DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/51

SUPPLEMENT APPROVAL

Amgen, Inc.
Attention: Sandeep Kumar, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 38-4-C
Thousand Oaks, CA 91320-1799

Dear Dr. Kumar:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received November 21, 2011, submitted under section 351 of the Public Health Service Act for Prolia® (denosumab).

We acknowledge receipt of your amendments dated January 11, 18 and 20, February 10 and 22, March 9 and 20, May 9, June 27, July 23, August 8, 9, 10, 17, 27 and 31, and September 19, 2012. We also acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated August 9, 2012.

This "Prior Approval" sBLA provides for a new indication for the treatment to increase bone mass in men with osteoporosis at high risk of fracture. This sBLA also includes a proposed modification to the approved REMS.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the lengths of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 and 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. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125320/51**"

Also within 14 days, amend all pending supplemental applications for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container 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 125320/51**." Approval of this submission by FDA is not required before the labeling is used.

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 pediatric studies are impossible (the indication does not occur in the pediatric population).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) 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.

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 (including atypical fractures, osteonecrosis of the jaw, and hypocalcemia).

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

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

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). This postmarketing required study (PMR) is described in the June 1, 2010, approval letter for Prolia.

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

   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. This PMR is described in the June 1, 2010, approval letter for Prolia.

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

   Study Completion Date: December 2021
   Final Report Submission: June 2022

4. Inclusion of a new target population, men with osteoporosis, in the required postmarketing study entitled, “The Denosumab Global Postmarketing Safety Observational Study” (Study 20090522), designated above as PMR #2.

   The timetable you submitted on September 19, 2012, states that you will conduct this study according to the following schedule:

   Submit Report providing information regarding Prolia (denosumab) use: June 2013
   Study Completion Date: December 2022

Final Report Submission: June 2023

5. Inclusion of a new target population, men with osteoporosis, in the required postmarketing study entitled, "The Prolia Postmarketing Active Safety Surveillance Program" (Study 20090601), designated above as PMR #3.

   The timetable you submitted on September 19, 2012, states that you will conduct this study according to the following schedule:

   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 assess a signal of a serious risk of teratogenicity through transmission of denosumab during sexual intercourse to the fetus of a pregnant partner.

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

6. A postmarketing required clinical trial to investigate the levels of denosumab in the semen of men treated with Prolia.

   The timetable you submitted on September 19, 2012, states that you will conduct this trial according to the following schedule:

   Final Protocol Submission: March 2013
   Trial Completion Date: June 2014
   Final Report Submission: December 2014

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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Prolia was originally approved on June 1, 2010, and REMS modifications were approved on September 16, 2011, and May 10 and June 7, 2012. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of updating the REMS to include revisions to the REMS document, a revised Dear Healthcare Provider (DHCP) letter and revised REMS website as part of the REMS Communication Plan (CP), and a revised Medication Guide to include information about the new indication in men with osteoporosis and the risk of atypical fracture.

Your proposed modified REMS, submitted on September 19, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on June 1, 2010.

There are no changes to the REMS assessment plan described in our June 1, 2010, letter.

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.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **BLA 125320 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYLTON V JOFFE
09/20/2012