DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125320/0

BLA APPROVAL
June 1, 2010

Amgen, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

Dear Dr. Burd:

Please refer to your biologics license application (BLA) dated and received December 19, 2008, submitted under section 351 of the Public Health Service Act for Prolia™ (denosumab).

We acknowledge receipt of your amendments dated January 13, 15, 20, 22, and 28, February 12, and 27, March 3, 5, 9, 11, 12, 13, and 18, April 6, 17, 15, 23, 29, and 30, May 1, 4, 15, 19, and 27, June 5, 9, 12, and 25, July 10, 13, and 20, August 7, 18, 26(2), and 31, and September 3, 10, 11, 18, and 28, 2009, October 8 and 12, and November 4, December 1 and 8, 2009, January 25, February 8, 19, and 26 (2), March 19 (email), 25 and 29, April 12 (email), 19, 20, and 22, May 4, 7, 12, 13 (2 emails), 17, and 28 (email), and June 1 (email), 2010.

The January 25, 2010, submission constituted a complete response to our October 16, 2009, action letter.

We have approved your BLA for Prolia™ (denosumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Prolia™ (denosumab), under your existing Department of Health and Human Services U.S. License No. 1080. Prolia™ (denosumab) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

Under this license, you are approved to manufacture denosumab drug substance at Amgen Colorado in Boulder, Colorado, (b) (4) The final formulated product will be manufactured, labeled, and packaged at Amgen Manufacturing Limited in Juncos, Puerto Rico. You may label your product with the proprietary name Prolia™ and market it as a single-use prefilled syringe containing 60 mg denosumab in a 1 mL solution and as a single use vial containing 60 mg denosumab in a 1 mL solution.

The dating period for denosumab shall be 30 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of (b) (4) 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 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 Prolia™ (denosumab) 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 Prolia™ (denosumab), 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 indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the required studies are impossible or highly impracticable because the indication for this drug product does not occur in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes 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)).

As described in our letters dated October 2, 2009, and October 16, 2009, we have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of the serious risks of serious infection including skin infection, dermatologic adverse events, or over-suppression of bone turnover.

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

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1. A retrospective cohort study using multiple existing observational databases to collect data from a 5-year period prior to the availability of denosumab. The study should identify women with postmenopausal osteoporosis and determine the occurrence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in each database in order to assess the background rates of those adverse events. The data obtained in this study will be used to inform the implementation of postmarketing requirement #2. The final protocol for this study was submitted on January 25, 2010.

   The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Study Completion Date:	May 2011
Final Report Submission:	August 2011

2. A long-term observational study in administrative databases to prospectively evaluate the incidence of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover in postmenopausal women administered Prolia (denosumab).

   The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2010
Submit Report providing information regarding Prolia (denosumab) use:	June 2013
Study Completion Date:	December 2022
Final Report Submission:	June 2023

3. A long-term surveillance study in postmenopausal women administered Prolia (denosumab) to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover.

   The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	August 2010
Study Completion Date:	December 2021
Final Report Submission:	June 2022

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of drug interactions of Prolia (denosumab) with CYP3A4 substrates.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

4. An *in vivo* drug-drug interaction clinical trial with a CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interactions of Prolia (denosumab) with CYP3A4 substrates.

   The timetable you submitted on May 28, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	August 2010
Trial Completion Date:	November 2011
Final Report Submission:	March 2012

Our October 16, 2009, action letter also stated that you would be required to conduct a long-term pregnancy exposure registry study in Prolia (denosumab) users who become pregnant on the drug. We have determined that this study would not be feasible because the drug does not have an indication for use in women of childbearing potential. Therefore, this study is not currently required.

Submit clinical protocols to your IND 009837, with a cross-reference letter to this BLA, STN 125320. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We acknowledge your written agreement to conduct the following postmarketing commitments, as described in your letter of May 28, 2010:

5. To confirm validation of the updated SE-HPLC method (MET-001208). The method was revised to add column conditioning using material containing the high molecular weight species. The protocol and final report will be included in an annual report to be submitted by February 28, 2011.
6. To submit proposed revisions to the (b) (4) and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method after 15 commercial manufacturing runs. The proposed revision to the specifications, the corresponding data from the 15 commercial manufacturing runs, and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by September 30, 2010.
7. To submit proposed revisions to the (b) (4) and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method to reflect increased manufacturing experience. The proposed revision to the specifications, the corresponding data from the commercial manufacturing runs to date and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by March 31, 2012.

We request that you submit all nonclinical and chemistry, manufacturing, and controls protocols and final reports to this BLA, STN 125320. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKEING COMMITMENT – FINAL REPORT**
- **POSTMARKETING CORRESPONDENCE**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes 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)).

As described in our letter dated October 2, 2009, in accordance with Section 505-1 of the FDCA we have determined that a REMS is necessary to ensure that the benefits of Prolia (denosumab) outweigh the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover.

Your proposed REMS, submitted on June 1, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of healthcare providers' understanding of the serious risks of Prolia (denosumab), including the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover, and how to select patients who are appropriate for treatment
b. An evaluation of patients' understanding of the serious risks of Prolia (denosumab), including the risks of serious infection including skin infection, dermatologic adverse events, and over-suppression of bone turnover
c. An evaluation of whether patients receive the Medication Guide and actions taken to ensure that patients receive the Medication Guide.
d. A summary of all reported serious infections including skin infection, dermatologic adverse events, and events possibly related to over-suppression of bone turnover, with analysis of adverse event reporting by prescriber type (e.g., endocrinologist, rheumatologist, primary care physician), when available
e. Provide the following details in the evaluation of the communication plan implementation: launch date of communication plan, number of recipients emailed the DHCP letter, number of recipients included in mass mailing of DHCP letter, dates of mailings (United States Postal mail and email), and a copy of the documents included in mailing.

The requirements for assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission 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 125320 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125320
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125320
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. 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, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations sent by courier or overnight mail should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20992-0002

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, Medication Guide). 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.

We remind you that pursuant to 21CFR 201.57(x)(18) and 201.80(f)(2) the Medication Guide must be reprinted immediately following the last section of the labeling, or alternatively, accompany the prescription drug labeling.

CARTON AND 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 (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 STN 125320**." 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 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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

POST-ACTION FEEDBACK MEETING

New molecular entities and important new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during the drug development and marketing application review process. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, contact the Division of Reproductive and Urologic Products.

If you have any questions, please call the Regulatory Health Project Manager, Nenita Crisostomo, R.N., at (301) 796-0875.

Sincerely,

/Julie Beitz, M.D./

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: REMS documents; Package Insert, Carton and Container Labels