, Inc.
ATTENTION: Mei-Ling Chang-Lok, Ph.D., RAC
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Chang-Lok:

We have approved your biologics license application for romiplostim effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, romiplostim under your existing Department of Health and Human Services U.S. License No. 1080. Romiplostim is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Under this license, you are approved to manufacture romiplostim drug substance at Amgen Inc, in Boulder, Colorado. The final formulated product will be manufactured, filled, labeled, and packaged at Amgen, Inc, Patheon Italia, Monza, Italy. You may label your product with the proprietary name, Nplate™, and may market it in 250 mcg and 500 mcg vials.

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

The dating period for romiplostim shall be [redacted] from the date of manufacture when stored at [redacted]. The date of manufacture shall be defined as the date of final [redacted] of the formulated drug product. The dating period for your drug substance shall be 36 months when stored at -30 °C. We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of romiplostim to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Romiplostim, or in the manufacturing facilities.

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) will not be sufficient to assess the signals of the following serious risks in patients with chronic ITP who are receiving romiplostim: bone marrow reticulin formation and a risk for bone marrow fibrosis; antibody formation to either romiplostim or thrombopoietin that results in worsened thrombocytopenia; off-target cardiac toxicities; or to identify unexpected serious risks of adverse reactions within the fetus of pregnant woman and in the nursing infants of women who are receiving romiplostim.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess these signals of serious risks or to identify unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies.

1. To conduct an "Antibody Registry Study" that will enroll subjects who have received romiplostim and whose blood samples contain antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack or loss of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers are to submit blood samples to Amgen for detection of antibodies to romiplostim and thrombopoietin.

The Antibody Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.

You will conduct this study according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
First interim report submission:	May 2010 then annually
Final Report Submission:	Within six months of FDA notification that sufficient data has been collected

2. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to romiplostim during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, bone marrow reticulin formation, thrombotic events, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

   You will conduct this study according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
First interim report submission:	May 2010 then annually
Final Report:	Within six months of FDA notification that sufficient data has been collected.

3. To conduct a milk only lactation study in the subset of women enrolled in the pregnancy registry that choose to breastfeed their infants. This study will be designed to detect the presence and concentration of romiplostim in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

   You will conduct this study according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
First interim report submission:	May 2010 then annually
Final Report:	Within six months of FDA notification that sufficient data has been collected.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) in which patients with defined underlying risks are carefully evaluated for at least 24 hours following administration of romiplostim will be sufficient to assess the signals of serious risk or identify unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial.

4. To conduct trial 20080009, "A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)." In this trial, at least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule will apply to the detection of antibody formation to romiplostim and thrombopoietin as well as the electrocardiographic (ECG) detection of cardiac conduction abnormalities.

   A first interim report will contain, in addition to any other items, ECG and the results of bone marrow evaluations for patients who have completed 12 months of trial participation. This information will be updated for patients who have completed 24 months of trial participation and submitted in a second interim report.

   You will conduct this trial according to the following timetable:

Protocol submission:	August 22, 2008
Trial start:	July 2009
First interim report submission:	June 2012
Second interim report submission:	June 2013
Final report submission:	December 2014

Submit the protocols to your IND 10205 with a cross-reference letter to this BLA, STN BL 125268/0. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125268/0. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies and clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of these studies and clinical trial pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 601.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with romiplostim.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Nplate (romiplostim) Subcutaneous Injection to ensure the benefits of the drug outweigh the risks of bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thromboembolic complications, an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and serious complications due to medication error. Pursuant to 505-1(f)(1), we have also determined that Nplate can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate these risks listed in the labeling.

Your proposed REMS, appended to this letter, submitted on August 12, 2008, in response to our July 25, 2008, information request letter, is approved. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for assessments of the REMS.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

- **BLA 125268 REMS ASSESSEMENT**
- **NEW SUPPLEMENT FOR BLA 125268 REMS ASSESSMENT PROPOSED REMS MODIFICATION**

Please note that:

- This Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18)] or 21 CFR 201.80(f)(2)];
- You are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];
- The final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and
- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)].

CONTENT OF LABELING

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125268/0." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft 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 (October 2005)*. 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 STN BL 125268/0**." Approval of this submission by FDA is not required before the labeling is used.

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

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

REPORTING REQUIREMENTS

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

We acknowledge your May 30, 2008, commitment to expedited reporting of bone marrow fibrosis, malignancy/malignancy progression, and medication error resulting in a serious adverse event.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact Florence Moore, M.S., Regulatory Project Manager, at (301) 796-2050.

Sincerely,

Richard Pazdur MD

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Package Insert
Carton and Vial Labeling
Medication Guide
Risk Mitigation and Evaluation Strategies (REMS)