

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125320

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: BLA 125320 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DRUP PDUFA Goal Date: 10/19/09 Stamp Date: 12/19/2008

Proprietary Name: Prolia

Established/Generic Name: denosumab

Dosage Form: subcutaneous injection, prefilled

syringe

Applicant/Sponsor: Amgen

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):4

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Background:

Denosumab is a fully human monoclonal antibody that is a receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) that inhibits human RANKL (huRANKL) with a mechanism of action similar to the endogenous RANKL inhibitor, osteoprotegerin (OPG). It is being developed by Amgen for the treatment and prevention of postmenopausal osteoporosis (PMO) and the treatment and prevention of bone loss in patients undergoing hormone ablation (HALT) for prostate or breast cancer. The sponsor submitted a BLA (BLA 125,320) on 12/19/08, which DRUP is currently reviewing for the treatment and prevention of postmenopausal osteoporosis indications. DBOP is reviewing the two cancer indications. Please note, each indication being pursued has been split into a separate BLA number as follows:

BLA 125,320: Treatment of osteoporosis in postmenopausal women

BLA 125,331: Prevention of osteoporosis in postmenopausal women

BLA 125,332: Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer

BLA 125,333: Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing

regimen; or route of administration?*

No. PREA does not apply. **Skip to signature block.**

Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): _____

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

This page was completed by:

{See appended electronic signature page}



Celia R. Peacock, MPH, RD
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

1. Debarment Certification

Amgen hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Randall Steiner, DPA, MS

Executive Director, Global Regulatory Affairs and Safety

13 May 2010
Date

1. Debarment Certification

Amgen hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Randall Steiner, DPA, MS
Executive Director, Regulatory Affairs

11/11/08
Date

1. Environmental Assessment [Biologics]

Denosumab is subject to a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(c), based on consideration of its effects when exposed to the environment.

Denosumab is a fully human monoclonal antibody (IgG2) consisting of a sequence of amino acids and a protein and has a molecular weight of 147 kilodaltons. Denosumab is expressed in a (CHO) cell culture line under defined and controlled conditions.

Denosumab is harvested and purified by a series of proprietary processing steps and is formulated in a buffer before sterile filtration and dispensing. The drug product is (b) (4) manufactured in a series of formulation and filling operations. The manufacturing and release of denosumab drug substance and drug product are conducted under current Good Manufacturing Practice (GMP) conditions.

Denosumab is supplied as a sterile, preservative free solution intended for (b) (4) use. The glass vial presentations contain denosumab at 60 or 70 mg/mL formulated with (b) (4) sodium acetate and (b) (4) sorbitol, at a pH of 5.2. The 60 mg/mL and 70 mg/mL vials are filled to a target deliverable volume of 1.0 mL and 1.7 mL, respectively. The prefilled syringe (PFS) drug product contains denosumab at 60 mg/mL concentration formulated with (b) (4) sodium acetate, (b) (4) sorbitol, and 0.01% (w/v) polysorbate 20, at a pH of 5.2, filled to a target deliverable volume of 1.0 mL.

Denosumab is administered via subcutaneous or (b) (4) injection. All excipients used conform to the United States Pharmacopoeia (USP) and European Pharmacopoeia (PhEur) and are commonly used in parenteral products.

Denosumab is considered to be a nonhazardous, biodegradable product. Patients injected with Denosumab are expected to fully metabolize it with negligible excretion of intact, biologically-active protein from the body. Any breakdown products are not expected to remain in the environment for any significant period as a biologically-active protein because of their susceptibility to biodegradation by a wide range of environmental microflora. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Tuesday, June 01, 2010 9:55 AM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: RE: BLA 125320: Prolia--REMS documents

Dear Nita,

Amgen has reviewed the proposed changes in each of the attached documents and accepts them all.

Many thanks for your continued support!

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

RESTRICTED INFORMATION: This e-mail, and attached documents and links contains information that is "Restricted Information" under Amgen's *Confidentiality and Proprietary Information Policy* and may only be shared internally with those Amgen staff members who have a true business "need to know" such information for the performance of their job duties. Disclosure outside of Amgen is permitted only with written permission of an Amgen officer and requires a confidentiality agreement with the recipient. If you have any questions about how this information may impact your ability to trade in Amgen securities, contact the Amgen securities trading hotline at x7-1222.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Friday, May 28, 2010 2:49 PM
To: Burd, Edward
Cc: Hovland, David
Subject: BLA 125320: Prolia--REMS documents

Hi Ed,

Please refer to your email on May 13, 2010, containing your proposed individual REMS documents and Dear Healthcare Provider letter. Attached below are the Division's final versions of the documents. Listed below is a summary of the editorial changes that were made to these documents. ***Please review and send an email confirming your concurrence.***

Resubmit your proposed REMS and other materials in WORD format. The entire REMS and appended materials should be a single WORD document. The Supporting Document should be submitted at the same time as a separate single WORD document. Provide a track changes and clean version of all revised materials and documents in a WORD version showing all changes. Please provide all materials in a PDF format as well.

Thank you so much,

6/1/2010

Nita
Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

<<Prolia REMS w-MG-CP cleared.052810.doc>> <<Prolia DHCP letter.052810.doc>>

No content was changed but there were minor technical edits made to the REMS document - see below:

Communication Plan:

1) added "s" after specialty groups:

"Initially, the DHCP Letter will be sent by mass mailing or electronic mailing to targeted endocrinologists, rheumatologists, gynecologists, and primary care physicians who have..."

2) semi-colon removed after "societies"

"In addition, Amgen will distribute the DHCP Letter to the following professional societies: ..."

Timetable:

period added after "Use" and new sentence beginning with "Therefore":

"The REMS for Prolia does not include Elements to Assure Safe Use. Therefore..."

**6 pages(s) have been Withheld in Full
immediately following this page as B4 (CCI/
TS)**

Crisostomo, Nenita

From: Hughes, Patricia
Tuesday, June 01, 2010 1:11 PM
Crisostomo, Nenita
Suvarna, Kalavati; Lolas, Anastasia
Subject: FW: BLA 125320 Prolia(denosumab): EER
Categories: 0 days

Here is the very latest and updated TB-EER which included the biennial inspection conducted last week. All sites listed in the BLA have an acceptable CGMP compliance status.

Patricia

From: Pohlhaus, Timothy
Sent: Tuesday, June 01, 2010 1:04 PM
To: Hughes, Patricia; Lolas, Anastasia
Cc: Cruz, Concepcion; Rothman, Barry; Pohlhaus, Timothy
Subject: FW: BLA 125320 Prolia(denosumab): EER

Updated 6/1/2010 to include most recent BI Pharma inspection info:

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 3218
Silver Spring, MD 20993
Phone - (301) 796-5224

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the list below to find the current compliance status of each site. There are no pending or ongoing compliance actions to prevent approval of STN 125320.

Manufacture, release and stability testing, and storage of drug substance. Also, storage of working cell bank:

Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No. 3003072024

Inspected June 8-12, 2009 and classified NAI. Denosumab drug substance manufacturing processes were covered and are acceptable.

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65 88397 Biberach an der Riss Germany
FEI No. 3002806518

(b) (4)

(b) (4)

Amgen Inc. (ACO) Longmont Facility
1000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484

Inspected January 31, 2008 and classified NAI. The BTP profile was covered, specifically including coverage of biological product raw material, drug substance, and drug product release testing, and is acceptable.

Storage of Master and Working cell bank, raw material testing and release, drug substance storage:

Amgen Inc. (ATO)
Amgen Center Drive Thousand Oaks, CA 91320 USA
No. 2026154

Inspected April 7-11, 2008 and classified NAI. The CTB profile was covered and is acceptable.

Raw material testing and release, drug substance storage, release and stability testing and Drug product manufacture, release and stability testing, packaging and labeling, and storage:

Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA
FEI No. 1000110364

Inspected July 27 - September 11, 2009 and classified VAI. The BTP and TRP profiles were covered and are acceptable.

(b) (4)

Drug product storage and distribution:
Amgen Inc. (LDC)
12000 Plantside Drive Louisville, KY 40299 USA
FEI No. 2026154 3003750095

Inspected January 5-6, 2006 and classified NAI. Drug product storage conditions were covered and are acceptable.

Drug product stability (container closure for vials) testing:
Amgen Inc. (AFR)
6701 Kaiser Drive Fremont, CA 94555 USA

FEI No. 3005925062

Inspected September 3-10, 2008 and classified NAI. The TRP profile and stability responsibilities were covered and are acceptable.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Pohlhaus, Timothy
Sent: Friday, May 28, 2010 2:35 PM
To: Lolos, Anastasia
Cc: Stock, Marisa
Subject: RE: BLA 125320 Prolia(denosumab): EER

Hi Anastasia,

A compliance check was sent to Laura, Don, Kala, and Patricia on February 12, 2010.
I have attached it for reference.

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 3218
Silver Spring, MD 20993
Phone - (301) 796-5224

From: Lolos, Anastasia
Sent: Friday, May 28, 2010 2:31 PM
To: Stock, Marisa; Pohlhaus, Timothy
Subject: FW: BLA 125320 Prolia(denosumab): EER

Can you please check on this? BLA 125320. I don't have the sites, just check to see if you ever received an EER for this submission.

Thanks,

Anastasia

From: Hughes, Patricia

Sent: Friday, May 28, 2010 2:28 PM
To: Lolos, Anastasia; Hoyt, Colleen
Subject: Fw: BLA 125320 Prolia(denosumab): EER

.tasia,

Can you find out if someone has done a compliance check for BLA 125320? The PDUFA date is June 1. BMT did not have any reviews to do for the amendment so we did not submit one.
Patricia

From: Crisostomo, Nenita
To: Hughes, Patricia; Suvarna, Kalavati
Cc: Benson, George; Kehoe, Theresa; Fuchs, Chana; Rivera Martinez, Edwin; Kober, Margaret
Sent: Fri May 28 11:48:57 2010
Subject: RE: BLA 125320 Prolia(denosumab): EER

Hi Patricia,

Just a follow-up from my email below, and to let you know that our planned goal date of June 1 (next Tuesday) is still the plan. Please update.

Thankss,
Nita

From: Crisostomo, Nenita
Sent: Thursday, May 27, 2010 10:35 PM
To: Hughes, Patricia; Suvarna, Kalavati
Subject: BLA 125320 Prolia(denosumab): EER

Hi Patricia & Kala,

I am almost complete in putting the Action Package together and ran into this section of the checklist:

BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date)

I am inquiring if we have an EER report as this item seems to require the report to be within 30 days of action date?

Thanks so much for your help,
nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/0

INFORMATION REQUEST

May 28, 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 January 25, 2010, submitted under section 351 of the Public Health Service Act for Prolia™ (denosumab).

We refer to our letter to you dated May, 3, 2010, containing the required postmarketing studies and your communication dated May 4, 2010, conveying your agreement in writing to perform the postmarketing requirements and commitments as listed.

Further revisions to these postmarketing requirements and commitments have developed during our review of your BLA application and we have determined that the following revised list of postmarketing studies will be required if this application is approved.

We request that you submit your agreement in writing to conduct postmarketing requirements and commitments listed in the attachment to this letter. We request a prompt written response in order to continue our evaluation of your BLA.

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

Sincerely,

A handwritten signature in cursive script that reads "George Benson".

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

Post-marketing Requirements

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.

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).

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.

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

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.

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

Post-marketing Commitments

Post-marketing commitments not subject to reporting requirements of Section 506B:

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 breakloose and extrusion release 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 breakloose and extrusion release 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.

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Friday, May 28, 2010 5:38 PM
To: Crisostomo, Nenita
Subject: RE: BLA 125320 Prolia: Package Insert

Dear Nita,

Amgen has reviewed the three changes to the 12.3 Pharmacokinetic section and accepts the changed sentence to read as follows:
After C_{max} , serum denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n=46).

Thanks so much for your continued efforts on our behalf.

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Friday, May 28, 2010 2:06 PM
To: Burd, Edward
Cc: Hovland, David
Subject: BLA 125320 Prolia: Package Insert

<<PI 052810 finalFDAedits.doc>>
Hi Ed,

Attached is the label as discussed with you this morning with revisions under Pharmacokinetic section. Please review and if your Team concurs, please send an email confirmation agreeing to this version which we consider final. If you have any questions, please feel free to contact me.

Thank you,
Nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

17 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4
(CCI/TS)

5/28/2010

Crisostomo, Nenita

m: Donohoe, Elizabeth A
: Friday, May 28, 2010 1:15 PM
Gassman, Audrey; Crisostomo, Nenita
Cc: Benson, George; Kehoe, Theresa; Kober, Margaret; Heinrich, Kate; Robottom, Suzanne Berkman
Subject: RE: Prolia - cleared: Need final REMS

Audrey -

No content was changed but there were minor technical edits made to the REMS document - see below:

Communication Plan:

1) added "s" after specialty groups:

"Initially, the DHCP Letter will be sent by mass mailing or electronic mailing to targeted endocrinologists, rheumatologists, gynecologists, and primary care physicians who have..."

2) semi-colon removed after "societies"

"In addition, Amgen will distribute the DHCP Letter to the following professional societies: ..."

Timetable:

period added after "Use" and new sentence beginning with "Therefore":

"The REMS for Prolia does not include Elements to Assure Safe Use. Therefore..."

I called Kristen Everett and she sent me the track changed version to the REMS - I will forward to you

no changes made by SWAT to DHCP letter..... when I asked Claudia if she was aware, she checked on e-room [I do not have access] and no changes apparent

Liz

Elizabeth A. Donohoe, M.D.
Drug Risk Management Analyst
FDA/CDER/OSE, Division of Risk Management
WO Bldg 22, room 2445
301-796-4841

From: Gassman, Audrey
Sent: Friday, May 28, 2010 1:01 PM
To: Donohoe, Elizabeth A; Crisostomo, Nenita
Cc: Benson, George; Kehoe, Theresa; Kober, Margaret; Heinrich, Kate; Robottom, Suzanne Berkman
Subject: RE: Prolia - cleared: Need final REMS

Liz -

We appreciate your hard work to get this done.

I just want to make sure that you did check these carefully because we did not get (and I do not see) any tracked changes on any of these documents.

Audrey

From: Donohoe, Elizabeth A
Sent: Friday, May 28, 2010 12:57 PM
To: Crisostomo, Nenita
Cc: Benson, George; Kehoe, Theresa; Kober, Margaret; Heinrich, Kate; Robottom, Suzanne Berkman; Gassman, Audrey
Subject: RE: Prolia - cleared: Need final REMS

Based on my review of the attached documents below, it appears that no changes have been made to the REMS Document or the DHCP letter compared to the May 13 emailed versions DRISK received from DRUP. [The same as referenced in our Final review dated May 19, 2010.] These documents are fine.

The Approval Letter is fine.

Hope this helps.

Liz

Elizabeth A. Donohoe, M.D.
Drug Risk Management Analyst
FDA/CDER/OSE, Division of Risk Management
WO Bldg 22, room 2445
301-796-4841

From: Crisostomo, Nenita
Sent: Friday, May 28, 2010 12:12 PM
To: Donohoe, Elizabeth A; Heinrich, Kate
Cc: Benson, George; Kehoe, Theresa; Kober, Margaret
Subject: FW: Prolia - cleared: Need final REMS
Importance: High

Hi Liz,

Below, is the finally cleared letter along with the REMS stuff. I need your clearance and DRUP's before I sent out the final documents to Amgen for their concurrence so that they can submit this officially.

Just FYI to All: I spoke with Amgen a few minutes ago and they can turn these things around asap, however, official submission do not happen until Tuesday due to EDR technical processes, and will not get posted likely until the end of the week.

Thanks,
nita

From: Gassman, Audrey
Sent: Friday, May 28, 2010 11:40 AM
To: Benson, George; Kehoe, Theresa; Crisostomo, Nenita
Cc: Monroe, Scott
Subject: FW: Prolia - cleared
Importance: High

George and Theresa -

Prolia letter has been cleared. I will work with Nita and Marty to move this along.

Audrey

From: Everett, Kristen
Sent: Friday, May 28, 2010 11:36 AM
To: Kaufman, Martin; Gassman, Audrey
Cc: Cleared SWAT letters; Robottom, Suzanne Berkman; Toyserkani, Gita

Crisostomo, Nenita

From: Crisostomo, Nenita
Date: Thursday, May 13, 2010 12:14 PM
To: 'Burd, Edward'
Subject: BLA 125320 Prolia: denosumab--Final PI
Attachments: PI.051310.final.doc



PI.051310.final.doc
(431 KB)

Hi Ed,

Attached is our version of the final Package Insert, seeking agreement from your Team.

Thank you,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

17 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as
B4 (CCI/TS)

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, May 13, 2010 11:45 AM
To: Gassman, Audrey; Kaufman, Martin; Voss, Stephen; Donohoe, Elizabeth A
Cc: Benson, George; Heinrich, Kate
Subject: FW: STN BL 125320/0 individual REMS documents in word and pdf formats
Attachments: rems-redline.doc; rems-redline.pdf; rems-supporting-document-clean.doc; rems-supporting-document-clean.pdf; rems-supporting-document-redline.doc; rems-supporting-document-redline.pdf; hcp-letter-clean.doc; hcp-letter-clean.pdf; hcp-letter-redline.doc; hcp-letter-redline.pdf; rems-clean.doc; rems-clean.pdf

Tracking:

Recipient	Read
Gassman, Audrey	Read: 5/13/2010 11:47 AM
Kaufman, Martin	
Voss, Stephen	Read: 5/13/2010 11:46 AM
Donohoe, Elizabeth A	
Benson, George	
Heinrich, Kate	

Hi All,

Please toss out the documents (4 emails) that were emailed last night. During the preliminary review by the Safety and Clinical Team, the DHCP language still contained the old language despite their acceptance in their **written response**.

Therefore, we asked them to resend by emailing us these documents separately, to be followed by a consolidated document as requested by DRISK's IR yesterday. I will email that to you as soon as received.

Thanks,
nita

From: Burd, Edward [mailto:eburd@amgen.com]
Sent: Thursday, May 13, 2010 10:54 AM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: STN BL 125320/0 individual REMS documents in word and pdf formats

Dear Nita,

Thanks for the opportunity to correct the oversight. Attached are the individual documents. Please note that the consolidated document will contain the appendices for the REMS document. WE will correct it and send it to you within the next two hours or sooner.

Edward S. Burd, Ph. D.
+1-805-447-3022 office

5/28/2010

+1-805-490-5237 cell

eburd@amgen.com

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Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Thursday, May 13, 2010 12:25 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: STN BL 125320/0: Response to Information Request of 12 May 2010 (REMS) email 2 of 2
Attachments: consolidated-rems-redline.doc; consolidated-rems-redline.pdf

Dear Nita,

Attached are our responses to the information request of 12 May 2010 from Dr. Benson requesting additional modifications to the REMS documents. In this email please find attached the consolidated rems documents in a single file in redline word and redline pdf formats. This is the second of two emails which will contain together a sum total of five files. The exact same files will be provided in a formal submission through the electronic gateway later this week.

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 13, 2010

TO: Memo to File

THROUGH :

FROM: Nenita Crisostomo

SUBJECT: Package Insert, Final--Amgen's Response to FDA's recommendations sent on May 13, 2010

APPLICATION/DRUG: BLA 125320 Prolia (denosumab)

Attached is Amgen, Inc.'s acceptance of FDA's final version of the Package Insert, as attached. This version was reviewed from the Sponsor's official submission dated April 20, 2010. See attached email.

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Thursday, May 13, 2010 12:41 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: RE: BLA 125320 Prolia: denosumab--Final PI

Dear Nita,

Amgen has reviewed the final PI and accepts it.

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Thursday, May 13, 2010 9:14 AM
To: Burd, Edward
Subject: BLA 125320 Prolia: denosumab--Final PI

<<PI.051310.final.doc>>

Hi Ed,

Attached is our version of the final Package Insert, seeking agreement from your Team.

Thank you,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

5/16/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/0

INFORMATION REQUEST

May 12, 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 January 25, 2010, submitted under section 351 of the Public Health Service Act for Prolia™ (denosumab).

We are reviewing your application and have the following recommendations from the Division of Risk Management regarding the Risk Evaluation and Mitigation Strategy (REMS) document, Dear Healthcare Provider Letter (DHCP), REMS Landing Page, REMS Link off of the Homepage, and REMS Supporting Document. We request a prompt written response in order to continue our evaluation of your BLA.

Division of Risk Management

We have reviewed your May 7, 2010, submission and have the following comments. Please be aware that we anticipate additional comments as your submission(s) undergoes further review. Also, see the attached WORD version of the REMS Document and the DHCP Letter (with track changes).

REMS Document

1. See attached track changes.
2. Under Communication Plan, include a statement to clarify that targeted providers who do not have known email addresses will be sent hardcopy mailings of the letter. (see Comment 2 under Supporting Document below).

Dear Health Care Provider Letter

1. See attached track changes.
2. Revise the language under “Serious Infections” to reflect what is in the label. This language was forwarded to you on May 5, 2010 via email from the review division.

REMS Landing Page

The submission is acceptable.

REMS Link off of the Homepage

The language you provided to direct users from the link off of the Prolia homepage to the REMS landing page is not clear. We recommend:

1. Add “Information” to the first line so that it reads: “Prolia Safety Information”; and
2. Spell out: Risk Evaluation and Mitigation Strategy (REMS).

REMS Supporting Document

Revise the Supporting Document as follows:

1. Make all information in the Supporting Document consistent with the REMS document, based on recommendations included in this communication.
2. Under Communication Plan, include a statement to clarify that targeted providers who do not have known email addresses will be sent hardcopy mailings of the letter.
3. Note in the Supporting Document that the protocol, survey instrument, and methodology for the patient and provider surveys will be finalized after the product labeling and educational materials are finalized, and will be provided to the FDA at least 90 days before the surveys are administered.

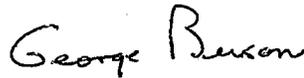
General Comments:

1. Resubmit the revised Proposed REMS with appended materials and the REMS Supporting Document.
2. Resubmit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. Please provide a track changes and clean version of all revised materials and document in a WORD version showing all changes. Please provide all materials in a PDF format as well.
3. If certain documents are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single WORD document.

4. Indicate "Appendix ___" at the top of the respective appendices.
5. Ensure that all REMS materials, including the communication materials, accurately reflect the most recent language used in labeling.

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

Sincerely,

A handwritten signature in cursive script that reads "George Benson".

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Crisostomo, Nenita

From: Crisostomo, Nenita
Wednesday, May 12, 2010 1:49 PM
'Burd, Edward'
Subject: BLA 125320 Prolia: MedGuide
Attachments: MedGuide.051210.doc



MedGuide.051210.
doc (79 KB)

Ed,

Here is the MedGuide that we consider final. We made those 2 changes that I mentioned to you last week Friday.

1. Changed [TRADNAME] to Prolia
2. Changed "onto your breastmilk" to "into your breastmilk"

If your Team agrees, it will be attached to the Action letter.

Thanks,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

4 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 12, 2010

TO: Memo to File

THROUGH :

FROM: Nenita Crisostomo

**SUBJECT: Medication Guide--Amgen's Response to FDA's recommendations sent on
May 12, 2010**

APPLICATION/DRUG: BLA 125320 Prolia (denosumab)

Attached is Amgen, Inc.'s acceptance of FDA's final version of the MedGuide, as attached. This Med Guide version was revised from the Sponsor's official submission dated May 7, 2010. See attached email.

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Wednesday, May 12, 2010 2:09 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: RE: BLA 125320 Prolia: MedGuide

Thanks! We discussed previously when we learned about the two changes and gladly accept. Please consider this final!

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, May 12, 2010 10:49 AM
To: Burd, Edward
Subject: BLA 125320 Prolia: MedGuide

<<MedGuide.051210.doc>>

Ed,

Here is the MedGuide that we consider final. We made those 2 changes that I mentioned to you last week Friday.

1. Changed [TRADNAME] to Prolia
2. Changed "onto your breastmilk" to "into your breastmilk"

If your Team agrees, it will be attached to the Action letter.

Thanks,
nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

5/22/2010

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Monday, May 10, 2010 1:23 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: RE: BLA 125320 Prolia: Medguide

Yes, this is acceptable to us. Many thanks!

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Monday, May 10, 2010 10:20 AM
To: Burd, Edward
Subject: BLA 125320 Prolia: Medguide

Ed,

As we discussed, the only 2 changes on the MG are to replace the TRADNAME with "Prolia", and change the "passes onto your breast milk" to "passes into your breast milk".

Please do not submit another version. If this is all ok with your Team, we will just make the change ourselves, and the edited version will be made on the MG attached to the Action letter.

Thanks,
nita

4 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, May 05, 2010 4:29 PM
To: 'Burd, Edward'
Cc: Hovland, David
Subject: RE: Answers to your questions of yesterday and an urgent request

Tracking:	Recipient	Read
	'Burd, Edward'	
	Hovland, David	
	Donohoe, Elizabeth A	
	Heinrich, Kate	Read: 5/6/2010 9:57 AM
	Kehoe, Theresa	
	Voss, Stephen	

Hi Ed,

Thanks again for your response and will look forward to your official submission.

In response to your inquiry, we believe it is appropriate to take out the (b) (4) in the letter and we felt that keeping the % in was not needed.

The language below is extracted right from the label.....

Serious infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in the Prolia-treated subjects.

Hope this helps. Please let me know if you have any questions.

Thanks,
nita

From: Burd, Edward [mailto:eburd@amgen.com]
Sent: Wednesday, May 05, 2010 12:45 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: Answers to your questions of yesterday and an urgent request

Dear Nita,

Below are the answers to your requests of yesterday for clarification. The exact same information will be included in our formal submission to made later this week. I will let you know the timing of this submission later today.

6/16/2010

We also have a rather urgent request regarding the DHCP letter where we have identified a factual error. Would it be possible to request the appropriate reviewers to take a look at our proposal for meeting FDA's request in the information request?. WE would like to settle this prior to making our submission this week. Thanks!

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

1. **Comments Received From Nenita Crisotomo via Email 04 May 2010**

Requesting clarification: When do you anticipate to launch?

Company Response:

Amgen anticipates being able to launch within approximately 3 weeks after approval.

Could you please provide a rationale for the delay in submitting the denosumab use data report?

Company Response:

The date (30 June 2013) for submitting a report of the analysis of data pertaining to the identification of denosumab users based upon use of temporary drug codes employed after shortly after launch was based upon the following assumptions and considerations:

- Denosumab will be approved on the PDUFA date (25 July 2010) and will be commercially available in the US in August 2010.
- The majority of the study population treated with denosumab will be Medicare beneficiaries.
- Six months of data is considered to be optimum to develop and evaluate an exposure algorithm in Medicare. Six months' of data includes data for the calendar year 2011.
- Medicare data are released on a calendar year basis, with an approximate 9- to 12-month time lag. For example, 2010 data will be released in the fourth quarter of 2011, and 2011 data will be released in the fourth quarter of 2012.
- Medicare data for 2011 are expected to be available in the fourth quarter of 2012. Allowing 3 months for data analysis and 3 months for preparation of the report, Amgen anticipates that the report submission date would be 20 June 2013.

Amgen considers that the appropriate analysis requires sufficient data to capture all of the temporary codes used in the populations that will be treated with denosumab in first years after launch. A report submission date of 30 June 2013 allows capture of data from 2010 and 2011 and will reflect usage among both early adopters and the general population of women with postmenopausal osteoporosis who are treated with denosumab.

2. Information request received 04 May 2010.

Amgen accepts the tracked changes [in the DHCP letter] with the following clarification.

FDA has proposed the following wording under "Serious infection":

[Redacted text block] (b) (4)

[Redacted text block] (b) (4)

[Redacted text block] (b) (4)



BLA 125320/0

INFORMATION REQUEST
May 4, 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 January 25, 2010, submitted under section 351 of the Public Health Service Act for Prolia™ (denosumab).

We are reviewing your application and have the following recommendations from the Division of Risk Management regarding the Risk Evaluation and Mitigation Strategy (REMS) document, Dear Healthcare Provider Letter (DHCP), REMS Landing Page, REMS Supporting Document, and Medication Guide, as well as clinical and safety biostatistics comments. We request a prompt written response in order to continue our evaluation of your BLA.

Division of Risk Management

We have reviewed your April 19, 2010, submission and have the following comments. Be aware that we anticipate additional comments as your submission(s) undergoes further review. Also, see the attached WORD version of the REMS and the DHCP, both with tracked changes.

REMS Document

1. See attached track changes.
2. REMS Goals are acceptable.
3. Standard language under “Medication Guide” is “The carton and container package.”
4. Communication Plan:
 - a. Describe how you plan to obtain email addresses for all targeted prescribers.
 - b. Clarify how new prescribers will be identified. Your current criteria “[prescribers] who have previously prescribed Prolia™ who had not prescribed it in the 12 months preceding” appear contradictory.

- c. Include the screenshot of the webpage as an Appendix to the REMS; add reference to REMS document.
 - d. See the attached track changes version of the Dear Healthcare Provider Letter and embedded comments.
5. Timetable for Assessment of the REMS is acceptable.

Dear Healthcare Provider Letter

1. See attached tracked changes.
2. The DHCP letter in your April 19, 2010, submission differs substantially from the version FDA sent to you on April 9, 2010. The attached version is the April 9, 2010, version and embedded comments address your April 19, 2010, submission.

REMS Landing Page

1. Add the phrase below as the first bullet to the second paragraph, ending "...communicate the risks of: ...".
 - a. Serious infections
2. In the fourth paragraph, re-word the goals to be consistent with the REMS goals:
 - a. To inform healthcare providers (HCP) about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover associated with Prolia™.
 - b. To inform patients about the serious risks associated with the use of Prolia™.

REMS Supporting Document

Revise the Supporting Document as follows:

1. Revise all information in the Supporting Document to be consistent with the REMS document, based on recommendations included in this communication.
2. Provide clarification of how new prescribers will be identified (see 2.c. above under Communication Plan).
3. Provide the specific wording to direct users from the link off the Prolia™ homepage to the REMS landing page. We recommend a single-click, direct, prominent link off the Prolia™ homepage to a REMS landing page. For example, the link could state: "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."
4. We acknowledge that you will include a statement on the Prolia™ carton and container labels. Indicate what statement you will use; we recommend that you use

one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” Or,
- “Dispense the accompanying Medication Guide to each patient.”

General Comments:

1. Resubmit the revised Proposed REMS with appended materials and the REMS Supporting Document.
2. Resubmit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. Provide a tracked and clean version of all revised materials and document in a WORD version showing all changes. Provide all materials in a PDF format as well.
3. If certain documents are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single WORD document.
4. Indicate "Appendix ____" at the top of the respective appendices.

Clinical

Regarding the Protocol 20090601, Questionnaire for Hypocalcemia Adverse Events (pp. 36-38):

We had previously requested two changes to this questionnaire, i.e. to specify the actual calcium level rather than ranges, and to specify the data of the most recent denosumab injection in relation to the hypocalcemic event. You had agreed to these changes, however, your April 16, 2010, protocol version includes only the former and not the latter.

Safety Biostatistics

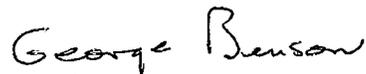
Accounting for the fact that true market experience of denosumab is unknown at this time, the following comments are based upon the review of Protocol 20090522.

1. You should submit to the Agency for comment a detailed statistical analysis plan (SAP) prior to study initiation and include plans for how to make revisions to the SAP based upon information that arises once denosumab has market exposure. The plan should provide details on all statistical analyses outlined in the study protocol, including definitions of exposure, the meta-analysis across the data bases, and the various methods discussed for adjustment for confounding when comparing across exposure groups.
2. Based upon the assumptions that you provided, and the simulation study using Fisher's Exact test, the planned study appears to be sufficiently powered. However, it should be noted that several assumptions are made in the power calculations which may not be precise based upon the lack of information to date about actual use of denosumab. With large deviations from the assumed estimates used in the power calculations, the study

may lack sufficient power to detect adverse events of special interest (AESI's). To protect against the use of inappropriate estimates used in the power calculations, you should conduct an analysis of the data base after several years to address the accuracy of their estimates and the potential for the study to be underpowered to detect AESI's.

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

Sincerely,

A handwritten signature in cursive script that reads "George Benson".

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Tuesday, May 04, 2010 3:17 PM
To: 'Burd, Edward'
Cc: Hovland, David
Subject: FW: Modified PMR acceptance letter for your consideration
Attachments: STN BL 125320 sn0058--PMR acceptance.pdf

Hi Ed,

Requesting clarification: When do you anticipate to launch?

Could you please provide a rationale for the delay in submitting the denosumab use data report?

Thanks,
nita

From: Burd, Edward [mailto:eburd@amgen.com]
Sent: Tuesday, May 04, 2010 12:16 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: Modified PMR acceptance letter for your consideration

Dear Nita,

Attached is the changed letter as requested. Please let me know if this meets your requirements. We will wait until we hear back from you regarding submission of this same letter through the electronic gateway.

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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Amgen
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799
805.447.1000
Direct Dial: 805.447.3022
Fax: 805.480.1330
E-mail: edward.burd@amgen.com

04 May 2010

Scott Monroe, MD Division Director
Division of Reproductive and Urologic Products
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: Denosumab (AMG 162; Human Monoclonal Antibody to RANK Ligand)
Response to Questions: Requested by the Agency in 03 May 2010 fax,
Post-Marketing Requirements and Post-Marketing Commitments
STN BL 125320/0, Sequence No. 0058

Attention: Nenita Crisostomo, Regulatory Project Manager

Dear Dr Monroe:

Amgen is in receipt of Dr. Benson's Information Request dated May 3, 2010 outlining the Agency's proposed Post-marketing requirements and Post-marketing commitments. Amgen agrees to perform all of these Post-marketing requirements and Post-marketing commitments as outlined in Dr. Benson's letter and provides the following information about the timing of these activities below:

Post-marketing Requirements

1. Conduct 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 denosumab (Protocols 20090521 and 20090522).

For Protocol 20090521:

Study Completion Date: May (b) (4) 2011

Final Report Submission: August (b) (4), 2011

For Protocol 20090522:

(b) (4)

(b) (4)

2. Conduct a long-term surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover (Protocol 20090601).

Final Protocol Submission: August (b) (4), 2010

Study Completion Date: December (b) (4), 2021

Final Report Submission: June (b) (4), 2022

3. Conduct an *in vivo* drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interaction of denosumab with CYP3A4.

Final Protocol Submission: August (b) (4), 2010

Study Completion Date: November (b) (4), 2011

Final Report Submission: March (b) (4), 2012

Post-marketing Commitments

Office of Biotechnology Products:

Post-marketing Studies not subject to reporting requirements of 21 CFR 601.70:

(b) (4)

2. 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.
3. To submit proposed revisions to the breakloose and extrusion release 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.

4. To submit proposed revisions to the breakloose and extrusion release 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.

The information contained herein is proprietary and confidential and should not be disclosed to any third party without the prior written consent of Amgen Inc. Amgen Inc. considers the contents of this submission confidential and exempt from disclosure under 21 CFR§20.61 and Freedom of Information Act 5 USC 552(b)(4). Should questions arise, please contact me at (805) 447-3022.

Sincerely,



Edward S Burd, PhD
Senior Manager
Regulatory Affairs



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125320/0

INFORMATION REQUEST

May 3, 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 January 25, 2010, submitted under section 351 of the Public Health Service Act for Prolia™ (denosumab).

We are reviewing your application and have determined that postmarketing studies will be required if this application is approved. We request that you provide a timetable for conducting each of the postmarketing requirements (PMRs) listed in the attachment to this letter. Provide the final report submission dates (commitments 1 and 2), number of runs (commitment 3), and your agreement to conduct the postmarketing commitments (PMCs), which are also listed in the attachment. We request a prompt written response in order to continue our evaluation of your BLA.

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

Sincerely,

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

1. Conduct 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 denosumab (Protocols 20090521 and 20090522).

For Protocol 20090521:
Study Completion Date:
Final Report Submission:

For Protocol 20090522:



2. Conduct a long-term surveillance study in postmenopausal women administered denosumab to prospectively evaluate the incidence of serious infection including skin infections, dermatologic adverse events, and over-suppression of bone turnover (Protocol 20090601).

Final Protocol Submission:
Study Completion Date:
Final Report Submission:

3. Conduct an *in vivo* drug-drug interaction study with CYP3A4 substrate (e.g., midazolam) in postmenopausal female patients with osteoporosis to characterize the potential risk of drug interaction of denosumab with CYP3A4.

Final Protocol Submission:
Study Completion Date:
Final Report Submission:

Post-marketing Commitments

Office of Biotechnology Products:

Post-marketing Studies not subject to reporting requirements of 21 CFR 601.70:



2. 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 [*Amgen to provide date for Final Report Submission*].

3. To submit proposed revisions to the breakloose and extrusion release and shelf-life specifications for pre-filled syringe drug product based on an appropriate statistical method after XX commercial manufacturing runs. The proposed revision to the specifications, the corresponding data from the XX commercial manufacturing runs, and the analysis plan used to create the revisions will be provided in a Prior Approval Supplement by September 30, 2010. [*Amgen to provide number of runs*].
4. To submit proposed revisions to the breakloose and extrusion release 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.

Crisostomo, Nenita

m: Crisostomo, Nenita
: Friday, April 23, 2010 4:22 PM
:' 'Burd, Edward'
Subject: BLA 125320: Preliminary list of PMCs for 4/26/10 TCON

Attachments: Prelim comments.042310 mtg.PMCs.pdf; Prelim comments.042310 mtg.PMCs.doc



Prelim

ments.042310 mtg.Pments.042310 mtg.P



Prelim

Hi Ed,

Attached is the DRAFT list of PMCs, in both Word and PDF formats, subject for discussion during our upcoming tcon scheduled on 4/26/10. Thanks and have a great weekend!

--nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

2 pages(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Friday, April 16, 2010 4:48 PM
To: 'Burd, Edward'
Cc: Hovland, David
Subject: RE: Checking in on status of redline med guide STN BL 125320/0
Attachments: MG.FDA edits.041210.doc

Tracking:

Recipient	Read
'Burd, Edward'	
Hovland, David	
Kehoe, Theresa	
Duer, Robin	Read: 4/18/2010 7:54 PM
Voss, Stephen	
Griffiths, LaShawn	

Hi Ed,

Thank you so much for your patience. We apologize for the delay. Attached is the MedGuide with the changes. If you have any questions, please feel free to contact me.

Have a great weekend!

--nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

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as B4 (CCI/TS)

6/16/2010

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Monday, April 12, 2010 7:11 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: Additional documents for support of Tuesday teleconferencel regarding STN BL 125320/0
Attachments: S-Dmab-US-MG-0.7_AR.pdf; S-Dmab-US-MG-0.7_C.doc; FDA Biostats RTQ 12APR10.doc

Dear Nenita,

Attached are the rest of the documents for tomorrow's call with the Prolia review team. We include the revised Medication Guide in clean and redline together with high level responses to the biostats questions received yesterday. Many thanks for distributing this to the review team prior to the call.

Our intention is that we will formally submit all the requested information discussed in the review letters on Friday April 16.

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

10 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4
(CCI/TS)

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Monday, April 12, 2010 12:55 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: Company response document for tomorrow's call part 1 (STN BL 125320/0)
Attachments: S-Dmab-US-PI-0.9_C.doc; S-Dmab-US-PI-0.9_AR.pdf; FDA RTQ 09APR10.doc

Dear Nita,

Attached are Amgen's high level responses to the letter received on Friday. We include a document in word with our high level responses, a redline and clean version of the full prescribing information.

Later today we will respond to the Biostats letter received on Sunday and also at that time will provide our proposal regarding the Medication Guide.

We hope to be able to discuss all topics at tomorrow's call and arrive at mutual agreement on all review items if possible.

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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Crisostomo, Nenita

From: Crisostomo, Nenita
: Sunday, April 11, 2010 6:39 PM
'Burd, Edward'
Subject: RE: BLA 125320 denosumab: Preliminary Comments for 4/13/10 tcon
Attachments: Prelim comments.Stats.041310 mtg.doc



Prelim
ments.Stats.041310

Hi Ed,

In addition to the Preliminary Comments sent to you on Friday, 4/9/10, here are the Biostatistics Preliminary Comments also subject for discussion, in relation to the 4/9/10 PMR comments.

Thank you so much and have a great weekend!
--nita

From: Crisostomo, Nenita
Sent: Friday, April 09, 2010 5:28 PM
To: 'Burd, Edward'
Subject: BLA 125320 denosumab: Preliminary Comments for 4/13/10 tcon

<< File: Prelim comments.PMR.REMS.HCP.PI.MG.041310 mtg.pdf >> << File:
w1.DRISK.REMS.040710.marked.doc >> << File: review1.DRISK.TK.HCP.040910.marked.doc >> << File:
ISED Prolia MG DRISK marked up copy 4 9 10.no format1.doc >> << File: PI.FDA edits.040910.doc >> << File:
REMS template.doc >>

Hi Ed,

For our discussion during our 4/13/10 tcon, and as I conveyed to you earlier, attached in PDF contains our DRAFT comments and the related documents, which are also provided to you in WORD versions for your convenience. If you have any questions, please feel free to contact me.

Thanks and have a great weekend,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

**2 pages(s) have been Withheld in Full immediately following
this page as B4 (CCI/TS)**

Crisostomo, Nenita

From: Crisostomo, Nenita
To: Friday, April 09, 2010 5:28 PM
From: 'Burd, Edward'
Subject: BLA 125320 denosumab: Preliminary Comments for 4/13/10 tcon

Attachments: Prelim comments.PMR.REMS.HCP.PI.MG.041310 mtg.pdf;
review1.DRISK.REMS.040710.marked.doc; review1.DRISK.TK.HCP.040910.marked.doc;
REVISED Prolia MG DRISK marked up copy 4 9 10.no format1.doc; PI.FDA
edits.040910.doc; REMS template.doc



Prelim
ents.PMR.REMS.HCMS.040710.mark... HCP.040910.ma... DRISK marked... s.040910.doc (399
REMS template.doc (64 KB)

Hi Ed,

For our discussion during our 4/13/10 tcon, and as I conveyed to you earlier, attached in PDF contains our DRAFT comments and the related documents, which are also provided to you in WORD versions for your convenience. If you have any questions, please feel free to contact me.

Thanks and have a great weekend,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

11 pages(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: March 22, 2010

To: Edward Burd Senior Manager, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Amgen, Inc.	Division of Reproductive and Urologic Products
Fax number: 805-480-1330	Fax number: 301-796-9897
Phone number: 805-447-3022	Phone number: 301-796-0875
Subject: BLA 125320 Prolia (denosumab) - Package Insert: FDA Recommendations #2	

Total no. of pages including cover: 19

Dear Ed,

As promised, attached is the Package Insert revised post-teleconference with you this afternoon. Please make your edits on a clean copy, complete with a rationale for each of your changes.

If you have any questions, please do not hesitate to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 19, 2010, at 8:04 P.M.

TO: Memo to File

THROUGH :

FROM: Nenita Crisostomo

SUBJECT: Package Insert--Amgen's Response to FDA's labeling recommendations sent on March 19, 2010

APPLICATION/DRUG: BLA 125320 Prolia (denosumab)

Attached is Amgen, Inc.'s version of the Package Insert sent via email at 8:04 P.M. in response to the first round of labeling negotiations sent this morning via email at 11:00 A.M. The email with the attachment was distributed via email to the Review Team.

Crisostomo, Nenita

From: Burd, Edward [eburd@amgen.com]
Sent: Friday, March 19, 2010 8:04 PM
To: Crisostomo, Nenita
Cc: Hovland, David
Subject: Amgen Redline label for Monday's call: STN BL 125320/0
Attachments: D-Dmab-US-PI-0.8_C.doc; D-Dmab-US-PI-0.8_PDF.pdf

Dear Nita,

Attached are redline and clean versions of Amgen's proposed label for discussion on Monday. Thanks for all your help in distributing this to the team.

Have a great weekend!

Edward S. Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125320/0

INFORMATION REQUEST

March 9, 2010

Amgen, Inc.
Attention: Edward 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 January 25, 2010, submitted under section 351 of the Public Health Service Act for denosumab, a human monoclonal antibody to RANK ligand.

We have reviewed the container labeling section of your application and have determined that the following information is necessary to take a complete action on your application:

A. General Comment for All Labels and Labeling

1. Per 21 CFR 601.2(a), denosumab is a "specified" biological product and should comply with 21 CFR 201.10 for placement and prominence of the established name and proprietary name. The presentation should include the established name in parenthesis, the dosage form, and route of administration in close proximity. The following format is recommended presentation:

Prolia
(denosumab)
Injection
For Subcutaneous Use
60 mg/mL

2. Add the statement "Discard unused portion" immediately following the statement, "Single use vial", or "Single use prefilled syringe".

B. Container Label - Syringe

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 201.100(b)(3) to avoid wrong route of administration errors.
2. Relocate the strength so that it immediately follows the established name and dosage form.

3. Please provide an explanation of visual inspection for the vial configuration to comply with 21 CFR 610.60(e).
4. Per 21 CFR 208.24(d) and 21 CFR 610.60 (g), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).

C. Carton Labeling - Syringe

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form, and strength.
2. Relocate the strength so that it immediately follows the established name and dosage form.
3. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."
4. Per 21 CFR 208.24(d) and 21 CFR 610.60 (g), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient). If space does not permit, the statement must appear on the carton.
5. Please provide clarification of the statement, "Protect from direct sunlight".
6. Please add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l) (m) (o) (p) (q).
7. Inactive ingredients should be listed in alphabetical order per USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients.
8. Consider revising the temperature statement from, "Store at ..." to "Refrigerate at..." for clarity.

D. Syringe Topweb Labeling

1. Relocate the strength so that it immediately follows the established name and dosage form.
2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."
3. Per 21 CFR 208.24(d) and 21 CFR 610.60 (g), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient). If space does not permit, the statement must appear on the carton.

E. Container Label - Vial

1. If space permits, include the route of administration (i.e. For subcutaneous use) per 21 CFR 200.100(b)(3) to avoid of wrong route of administration errors.

2. Revise the strength unit in the green circle (i.e. 60 mg) to "60 mg/mL."
3. Per 21 CFR 208.24(d) and 21 CFR 610.60 (g), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient). If space does not permit, the statement must appear on the carton.

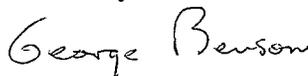
F. Carton Labeling - Vial

1. Remove the line between the drug name and strength so that it does not interfere with the presentation of the drug name, dosage form, and strength.
2. Revise the strength unit in the green circle (i.e. 60 mg) as "60 mg/mL."
3. Increase the prominence of the route of administration (i.e. For subcutaneous use only) to avoid wrong route of administration errors.
4. Per 21 CFR 208.24(d), include the Medication Guide statement (e.g. Dispense the enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient).
5. Please provide clarification of the statement, "Protect from direct sunlight".
6. Please add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l) (m) (o) (p) (q).
7. Inactive ingredients should be listed in alphabetical order per USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients.
8. Consider revising the temperature statement from, "Store at ..." to "Refrigerate at..." for clarity.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

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

Sincerely,



George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

- c. Provide a comprehensive narrative and relevant case information (e.g. oral surgery reports, pathology results) for the following subjects:

Study	Site	USUBJID	Verbatim term	Dictionary coded term
20010223	5	20010223-005025	lesion (r) lower gum	Oral disorder
20030216	304	20030216-304023	bone deterioration below bad tooth	Bone disorder
20030216	632	20030216-632004	tooth implantation in jaw	Dental prosthesis user
20030216	719	20030216-719015	dental implant	Dental prosthesis user
20030216	823	20030216-823504	periostitis of teeth	Periostitis
20030216	633	20030216-633273	local infection after removal of tooth	Post procedural infection
20030216	412	20030216-412461	left maxilla dental abscess	Tooth abscess
20030216	731	20030216-731044	dental abscess lower jaw	Tooth abscess
20030216	661	20030216-661158	teeth implantations	Dental implantation
20030216	632	20030216-632286	tooth implantation	Dental prosthesis user
20030216	723	20030216-723055	tooth implantation	Dental prosthesis user
20030216	632	20030216-632141	infection in mouth after removal of teeth	Post procedural infection
20030216	743	20030216-743119	dental abscess right lower jaw	Tooth abscess
20040132	309	20040132-309007	dental implant surgery	Dental implantation
20040132	309	20040132-309007	dental surgery	Dental operation
20040132	307	20040132-307022	bone implant-receding gums-outpatient	Bone graft
20040138	188	20040138-188004	dental surgery	Dental operation
20040138	214	20040138-214005	dental implant	Dental prosthesis user
20040138	639	20040138-639003	infection after molar traction jaw	Postoperative wound infection
20050141	125	20050141-125040	jaw lesion	Bone lesion
20050233	29	20010223-029028	dental abscess r upper jaw	Tooth abscess
20050234	502	20050234-502003	big trouble chewing (problems chewing with missing teeth)	Mastication disorder
20060286	1	20060286-001024	post-operative infection in jaw	Post procedural infection

3. Questions about Coding Practices:

We have questions about the medical event coding for several cases based upon our review of narratives and case report forms. Please provide your rationale for medical event coding for the following subjects:

Study Number	Unique SID	Preferred Term	AE onset	Additional question(s) / comment(s)
20030216	6102040	Myocardial infarction	24-Oct-2006	Was an autopsy done? Was a death certificate available?
20030216	6432053	Bronchopneumonia	22-Jun-2007	SAE narrative mentions cardiogenic or septic pre-shock, atrial fibrillation and hypotension.

4. There are two datasets submitted in the ISS: AAE and AAEFX. There are 217 fractures in the AAE file that are not included in the AAEFX file. We are aware of different number of studies included in each dataset. However, there are a few instances where clinical fractures from study 20030216 are in the AAE dataset and not in AAEFX dataset. Explain the discrepancy.

Provide a written response to these requests within two weeks of receipt of this letter.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,



George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII**

FACSIMILE TRANSMITTAL SHEET

DATE: February 19, 2010

To: Edward S. Burd, Ph.D. Senior Manager, Regulatory Affairs	From: Nenita Crisostomo, R.N. Regulatory Health Project Manager
Company: Amgen, Inc.	Division of Reproductive and Urologic Products
Fax number: 805-480-1330	Fax number: 301-796-9897
Phone number: 805-447-3022	Phone number: 301-796-0875

Subject: STN: BLA 125320: Acknowledgment: Complete Response dated January 25, 2010 - Resubmission

Total no. of pages including cover: 3

Dear Ed,

Attached is the letter acknowledging your resubmission dated January 25, 2010, in response to our October 16, 2009, Complete Response letter.

If you have any questions, please feel free to contact me.

Best Regards,
Nita

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125320

ACKNOWLEDGE COMPLETE RESPONSE

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

Dear Dr. Burd:

We have received your January 25, 2010, resubmission to your biologics license application for denosumab, a human monoclonal antibody to RANK ligand.

The resubmission contains additional information in response to our October 16, 2009, complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is July 25, 2010.

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

Sincerely,

A handwritten signature in cursive script that reads "Margaret Kober".

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

December 10, 2009

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We also refer to your September 14, 2009, and October 14, 2009 submissions, in which you submitted your proposed postmarketing studies for denosumab protocols 20090521, 20090522, and 20090601.

We have the following comments and recommendations:

Protocol 20090521 (Phase A):

1. Clearly describe the methods for assessment of exposure to denosumab in the feasibility study.
2. Include events of pancreatitis as an adverse event of special interest (AESI).
3. "Serious" infections should include events leading to administration of intravenous antibiotics and emergency room visits or hospitalizations, in addition to the regulatory definition of a serious event. Similarly, dermatologic events should include those leading to emergency room visits as well as hospitalizations in addition to the regulatory definition of a serious event.
4. This feasibility study should be completed and the information it generates should be included in your resubmission.
5. Provide the details of deaths, missing values, lost to follow-up and drop out rates for each of the four datasets.

Protocol 20090522 (Phase B):

1. Include events of pancreatitis as an AESI.
2. A study duration of 5 years is inadequate to assess the long term consequences of suppression of bone turnover. The study duration should be 10 years or longer.

3. According to the protocol, based on the advantages and limitations of the candidate data systems and the assessments conducted in Phase A, the denosumab postmarketing global safety assessment (DPMGSA) team will assign specific objectives to each selected database. This should be done as a part of the feasibility study (protocol 20090521).
4. Include detailed methods of assessment of denosumab use exposure based on findings of study 20090521.

Protocol 20090601:

1. We consider your proposed protocol PHCPS (Prolia Healthcare Provider Survey) to be similar to a registry. Therefore, in order to adequately capture the adverse event profile of denosumab, the response rate for this survey study should be robust. Provide a discussion of the anticipated response rate for this survey study and what you consider to be the minimum rate that would be effective in capturing the adverse event data sought.
2. You propose a healthcare provider (HCP) voluntary survey that is only web-based. Providers without office access to the web or ones who prefer paper communication are less likely to participate. A paper option should be available to all providers. This paper record could then be entered into the web based program by the office staff or could be faxed to the study management. To enhance participation, we strongly recommend that the survey be dispensed with the prescription and given to the provider to be completed at the time the medication is administered.
3. A survey reminder e-mail will be sent automatically by the PHCPS Web System every six months to HCPs who have registered previously on the PHCPS website or to those HCPs whose e-mail addresses are available to Amgen. The timing of this approach may be inadequate to capture the data from all patients receiving denosumab from a particular provider. To adequately capture the events sought, the survey should be completed at the time of denosumab administration. Reporting at the time of administration will facilitate better recall of the adverse events of special interest (AESI) in a timely manner.
4. As currently proposed, prescribers provide a minimum amount of information for the survey and are encouraged to complete a MedWatch form. This is not an acceptable approach because it may be overly burdensome to the healthcare provider to report the same event twice. You should propose a secure mechanism to collect adverse event information with patient identification information that will allow for appropriate follow-up for these events.
5. In addition to serious infections and dermatologic adverse events, complications related to suppression of bone turnover must be included in the survey. We do not agree with the rationale for not including fractures, fracture healing, or osteonecrosis of the jaw (ONJ). It is important to capture information as completely as possible in the survey because these events can occur after an extended duration of therapy. In addition, these events may be difficult to retrieve from safety or epidemiologic databases.
6. It may be beneficial to include information about potential confounders (such as prior bisphosphonate use) in the survey and a plan to follow-up on patients developing AESI. Supporting information such as emergency room use, oral surgery/other physician documentation, or x-ray and lab values could be reported using pull down menus or checkboxes with comments sections.

7. A study duration of 3 years is inadequate to evaluate long-term consequences of over suppression of bone remodeling and new primary malignancies. We recommend a duration of 10 years or more.

The Division of Epidemiology recommends the following for the data systems studies (Phases A and B) and the survey (loosely ordered by Phase A, Phase B, survey, and clarification requests):

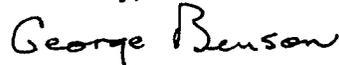
1. Because capture of denosumab use may be challenging in administrative databases, Phase A should examine the ability of capturing a drug product administered in a similar fashion to denosumab in each data system.
2. Uniform case-ascertainment algorithms are important to compare findings across the data systems; therefore, the mapping of ICD-9 to ICD-10 codes should be done in Phase A (this was mentioned in the Phase B protocol, page 27).
3. Drop-out rates, missing values, and codes for deaths and malignancies should be assessed for each database during Phase A.
4. Document the timeliness and completeness of medical chart reviews in each data system, especially in those databases which will utilize paper chart review.
5. Consider a pilot study of the proposed use of 100% of the Medicare database as the sampling domain for the selection of the postmenopausal osteoporosis (PMO) base cohort and the validation of cases by medical chart review.
6. Include all the AESIs that we requested in each of the data systems for Phases A and B and for the survey (hypocalcemia, ONJ, infections, hypersensitivity, dermatologic events, atypical fracture, fracture wound healing, and new primary malignancies).
7. Include all postmenopausal women (not just PMO women) in Phases A and B (protocol numbers 20090521 and -522). Analyze background AE incidence rates in both postmenopausal and PMO women.
8. Perform power calculations in each data system for detection of an increase in the incidence rates for the AESIs based on the estimated sample sizes for postmenopausal women and for PMO women.
9. Phase A, revised to include all postmenopausal women, should be completed and the information it generates should be included in your resubmission.
10. Phase B should identify and follow any denosumab exposure.
11. Consider the ease of collection of the survey data and data entry. A paper survey attached to the denosumab product and data entry by office staff may help to increase the reporting rate and provide timely survey reports.
12. Follow-up of survey patients is recommended. This should include information on drug exposure, AESIs, potential confounders, and supporting data (x-ray, lab, and physician consult data).
13. Extend the follow-up of both the database study and the survey to at least 10 years to capture those AEs with long latencies such as ONJ and malignancies.

14. Clarify:

- a. The differences in numbers of PMO women and estimated denosumab users as reported in Phase A protocol and the Information Package.
- b. “Significant risk” noted in the annual assessment that would prompt reporting to FDA.
- c. Timeframe for reporting “significant risk” information to FDA.
- d. The rationale for using random index dates for PMO-naïve patients (Phase B protocol, page 26).
- e. Specific objectives assigned to each selected database (Phase B protocol, page 17).
- f. An “aggregated report” and the “appropriate context” mentioned in the survey protocol (page 5).

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,



George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

1R

Peacock, Celia

From: Peacock, Celia
Sent: Thursday, October 22, 2009 3:14 PM
To: Peacock, Celia
Subject: PRINT for AP...ASAP: denosumab pregnancy registry protocol deficiencies

From: Peacock, Celia
Sent: Thursday, October 22, 2009 2:55 PM
To: 'Burd, Edward'; Lepin, Julie
Cc: Peacock, Celia
Subject: denosumab pregnancy registry protocol deficiencies

1. A 5-10 patient enrollment over a 5 year period of time will not allow you to achieve any of your specified primary or secondary objectives due to the small sample size. Enroll patients for at least a 10-year period at which time FDA will decide if adequate and meaningful data has been collected to terminate the denosumab pregnancy registry.
2. Following pregnancy-exposed denosumab children for only 12 months may not be sufficient to completely assess for potential effects (impaired growth and dentition, or immune system problems caused by lymph node agenesis) resulting from potential in-utero disruption in the RANKL signaling pathway. Follow pregnancy-exposed denosumab children for potential impaired growth and dentition, and immune system problems. Provide a timeframe for follow-up with a scientific justification.
3. Resubmit your revised draft denosumab pregnancy registry protocol at the time of your denosumab Complete Response submission.

Celia R. Peacock, MPH, RD
Captain, U.S. Public Health Service
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5357
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.4154
Fax 301.796.9897
celia.peacock@fda.hhs.gov

October 8, 2009
Information Request

Question 1:

Submit the data or references Amgen is using to justify the age > 65 instead of 70 as increased risk of fracture.

Question 2:

In the original BLA submission for Prolia, the Sponsor provided calculated exposure multiples for denosumab for the recommended human dosing regimen (60 mg, s.c., once every 6 months) relative to the NOAEL in pivotal toxicology studies 102090, 103981 and 102842 in cynomolgus monkeys. These dose multiples were based on AUC, and represented 150, 95 and 99-fold multiples respectively for each study. These results were provided in the original BLA submission (Section 2.4 – Nonclinical overview; page 32), and are represented in the table below:

Table 2. Calculated Exposure Multiples for Denosumab for the Recommended Dose Relative to the NOAEL in the Pivotal Toxicology Studies

Study Type	NOAEL (mg/kg)	C _{max} ^b (µg/mL) Mean (SD)	AUC _{0-tau} ^b (µg*hr/mL) Mean (SD)	Exposure Multiple Based on AUC ^c
12-month repeated-dose in cynomolgus monkeys (102090)	50	666 (156)	268000 (90300)	150
16-month repeated-dose in cynomolgus monkeys (103981)	50	413 (160)	171000 (72400)	95
Embryo-fetal toxicity in cynomolgus monkeys (102842)	12.5	282 (89.6)	41000 (10600)	99

^a 60 mg, subcutaneously, once every 6 months. ^b At the end of dosing. Details of the multiple dose toxicokinetics are discussed in Module 2.6.4, Section 8.2.2. ^c Human C_{max} and AUC_{0-6 month} values (6.94 µg/mL and 10752 µg-hr/mL) were derived from Study 20010223. To take into account the differences in dosing frequency, the AUC for a 6 month interval in monkeys was approximated by multiplying by 26 and 6 for weekly (Study 102842) and monthly (Studies 102090 and 103981) dosing, respectively.

AUC = area under the plasma drug concentration-time curve; C_{max} = maximum observed concentration; NOAEL = no observed adverse effect level.

During nonclinical review of these studies, the Agency sent a letter to the Sponsor requesting additional information as to 1) how they calculated the clinical exposure margins/levels both in the denosumab label, and nonclinical summary (Section 13.1 of labeling: 100-150 fold higher than clinical dose; Nonclinical overview: 95-150 fold); 2) which clinical and nonclinical studies were chosen for comparison; 3) which doses were used; and 4) how the dosing regimen (monthly for nonclinical and every 6 months for clinical) factored in to the calculations to determine these margins. The Sponsor replied, but the overall response did not provide any additional information other than an overview of what is noted in the table above.

After review of this information and the pharmacokinetic data provided in the pivotal toxicology studies, a decision was made by the Agency to calculate human dose multiples of the nonclinical doses based on body weight (mg/kg) comparison. The basis for this decision was 4-fold: 1) nonclinical exposure to denosumab was either monthly or weekly, compared to the Q6M clinical regimen of treatment, so timing of exposure was not equivalent; 2) systemic exposure from nonclinical subcutaneous dosing correlated with exposure following nonclinical intravenous dosing; 3) only $AUC_{0-\tau}$ data were provided for nonclinical and clinical PK, and not $AUC_{0-\infty}$; and 4) high incidence of immunogenicity that included the presence of neutralizing antibodies. In addition, other approved monoclonal antibodies such as trastuzumab, alemtuzumab, panitumumab, infliximab, and bevacizumab have been labeled with dose multiples based on mg/kg, and a clinical mg/kg dosing schedule was utilized for each of the agents, respectively. When high levels of immunogenicity are present, it is difficult to obtain an accurate estimate of the exposure based on AUC. Therefore, for products with a limited and well-defined volume of distribution an exposure multiple based on the mg/kg basis has been utilized to extrapolate relative exposure differences between species.

In the most recent label that was sent to the Sponsor (9-21-09), a complete review of Sections 8.1, 8.3, 13.1 and 13.2 had not been finalized by the nonclinical team, and review is currently ongoing. However, the dose multiples that the Agency proposes for the final label were included in this version, and based on our rationale above, we consider this a conservative approach to estimating risk. The dose multiples calculated on a mg/kg basis do provide acceptable safety margins of 13-50-fold. We acknowledge the Sponsor's rationale for their changes to the labeling that comparison to AUC is their desired approach, and that other monoclonal antibodies and osteoporosis therapies that they have cited (Humira, Xolair, Reclast, and Evista) have used comparison to AUC in their respective labels (as well as comparison to body surface area for the non-antibody products). In order for us to accept the use of AUC as a comparison for the denosumab product, we request the following information: 1) values for $AUC_{0-\infty}$ in each of the pivotal nonclinical/clinical studies used for comparison, or 2) an AUC value with a designated time-frame of exposure in animals with a comparable time-frame of exposure in humans (not an approximation based on multiplication).

Peacock, Celia

From: Peacock, Celia
Sent: Wednesday, August 26, 2009 11:04 AM
To: 'Burd, Edward'
Cc: Lepin, Julie
Subject: FW: Clinical Information Requests.doc

Attachments: Clinical Information Requests.doc



Clinical Information
Requests....

Hi Ed and Julie, attached is a clinical IR. Thanks, Celia

Clinical Information Request:

1. Based on the phase 2 dose-finding study 20010223, a dose lower than 60 mg q 6 months (such as 30 mg q 6 months) may be efficacious in the postmenopausal osteoporosis population. You stated at the August 13th advisory committee meeting that a number of analyses were conducted when considering the dose regimen to take into Phase 3. Please provide a detailed justification of your chosen dose.
2. Please submit the complete Month 48 study report with datasets for study 20040132.
3. Please provide fracture incidence data for study 20060289.
4. 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 the potential serious risk of serious infection including skin infection, dermatologic adverse events, and consequences related to over-suppression of bone turnover.

Therefore we have determined that you will need to conduct the following postmarketing studies of denosumab to assess these potential serious risks.

(1) Denosumab Post-Approval Surveillance Study in PMO

Denosumab is to be administered by health care providers. This provides a unique opportunity to collect data regarding the adverse events of concern in patients being treated with denosumab outside of the controlled clinical trial environment. We envision this to be a short survey either dispensed with the drug or provided to prescribers. This survey should include evaluation of the occurrence of new fractures including fracture location, fracture healing complications, osteonecrosis of the jaw, infections including skin infections, and dermatologic adverse events. Please submit a protocol including the questionnaire for review.

(2) Denosumab Population-Based Prospective Observational Study in PMO

You have proposed such a study in the risk management plan submitted with the original BLA. Please submit a detailed protocol as well as any feasibility assessments that have been performed.

(3) Denosumab Pregnancy Registry

You have proposed such a registry in the risk management plan submitted with the original BLA. Please submit a detailed discussion and protocol for this planned registry.

Suvarna, Kalavati

From: Stock, Marisa
rt: Tuesday, August 25, 2009 1:55 PM
Subject: Suvarna, Kalavati
RE: BLA STN 125320/0 for Denosumab from Amgen, Inc.

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below to find the updated compliance status of each establishment. There are no pending or ongoing compliance actions to prevent approval of STN 125320/0 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Suvarna, Kalavati
Sent: Monday, January 05, 2009 4:32 PM
To: CDER-TB-EER
Cc: Chi, Bo; Obenhuber, Donald; Abduldayem, Maan S; Suvarna, Kalavati; Hughes, Patricia; Randazzo, Giuseppe
Subject: BLA STN 125320/0 for Denosumab from Amgen, Inc.

Please conduct an establishment evaluation in support of the BLA STN 125320/0 for Denosumab from Amgen, Inc. The sites for manufacture of drug substance, drug product, raw material testing, storage of cell banks, contract testing laboratories, release and stability testing are listed below. The PDUFA date is 06/18/2009.

Manufacture, release and stability testing, and storage of drug substance. Also, storage of working cell bank:

Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard Boulder, CO 80301 USA
FEI No. (b) (4) 3003072024

A pre-license inspection was conducted for Denosumab on June 8-12, 2009 and classified NAI. The CBI profile was covered and is acceptable.

Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma)
Birkendorfer Strasse 65 88397 Biberach an der Riss Germany
FEI No. 3002806518

(b) (4)

Storage of Master cell bank, raw material testing and release, drug substance and drug product release and stability testing:

Amgen Inc. (ACO) Longmont Facility
4000 Nelson Road Longmont, CO 80503 USA
FEI No. 3002892484

Inspected January 31, 2008 and initially classified NAI. The BTP profile was covered, however a final district decision has not yet been made. Although this case has not been finalized, we consider this site to be acceptable for this application.

Storage of Master and Working cell bank, raw material testing and release, drug substance storage:

Amgen Inc. (ATO)

One Amgen Center Drive Thousand Oaks, CA 91320 USA

FEI No. 2026154

Inspected April 7-11, 2008 and classified NAI. The CBI and CTB profiles were covered and are acceptable.

Raw material testing and release, drug substance storage, release and stability testing and Drug product manufacture, release and stability testing, packaging and labeling, and storage:

Amgen Manufacturing, Limited (AML)

State Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA

FEI No. 1000110364

Inspected January 8-12, 2007 and classified VAI. The BTP profile was covered and is acceptable. This site is a Tier 1 inspectional priority for FY '09.

(b) (4)

Drug product storage and distribution:

Amgen Inc. (LDC)

12000 Plantside Drive Louisville, KY 40299 USA

FEI No. (b) (4) 3003750095

Inspected January 5-6, 2006 and classified NAI for warehousing responsibilities. This site is not profiled.

Drug product stability (container closure for vials) testing:

Amgen Inc. (AFR)

6701 Kaiser Drive Fremont, CA 94555 USA

FEI No. 3005925062

Inspected September 3-10, 2008 and classified NAI. The TRP profile was covered and is acceptable.

Thank you.

Kala

Peacock, Celia

From: Peacock, Celia
Sent: Thursday, August 20, 2009 5:26 PM
To: 'Burd, Edward'; Lepin, Julie
Subject: CMC Denosomab IR

Importance: High

Attachments: Denosumab CMC IR 4.doc

Hi Ed, if possible, we would like a response to this CMC IR by Monday. Thank you, Celia



Denosumab CMC IR
4.doc (36 KB)...

1. Breakloose and extrusion testing should be added to the lot release specifications of the pre-filled syringes, and justification for the proposed acceptance criteria should be provided.
2. 21 CFR 610.14 requires that identity testing be performed on each filled lot after all labeling operations have been completed. From the batch records supplied, it is not clear that any samples are taken for identity testing after labeling of the vials and pre-filled syringes. Please identify your current process and correct, if necessary, to conform to the regulation identified.
3. For additional characterization assays that will be used post approval either for comparability studies or for characterization of new reference standards, please submit the validation or qualification reports to the BLA for review. Additionally, a number of these assays have subjective acceptance criteria such as “visually similar..”, “similar pattern..”, and “comparable to..”. For such acceptance criteria, please provide a more specific and less subjective description of the parameters Amgen uses to specify whether products are “similar” and “comparable”.
4. Justify the proposed adjustment of the release specification acceptance criteria based on stability changes during storage, given that the released material is intended to also have an approved storage period. This could result in use of product with quality attributes that are outside the range of clinical experience as product nears its expiration point. Additionally lots released at the lower limit of the proposed specification would fail stability at the end of shelf life for quality attributes that change during product storage.
5. The post approval stability protocol for DS identifies that Amgen intends to alternate annual lots placed on stability between ACO and BIP. Please modify the protocol to require an annual stability lot for each site that has manufactured denosumab during that year.
6. The information provided regarding the tungsten spiking studies states that the tungsten was obtained from used tungsten pins. Please clarify if these pins were used in a process in which the tungsten would undergo oxidation (i.e. not in a nitrogen overlay process). Additionally, please submit any available data on levels of tungsten in denosumab from the denosumab PFS.
7. The BLA proposes implementing an increase in batch size post approval with a (b) (4) batch size of (b) (4) a validation protocol (PTC-003542 v 1.0) for the (b) (4) batch scale-up is provided in the BLA. In this protocol, Amgen states that the new batch size “will support launch and commercialization of the 60 mg/ml drug product upon approval of the marketing application” and that “the data for this validation exercise will be summarized and evaluated at the completion of the

required tests and a final report will be generated.” Please note that the final validation report and any other relevant information on the process and its validation will have to be submitted to the FDA for review as a CBE 30.

8. Regarding subvisible particulates testing:
 - a. Please define when each of the two subvisible particulates methods is being used.
 - b. Please provide complete qualification/validation reports for AML.
9. Regarding the AML drug substance and drug product comparability protocols COMP-000042 and COMP-000050:
 - a. Stability/elevated temperature sections (DS section 3.0; DP sections 3.3.2.1 and 4.0) state that “in the event that a statistically significant difference exists, and analytical comparability is not demonstrated, the magnitude and significance of the difference will be evaluated to determine the impact to safety or efficacy.” Please be aware that if there are statistically significant differences, this would require comprehensive assessment by FDA prior to release of AML-produced materials and therefore may require submission of the data under a PAS.
 - b. COMP-000042 section 4.1.4, Table 9 states that the comparability acceptance criterion for the (b) (4) (b) (4) Please define the criteria Amgen uses for assessment of pattern similarities of (b) (4)
 - c. In COMP-000042, section 4.1.6, Table 11 lists the comparability acceptance criterion for reporter gene assay as (b) (4) relative potency, but Appendix B states that the acceptance criteria were established as (b) (4) of relative potency. Please clarify if there is a reason Amgen would like to maintain this discrepancy or update to the final specifications.
 - d. For the CE-HPLC, rCE-SDS, SE-HPLC, and potency methods (rCE-SDS and SE-HPLC for DP), the justification of acceptance criteria sections in Appendix A state that the acceptance criteria were based on the (b) (4) encompassing (b) (4) of the clinical and commercial data at (b) (4) confidence; however, Appendix C states that (b) (4) and (b) (4) were used to establish the limits for CE-HPLC, SE-HPLC, and potency. Please clarify.
10. Regarding reference standard:
 - a. The BLA states that a new reference standard (RS) will be prepared to ensure sufficient inventory, if the current RS shows a loss of integrity, or when the stability program for an existing RS is completed or terminated for any reason. Please provide the protocol for monitoring the denosumab

reference standard, and describe how loss of integrity is assessed, including any action/alert limits that have been set.

- b. Please provide the protocols for preparation and characterization of a new denosumab reference standard.
11. Amgen Europe B.V. (ABR) was used as a site for transportation validation. Please clarify if denosumab is to be processed at ABR.
12. Please clarify your intent to submit the reports on concurrent validation of resin and membrane lifetime when each is completed.
13. For some specifications, acceptance criteria are relative to the reference standard. Clarify how Amgen plans to maintain consistency of testing results and prevent drift when replacing reference standards which are not equivalent to the previous reference standard.



8/6/09

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125320/0

INFORMATION REQUEST

Amgen, Incorporated
Attention: Edward S. Burd, Ph.D.
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Dr. Burd:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act for Prolia[®] (denosumab).

We are in the process of completing our review of your application and have the following requests for additional information:

1. Provide a detailed description of the serum CTX1 assay for study numbers 102624 and 107085.
2. Provide the assay validation reports for the serum CTX1 assay for study numbers 102624 and 107085.

If you have any questions, please contact Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

George Benson

George Benson
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Peacock, Celia

From: Greeley, George
nt: Friday, June 19, 2009 2:52 PM
o: Peacock, Celia
Cc: Stowe, Ginneh D.
Subject: BLAs 125,320; 125,331; 125, 332; 125, 333 Prolia

Importance: High

Hi Celia,

The Prolia (denosumab) full waivers were reviewed by the PeRC PREA Subcommittee on June 03, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children. The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
1.796.4025

 Please consider the environment before printing this e-mail.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0

STN: BL 125331/0

MAY 27 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following request for clinical information:

In study 216, we note the following imbalance for PT "vision blurred": AE denosumab 11, placebo 2; SAE denosumab 1, placebo 0. On review of the data tables from study 104105, we note denosumab accumulation in the eye/cornea. These findings may indicate an adverse effect of denosumab. Please provide any clinical or nonclinical analyses that have been performed to address these findings.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

MAY 11 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. Regarding clinical pharmacokinetic (PK) assays:
 - a. Provide the protocol for assay MET-001831 (validated in report 107381).
 - b. PK analyses for many clinical studies were performed using protocols different from MET-001831. Provide a list of PK studies and the associated protocol used for each study as well as the protocols and validation reports for these methods as performed at (b) (4) and at Amgen (e.g. (b) (4) validation report/Amgen study number 102110 and Amgen validation report PK# 101782).
2. A partial list of drug product (DP) lots utilized in the studies for the PMO indications was submitted on March 12, 2009. Submit a complete list for all studies included in the BLA with associated lots used for each.
3. The comparability study reports for ATO/AML 60 mg/ml vial and ATO/AML 70 mg/ml vial were not completed at the time of submission due to pending 6-month stability data. Submit the complete comparability study reports when these data become available.
4. We note that 3.2.S.3.1 Table 9 suggests that (b) (4) of drug substance (DS) is consistent among lots and that (b) (4) denosumab may be characterized as a

product-related substance based on *in vitro* potency. However, we also note that there is a potential for (b) (4) to occur during manufacture of DP and this may be indicative of process quality and control. Please provide any available data from the analyses of levels of (b) (4) for denosumab DP.

5. Regarding appearance testing:

- a. MET-000286 section 6.7.4.3 indicates that the necessity of inspection for DS is determined using FORM-002515 and that this form is also used for assessing DP. Please provide FORM-002515 and any associated standard operating procedures (SOP) instructing on the determination of inspection.
 - b. MET-00286 section 6.6.3 states that “sample requirements and acceptance criteria are described in the Acceptance Sampling Plan (ASP) per site specific procedure.” In addition, the Justification of Specification section of the BLA states that if the ASP evaluation fails, an investigation is conducted to assess re-evaluation or rejection and that a second ASP evaluation may be performed under a more aggressive sampling plan. Provide the ASPs for all the denosumab DS and DP manufacturing sites, and provide a more detailed description of the investigation and criteria for re-evaluation versus rejection in the event of failure. Include a description of the more aggressive sampling plan for the second ASP evaluations if it is not included in the main ASP.
6. 3.2.P.6 section 2 states that future reference standard stability will be assessed according to a defined stability program. Provide details of this program, including relevant SOPs.
7. We note that there is an action limit of — (b) (4) cell viability for the master cell bank and the working cell bank. Provide the relevant SOPs that relate to cell bank stability analysis, and provide details of the actions taken if the action limit is exceeded.

b(4)

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

W A Y - 5 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

Provide complete SDTM and Adam datasets, with define.xml files, for the follow up Safety Data for the following studies:

- 20040132 (48 month data)
- 20050135 (48 month data)
- 20040138 (update through 02 December 2008)

The format you used to submit the original data on December 19, 2008, is acceptable.

Additionally, we also request that you provide complete and source verified SDTM and Adam datasets, with define.xml file, for study 20060289. Please use the unique subject identifiers from study 20030216 for study 20060289. If this is not possible, please provide a key linking unique subject identifiers between studies 20030216 and 20060289.

Please submit narratives and CRF's for deaths and serious adverse events for all four requested studies.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic

Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
STN: BL 125332/0
STN: BL 125333/0

APR 20 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. Explain the protocol that was used for transfer of bioburden and endotoxin tests from the drug manufacturing site at Amgen Colorado to BI Pharma. Explain why different methods were used for bioburden and endotoxin testing and how the comparability of the different methods was evaluated.
2. Provide full details of the contamination control test used for bioburden testing of denosumab production bioreactor pre-harvest samples at BI Pharma site including volume of sample tested, positive control, negative controls and analysis of results.
3. Provide full details of the aerobic and anaerobic bioburden test method used for bioburden testing of denosumab production bioreactor pre-harvest samples at your Colorado site including the media used, incubation conditions, controls, and analysis of results.
4. Explain when the aerobic and anaerobic bioburden test will be implemented at BI Pharma.
5. Clarify if isolates obtained from a positive bioburden test from production bioreactors are identified.

6. Provide summary data for validation of bioburden and endotoxin tests for denosumab process intermediates and buffers. Data from each site should be provided if different methods are used.
7. Provide a summary table with bioburden and endotoxin data for all in process steps and the drug substance fill step from all batches manufactured so far at your Colorado site and the BI Pharma site.
8. Clarify if endotoxin testing is performed on harvest samples.
9. Explain why the endotoxin levels for the BI Pharma and ACO batches vary.
10. Provide calculation of the endotoxin limit based on worst-case minimal patient weight of 50 kg and the maximum single human dose for denosumab.
11. Explain the rationale for the endotoxin acceptance criterion at each process step at the ACO and BI Pharma sites.
12. Provide a table with side-by side comparison of column chromatography cleaning (Protein A, cation exchange, and hydrophobic interaction chromatography) performance parameters and acceptance criteria for post-cleaning and post regeneration blank elutions at the BI Pharma and ACO sites.
13. Provide in tabular form all differences (including media/ equipment/ steps/filters) at your Colorado and BI Pharma sites. The table should indicate if steps are repeated at one site versus another and the number of filter cartridges used at each site . All differences between the two sites should be justified.
14. You indicate that number of (b) (4) filter cartridges used after (b) (4) step varies with the load. Please explain this statement further and provide details of the (b) (4) filter used at the (b) (4), including loading capacities.
15. Provide summary data from the media and buffer hold studies at BI Pharma and ACO sites demonstrating microbial control. The hold conditions (temperature/time) should be specified.
16. Provide bioburden data for process intermediates held for (b) (4) hours at the BI Pharma site.
17. Explain how you evaluated worst case scenarios for drug substance container closure integrity. Details of the container closure integrity test such as inoculum used to generate the aerosol and incubation conditions should be provided.
18. For shipping validation studies, please provide the routine conditions (temperature and time) for shipping from both drug substance manufacturing sites (ACO and BI Pharma) to fill finish site (AML). The torque value for the container closure system should be included. The details of how the shipping validation was performed (simulation versus

real time studies) and worse case conditions (temperature and time) evaluated should be provided for review.

19. Provide details of the filter integrity test used for drug substance filtration.

Provide a written response to these requests by May 1, 2009.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic
Products

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Center for Drug Evaluation and Research



STN: BL 125320/0
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STN: BL 125332/0
STN: BL 125333/0

APR 20 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. Regarding media (b) (4)
 - a. The method for selection of (b) (4) is not clear, and we note that there is no mention of (b) (4) in the ACO and BIP batch records that were included in the submission. Please clarify how media (b) (4) are selected.
 - b. In 3.2.S.2.6 (Cell Culture Process Characterization), Amgen states that “no practically important differences” were observed between performance parameters when cells are grown plus or minus additional (b) (4). However, Amgen also states that the extra (b) (4) provides additional robustness for high cell density or extended duration cultures. Please clarify, and please discuss if and when the media options containing additional (b) (4) are intended for use.
2. You state that the current validated product pool hold times are used as controls in manufacturing. Also included in this submission is a table of acceptable characterized hold times, which are different from the validated hold times. Describe how you intend to use the acceptable pool hold times.
3. For potency evaluations used to classify variants as product-related substances, identify how many independent analyses were conducted and how many lots were analyzed. If more than one, provide the individual datapoints.

4. For the system suitability of many analytical methods, you state that “acceptance criteria might vary between sites, however, equivalence of the methods has been demonstrated.” Explain and provide supporting data for this statement.
5. Provide the endotoxin qualification or validation report for the ACO turbidimetric kinetic LAL method.
6. Explain how “as needed” is determined for (b) (4) addition. Batch records do not identify how this is supposed to be determined by the manufacturing personnel.
7. Submit the protocols and results for tungsten spiking studies and for biological reactivity studies.
8. The stability summary of 60 mg/ml vial drug product at the recommended storage condition of (b) (4) section (3.2.P.8.3) contains only the 1 month data for the commercial lots. Provide the tabular data for the primary lots (049A059685, 049A061752, 049A069739) and the supporting lots (049A114210, 049A119654, 049A119655, 049A027110, 049A031407).
9. Regarding the identity testing of the cell culture raw materials media powders:
 - a. We note that the amino acid analysis acceptance criteria for identity testing of (b) (4) (3.2.S.2.3, Raw Materials, Table 5) are different from the amino acid analysis acceptance criteria listed on the manufacturer’s certificate of analysis (3.2.R, CoA Raw Materials – BI Pharma, p. 3). Please justify your acceptance criteria listed in Table 5.
 - b. The footnotes to Table 4 and Table 5 (3.2.S.2.3, Raw Materials) state that identity testing can be performed by either amino acid analysis or infrared analysis. (b) (4) and (b) (4)/2x Enriched (b) (4) cannot be distinguished using the listed amino acid acceptance criteria; the criteria listed on the tables are within the same range for all listed amino acids, and the manufacturer’s amino acid acceptance criteria for (b) (4) are identical (see question 9, part a, above). Explain how these raw materials can be accepted based on this testing scheme.
10. We note that the validation of pool hold times at BI Pharma was performed at small scale, using commercial scale material and representative containers. Please provide additional information regarding the scaled-down model, including a comparison of all relevant parameters to demonstrate that the small scale process is representative of the commercial scale hold.
11. In section 3.2.S.4.2 (Validation of Analytical Procedures), you state that system suitability has been demonstrated for all compendial methods. Please define “system suitability” in this context, and identify what was done for each assay.

12. We note that there is a difference in the CE-HPLC charge variant profiles of denosumab produced at ACO and BI Pharma and that you identified this as potentially resulting from differences in the (b) (4) content of a raw material. As limits for charge profiles of denosumab are global for both the production bioreactor action limit and the DS specification, provide information regarding any additional internal system controls used at BI Pharma to identify changes in their normal charge variant profile, as this can be utilized as an indicator of consistency of the manufacturing process and raw materials.
13. The osmolality acceptance criteria range (b) (4) is significantly wider than is the range of measured osmolalities of denosumab lots (b) (4). Provide information regarding internal controls that are in place to assure that deviations from the historical range are investigated.
14. Provide details of the sampling scheme (including timing and vial quantity) for fill volume testing of the 60 mg/ml vial (3.2.P.3.5, section 3.5.4).
15. In the drug product release specification testing sections for both vial and PFS DP (3.2.P.3.5, section 3.7), you state that samples were taken from the beginning, middle, and end of the lot. Identify the derivation of the data that were provided in the tables of specification testing results (Tables 42 and 40, respectively) and provide the data points of the test results from the samples that were taken from each stage of fill.
16. Regarding DP transportation validation operational qualification:
 - a. Describe the testing procedure, including the number of vials/syringes and number of shipping containers tested.
 - b. Provide a more detailed summary of the vial and PFS assay results that were listed in 3.2.P.3.5 section 1, Table 2, to include the range of results and SD.
17. Regarding DP transportation validation performance qualification:
 - a. For air and ground transportation, 2 scenarios are listed for each mode (plus work in progress packaging), and 3 separate shipments were performed for each. Please clarify the type of shipping that was done for each run (e.g. insulated shipping containers, temperature controlled truck, etc.) and the standard method that will be used for shipment of commercial product.
 - b. Provide a more detailed summary of the PFS assay results that are listed in tables 3-5, to include the range of results and SD.
 - c. The results of the transport validation studies for the 60 mg/ml vial should be submitted to the BLA when they become available.
 - d. Provide additional information regarding the qualification of the shipping containers used for transportation of denosumab DP.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125320/0
STN: BL 125331/0
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STN: BL 125333/0

MAR 20 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for information:

1. The threshold values for the binding antibody screening assays and the neutralizing antibody bioassays were determined based on the S/N ratios of healthy donors.
 - a. We note that for the screening assay, you state that the threshold was evaluated in study subjects with osteoporosis and breast or prostate cancer and found to be similar. Provide the data demonstrating similar threshold values for the healthy donors and the donors examined for analysis of each indication.
 - b. You state that the threshold may be determined on a study- or disease-specific basis if the population differs significantly from the normal population. Define the criteria used to assess the need for a study- or disease-specific threshold.
2. Regarding the negative control for the screening assays, you state that for new lots of pooled normal human serum, the assay threshold must be explored and, if necessary, re-established. Provide the criteria for determining if and how the threshold is re-established. Additionally, clarify if the bioassay thresholds are also re-established following the same criteria.
3. Regarding the positive control, we note that the concentration of the positive control used in the screening assays (50 ng/ml) is significantly higher than the assay LOD and QL (2.4 ng/ml and 15 ng/ml). Provide justification for the concentration selected for the positive control, and clarify the method by which you assure that the assay LOD and QL are met for each assay run as you do not have an internal positive control for these parameters.

4. Provide data regarding assessment of interference of serum components (e.g. hemoglobin, lipids) with the screening assays and bioassays.
5. In the confirmatory bioassays, the assay performed in 1% serum includes the use of depletion control value in assessing the presence of ADA, while the assay performed in 5% serum does not. Explain the rationale for this.
6. We note that the intermediate screening assay (2260.6085) showed evidence of a “hook” effect that appeared between (b) (4) anti-AMG 162. The data provided in the validation report for the current assay (2260.6114, validation 2260.7185, table 3) includes anti-AMG 162 concentrations up to only (b) (4) however, we note that there were subject samples with levels of anti-AMG 162 of up to (b) (4) identified in the Denosumab Integrated Immunogenicity Report (section 3.5). Provide rationale for the upper limit of (b) (4) in assay 2260.6114, and any data regarding higher concentrations of anti-AMG 162 in this assay.
7. In the confirmatory immunoassay analytical procedure (document 2260.6119.02), the antibody result reporting criteria (sections 8.6.1 and 8.6.2) does not include use of the ARC in the assessment of the presence of anti-drug antibodies. However, in the confirmatory immunoassay validation report (document 2260.7190.00), Amgen states that samples with S/N above the threshold and below the ARC are positive and below the quantifiable limit and that samples above the ARC are further characterized. In addition, the conclusion of the validation report states that the results will be interpreted based on comparison to the threshold and the ARC. Clarify the discrepancies between the analytical procedure and the validation report, and identify which, if any, assessments are based on the ARC. Additionally, justify why samples between the threshold and ARC levels are excluded from further testing.
8. Provide justification and supporting data for using 50% depletion as part of the sample reporting criteria for AMG 162- and OPG-treated samples in the confirmatory immunoassay.
9. We note that demonstration of depletion of up to 5,000 pg/ml RANKL by 2 µg/ml OPG is provided in the confirmatory immunoassay validation report and that this concentration of OPG is used for the immunogenicity assay. Justify the use of this concentration of OPG with respect to physiological levels of RANKL that may be found in the patients’ serum samples.
10. We note that the screening immunoassay is performed at both ATO and (b) (4); however, the validation report appears to have been conducted at ATO and does not include an assessment of assay of relevant parameters such as ruggedness (i.e. precision and robustness between labs). Provide relevant validation of ruggedness and the method transfer qualification report.
11. Validation of robustness of the immunoassays and bioassays should include assessments of factors in addition to plate lot, to demonstrate that variations in factors such as time,

temperature, instrument, etc. do not affect the assay. Additional data supporting assay robustness should be provided for all immunogenicity assays.

12. Regarding validation of precision:

- a. We note that validation of some aspects of the confirmatory immunoassay is supported by the validation of the screening immunoassay. However, as the confirmatory assay includes additional manipulations, differences in precision may occur. Provide data to support precision of the confirmatory immunoassay.
- b. Provide data regarding precision of the bioassays.

13. For some assays, edge effects and other effects that are dependent on the specific location of the sample wells on a plate are seen. Provide data to demonstrate that the immunoassays and bioassays are not affected by the assay plate well locations of positive controls, negative controls, and samples.

14. Regarding stability of immunoassay and neutralizing antibody bioassay components, provide information on your procedures for assessing stability of all critical reagents and whether they were implemented for these assays. Included in this should be information about stability of diluted samples, as we note that Amgen also stores aliquots of diluted positive control, diluted RANKL, diluted AMG 162, and diluted RANKL/OPG solution.

15. We note that Amgen states that for the bridging immunoassays, minimal washes were required, which reduced the loss of low affinity antibodies when compared to a traditional ELISA (Denosumab Integrated Immunogenicity Report, section 5.2). Provide data that demonstrates that antibodies with low affinity or rapid on/off rates can be detected by the screening immunoassay.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



STN: BL 125320/0

STN: BL 125331/0

APR 29 2009

AMGEN, Inc.
Attention: Edward S. Burd, Ph.D.
Senior Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Dr. Burd:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under Section 351 of the Public Health Service Act.

We have the following requests for clinical information:

Question 1

We continue to be concerned about the dental/bone events that may potentially represent Osteonecrosis of the Jaw (ONJ). We reviewed your submission dated March 12, 2009, and require clarification of several points.

- a. Table 2 is titled "Listing of All Potential ONJ Cases Sent to the Adjudication Committee" and the table lists the number of subjects enrolled. Clarify the number of subjects within each of these studies that were adjudicated by the committee.
- b. Table 3 is also titled "Listing of All Potential ONJ Cases Sent to the Adjudication Committee." Provide the adjudication results with the specific number of committee members voting Yes or No for each case reviewed and number of days it took to resolve the event.

Question 2

In our information request dated February 25, 2009, we requested that you provide a comprehensive narrative and relevant case information (e.g. oral surgery reports, pathology results) for a list of subjects with adverse events suggestive of ONJ. The narratives in your response dated March 12, 2009, did not provide much information about these events and many were designated as "non-serious." In follow-up, we have the following request:

- a. Describe your standard operating procedure for determining whether or not an adverse event is considered an important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent other serious outcomes.

- b. Provide Case Report Forms and any information from dentists or oral surgeons that would help clarify the following adverse event reports:

Study	Site	USUBJID	Verbatim term	Dictionary coded term
20030216	304	20030216-304023	Bone deterioration below tooth	Bone disorder
20030216	632	20030216-632004	Tooth implantation in jaw	Dental prosthesis user
20030216	719	20030216-719015	dental implant	Dental prosthesis user
			local infection after removal of tooth	Post procedural infection
20030216	633	20030216-633273		
20030216	412	20030216-412461	left maxilla dental abscess	Tooth abscess
20030216	731	20030216-731044	dental abscess lower jaw	Tooth abscess
20030216	661	20030216-661158	Teeth implantations	Dental implantation
20030216	632	20030216-632286	Tooth implantation	Dental prosthesis user
20030216	723	20030216-723055	Tooth implantation	Dental prosthesis user
			infection in mouth after removal of teeth	Post procedural infection
20030216	632	20030216-632141		
20030216	743	20030216-743119	dental abscess right lower jaw	Tooth abscess
20040132	309	20040132-309007	dental implant surgery	Dental implantation
20040132	309	20040132-309007	dental surgery	Dental operation
			bone implant-receding gums-outpatient	Bone graft
20040132	307	20040132-307022		
20040138	188	20040138-188004	dental surgery	Dental operation
20040138	214	20040138-214005	dental implant	Dental prosthesis user
			infection after molar traction	Postoperative wound infection
20040138	639	20040138-639003	jaw	
20050141	125	20050141-125040	jaw lesion	Bone lesion
20050233	29	20010223-029028	dental abscess r upper jaw	Tooth abscess
			big trouble chewing (problems chewing with missing teeth)	Mastication disorder
20050234	502	20050234-502003		Post procedural infection
20060286	1	20060286-001024	post-operative infection in jaw	

Question 3

Provide responses to the following coding questions from Study 132 (events from 36 month listing).

- a. Subject ID: 132103042

Coded Event: Benign ovarian tumor ileus

Explain why the following events were not coded as either an SAE or an AE: Post surgery subject experienced a reaction to general anesthesia characterized by bradycardia, hypoxia and an EKG result possibly suggestive of inferior ischemia.

- b. Subject ID: 132109002

Coded Event: uterine perforation

Explain why uterine fibroids were not coded as either an SAE or an AE. Please explain why the intra-abdominal hemorrhage requiring 3 units of PRBCs and surgical repair was

considered non-serious. Please describe your standard operating procedure for determining whether an adverse event prolongs hospitalization or is considered an important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent other serious outcomes.

Question 4

- a. For the following subjects, provide the causative pathogen for the reported endocarditis. Also, provide more detailed narratives and/or hospital discharge summaries or death summaries related to the reported endocarditis.
 1. SID 20030216-762526
 2. SID 20030216-430063
 3. SID 20030216-631230
 4. SID 20010223-007082
- b. Specifically for SID 20030216-430063, what was considered the primary cause of death? Was this subject considered a fatal infection case in your summary of infections?
- c. Specifically for SID 20030216-631230, provide your rationale for categorizing this event of endocarditis as non-serious.

Question 5

Provide an electronic listing (i.e. “.xpt” file) of all fatal events in the denosumab clinical program for all indications and Phases of development. This listing should include the information listed separately in Appendix 1.

If you have any questions, contact Celia Peacock, MPH, RD, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

George Benson

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Attachment

Attachment: Appendix 1

Appendix 1. Fatality Listing

Uniq. SID	Country / Site ID	Age	IP Rec'd	Date IP Started	Date Last IP Given (Day*)	Date of Death (Day*)	Special Interest Category**	End of Study Date (Day*) & Reason	Verbatim Term for Fatal Event	PT for Fatal Event	Autopsy available (Yes / No)

* Day calculated relative to first dose

** Specify if the fatal event was an adverse event of interest, i.e. indicate if the fatal event was classified as an infection, cardiovascular event, malignancy, hypocalcemia, hypersensitivity, etc.

Please provide name of investigational product, dose and dosing frequency in the column labeled "actual treatment received."

Please provide AE information in MedDRA 11.0.

Peacock, Celia

From: Peacock, Celia
Sent: Monday, April 06, 2009 1:52 PM
To: 'Burd, Edward'
Cc: Lepin, Julie
Subject: RE: Request for confirmation of plan of response to TOX request for IND 125320; update request on 74 d boxed warning telecon request

Also, I wanted to let your know that your proposal for submitting the historical control data below is fine. Thanks again, celia

From: Burd, Edward [mailto:eburd@amgen.com]
Sent: Friday, April 03, 2009 4:43 PM
To: Peacock, Celia
Cc: Lepin, Julie
Subject: Request for confirmation of plan of response to TOX request for IND 125320; update request on 74 d boxed warning telecon request

Dear Celia,

We are collating the information you requested regarding historical control data for Amgen Study #102090 (b) (4) study #1052-011) (6/12 month toxicity study with denosumab). Due to the necessity of manual retrieval and compilation of some of the historical data, not all can be provided immediately. We propose to submit the readily retrievable data of organ weights, hematology and clinical chemistry as early as Monday. The histological data requiring manual retrieval and tabulation **will follow later, within several week**, however we have prioritized the CV data and this may be available sooner and will be submitted as soon as available. Please confirm whether this is acceptable.

Regarding Amgen's response to the 74 day deficiency letters, we have not heard whether FDA will grant us a teleconference of a date and time of their choosing to learn more about the rationale for requesting boxed warnings. Can you confirm whether our request will be granted?

Thanks so much for your help,

Edward S Burd, Ph. D.
+1-805-447-3022 office
+1-805-490-5237 cell
eburd@amgen.com

Peacock, Celia

From: Peacock, Celia
nt: Monday, March 30, 2009 6:54 PM
o: 'Burd, Edward'; 'Lepin, Julie'
Cc: Peacock, Celia
Subject: denosumab info request

Hi Ed,

We would like to ask for historical control data for the cynomolgus monkeys used in Sponsor study #102090 (b) (4) study #1052-011) (6/12 month toxicity study with denosumab). This should include histopathology, organ weight, hematology and clinical chemistry.

Thanks!



STN: BL 125320/0
STN: BL 125331/0

AMGEN, Inc.
Attention: Julie Lepin
Director, Global Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4-C
Thousand Oaks, CA 91320-9978

Dear Ms. Lepin:

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 denosumab.

Also refer to our filing letter dated February 17, 2009. While conducting our filing review we identified the following potential review issues and have the following requests for information:

1. The narrative listings are cumbersome and difficult to read even in larger print (certain listings appear faded). Please resubmit comprehensive case summaries in narrative form for the following SAEs: all fatalities, hypocalcemia, hypersensitivity reactions, malignancies, cardiovascular events and fracture healing complications for studies 20030216, 20040132, 20010223, and 20050141. If a subject had multiple events, please create one case summary in narrative form for each subject.
2. For both Studies 20030216 and 20040132, Appendix 22: *Safety/Data Monitoring Committee Meeting Minutes and Correspondence* only includes the DSMB charter. The DSMB meeting minutes, correspondence, and list of meeting dates for each study should be submitted to each application.
3. For study 20030216, provide the following:
 - A justification for changing the primary efficacy analysis from a Cochran-Mantel-Haentzel analysis to a logistic regression model analysis prior to data unblinding.
 - The Amgen (b) (4) quality assurance audit documentation and the subsequent monitoring documentation for Lithuanian site 803 where you identified GCP noncompliance.
4. Provide an explicit definition of the Safety Population Flag, SAFETY. This variable is used across all datasets.

5. Clinical Pharmacology:

- a. Address denosumab's effect on CYP activities and drug interaction potential.
- b. To facilitate the review, please provide the following:
 - A Table summarizing immunogenicity that includes respective study numbers, number of subjects enrolled and tested for immunogenicity, number of subjects that showed a positive response and whether or not there was any impact on the safety and efficacy of denosumab in those subjects due to immunogenicity.
 - A table summarizing the in-process bioanalytical assay performance of each analyte of interest in each respective clinical study that includes the study number, analyte(s) of interest, and statistics.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 26, 2009.

If you have any questions, call Celia Peacock, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

A handwritten signature in black ink that reads "George Benson." The signature is written in a cursive style with a prominent initial "G".

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



FILING ISSUES

STN BL 125320/0
STN BL 125331/0

AMGEN, Inc.
Attention: Julie Lepin
Director, Global Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4-C
Thousand Oaks, CA 91320-9978

Dear Ms. Lepin:

This letter is in regard to your biologics license application (BLA), dated and received December 19, 2008, submitted under section 351 of the Public Health Service Act for denosumab.

We have completed an initial review of your applications for the treatment of osteoporosis in postmenopausal woman (STN BL 125320/0) and the prevention of osteoporosis in postmenopausal women (STN BL 125331/0) to determine their acceptability for filing. Under 21 CFR 601.2(a) we have filed your applications today. The user fee goal date is October 19, 2009. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

Potential review issues will be communicated to you on or before March 3, 2009.

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. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients age 0 through 16 years.

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, call Celia Peacock, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

A handwritten signature in cursive script that reads "George Benson".

George Benson, M.D.
Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

1/28/09
Denosumab
Filing Meeting Minutes
STN BLA Numbers 125-320 and 125-331

1. Introduction of application, including important dates

Stamp Date: December 19, 2008

Filing Date: February 17, 2009

Day 74 Letter Date: March 3, 2009

Review Completion Goal Date according to GRMP: Primary and secondary reviews should be completed by end of month 8 = August 19, 2009

PDUFA Goal Date: October 19, 2009

Review Team:

- Team Lead - Theresa Kehoe
- RPM - Celia Peacock
- CMC – Sarah Kennett, Michele Dougherty
- Pharm Tox – Kim Hatfield
- Clin Pharm – Chongwoo Yu (Primary CP reviewer), Ping Ji (PM reviewer)

- Clinical – Vaishali Popat, Adrienne Rothstein
- Stats – Sonia Castillo
- Labeling – Cheryle Milburn, Kellie Taylor, Judy Park, Janice Maniwang, others
- Biotech Manufacturing Team - Kalavati Suvarna, Pat Hughes
- Quantitative Safety and Pharmacoepidemiology Group (QSPG) Jenise Gillespie-Pedersen, George Rochester, Paul Schuette

2. Review of Consults:

- OSE – submitted 1/27/09
- Trade Name – submitted 1/10/09 (due 4/10/09)
- DDMAC – submitted 1/16/09
- DSI – waiting for additional info on sites from sponsor
- SEALED – will request during labeling negotiations
- Maternal Health – submitted 1/28/09
- Peds PeRC – PeRC Committee Date Set for 6/03/09
- Office of Biotechnology Product (sent in by Clin Pharm)

1/28/09
Denosumab
Filing Meeting Minutes
STN BLA Numbers 125-320 and 125-331

3. Discussion:

- Pharm Tox: Noted that there is a discrepancy in the drug formulation as stated in the clinical and nonclinical reports from what is stated in the current version of labeling. This has been noted for reference as the reviews proceed.
- Statistics: No issues identified at this time
- Clinical: No issues identified at this time.
- CMC: FDA will check to determine if the CP1 and CP2 manufacturing processes are comparable.

4. Access to CBER edr and role of RPM in BLA management. Original, signed, hard copies of reviews go to Celia. DRUP Reviewers need to note BOTH BLA numbers on all reviews. Reviewers for both DRUP and DBOP need to put all four BLA numbers on reviews.

5. Action Items:

- a. OSE will be consulted to determine if the submitted package insert should be separated out into a patient package insert and or medication guide.
- b. Labeling meetings will be conducted individually and jointly.



BLA ACKNOWLEDGEMENT

STN BL 125320/0
STN BL 125331/0
STN BL 125332/0
STN BL 125333/0

AMGEN, Inc.
Attention: Julie Lepin
Director, Global Regulatory Affairs and Safety
One Amgen Center Drive
Mail Stop 38-4-C
Thousand Oaks, CA 91320-9978

Dear Ms. Lepin:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

Name of Biological Product: denosumab

Date of Application: December 19, 2008

Date of Receipt: December 19, 2008

Our Submission Tracking Numbers (STN): BL 125320/0, BL 125331/0, BL 125332/0, BL 125333/0

Proposed Use: Treatment and prevention of osteoporosis in postmenopausal women and for the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer.

This submission has been administratively split into four applications as follows:

1. STN BL 125320 – Treatment of osteoporosis in postmenopausal women
2. STN BL 125331 - Prevention of osteoporosis in postmenopausal women
3. STN BL 125332 – Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer
4. STN BL 125333 – Treatment and prevention of bone loss associated with hormone ablation therapy in patients with prostate cancer.

STN BL 125320 and 125331 will be managed and reviewed by the Division of Reproductive and Urologic Products. STN BL 125332 and 125333 will be managed and reviewed by the Division of Biologic Oncology Products. For additional information regarding the eCTD requirements for this STN administrative split, please contact Virginia Ventura in the Office of Business Process Support, Electronic Submissions at (301) 796-1016.

STN BL 125320 will be considered the “parent” BLA. When you submit application amendments containing information that is applicable for all four indications, please submit that information in an amendment to the parent BLA, STN BL 125320 and also submit a letter of cross-reference for that information to the other 3 BLA STNs identified above. When you submit indication-specific information to the BLA, please submit that information to the appropriate STNs as identified above and also submit letters of cross-reference for that information to the other 3 STNs. All cross-reference letters should include a copy of the cover letter describing the contents of the amendment.

We will notify you within 60 days of the receipt date regarding whether each application is sufficiently complete to permit a substantive review.

The appropriate STNs provided above should be cited at the top of the first page of all submissions to this application. Send all submissions in the eCTD format. If sending the submission on physical media, please send by overnight mail or courier, to the following address:

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

If you have any questions regarding the osteoporosis indications, call Celia Peacock, MPH, RD, Regulatory Project Manager at (301) 796-4154. For questions regarding the oncology indications, call Melanie Pierce, Regulatory Project Manager in the Division of Biologic Oncology Products at (301) 796-1273.

Sincerely,



Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

BB IND 009837

Amgen, Inc
Attention: Bradley Glasscock
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Glasscock:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for denosumab.

We also refer to the meeting between representatives of your firm and the FDA on October 21, 2008. The purpose of this Type B Pre-BLA meeting was to discuss clinical and nonclinical aspects of denosumab.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Celia Peacock, MPH, RD, Regulatory Health Project Manager at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Medical Officer Team Leader
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure - Meeting Minutes and Amgen Meeting Slides

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 21, 2008
TIME: 1:00 – 2:30 p.m.
LOCATION: FDA, White Oak Campus, Silver Spring, MD
APPLICATION: BB IND 009837
DRUG NAME: Denosumab (AMG 162)
TYPE OF MEETING: Type B, Pre-BLA

MEETING CHAIR: Theresa Kehoe, M.D.

MEETING RECORDER: Celia Peacock, M.P.H., R.D.

FDA ATTENDEES:

Celia Peacock, MPH, RD	Regulatory Project Manager	Division of Reproductive and Urologic Products
George Benson, M.D.	Deputy Director	Division of Reproductive and Urologic Products
Gerald Willett, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Margaret Kober, R.Ph., MPA	Chief, Project Management Staff	Division of Reproductive and Urologic Products
Kimberly Hatfield, Ph.D.	Pharmacologist	Division of Reproductive and Urologic Products
Lynnda Reid, Ph.D.	Pharmacology Supervisor	Division of Reproductive and Urologic Products
Theresa Kehoe, M.D.	Medical Team Leader	Division of Reproductive and Urologic Products
Vaishali Popat, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Stephen Bienz, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Marcea Whitaker, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Chongwoo Yu	Clinical Pharmacology Reviewer	Office of Clinical Pharmacology/Division of Clinical Pharmacology III
George Rochester, Ph.D.	Lead Statistician for Safety	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Anita Abraham	Math Statistician	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group

Antonio Paredes	Math Statistician	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Mandi Yu	Math Statistician	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Sarah Kennett, Ph.D.	Biologist	Office of Pharmaceutical Science/Office of Biotechnology Products/Division of Monoclonal Antibodies
Mina Hohlen	Regulatory Information Specialist	Office of Business Process Support/Division of Regulatory Review Support
Chuck Cooper, M.D.	Medical Officer	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
Jenise Gillespie-Pedersen	General Health Scientist	Office of Biostatistics/Quantitative Safety and Pharmacoepidemiology Group
John Yap	Visiting Associate (Math Statistician)	Office of Biostatistics
Mahboob Sobhan	Math Statistician Supervisor	Office of Biostatistics/Division of Biostatistics III
Paul Schuette	Math Statistician	Office of Biostatistics
Chana Fuchs, Ph.D.	CMC Team Leader	Office of Pharmaceutical Science/Office of Biotechnology Products/Division of Monoclonal Antibodies

EXTERNAL CONSTITUENT ATTENDEES:

Matt Austin, MS	Director, Biostatistics
Laura Bloss, PhD	Executive Director, Clinical Development
Andre Daniels, MD	Executive Director, Global Safety
Roger Dansey, MD	Executive Director, Clinical Development
Beth Hinkle, PhD	Senior Scientist, Preclinical Development
David Feigal, MD	Vice President, Regulatory Affairs
Bradley Glasscock, PharmD	Senior Manager, Regulatory Affairs
Carsten Goessl, MD	Director, Clinical Development
Graham Jang, PhD	Director, Pharmacokinetics and Drug Metabolism
Qi Jiang, PhD	Executive Director, Biostatistics
Julie Lepin, MS	Director, Regulatory Affairs
Cesar Libanati, MD	Director, Clinical Development
Peter McCroskery, MD	Director, Global Safety
Rick Lit	Executive Director, Regulatory Affairs CMC
Barrie Nelson, LRSC	Senior Manager, Biostatistical Programming
Javier San Martin, MD	Executive Director, Clinical Development
Steven Snapinn, PhD	Vice President, Global Biostatistics & Epidemiology
Catherine Stehman-Breen, MD	Vice President, Global Development
Randy Steiner, DPA, MS	Executive Director, Regulatory Affairs

BACKGROUND:

On September 11, 2008, Amgen submitted a request and a briefing package for a Type B meeting to discuss their questions regarding the clinical and nonclinical aspects of the denosumab program. The package contained the questions listed below. DRUP's responses to the questions were faxed to the sponsor on October 17th, 2008, and are also included below. Additional meeting discussion is shown in bold italicized font after each response.

QUESTIONS, DIVISION RESPONSES, AND FURTHER DISCUSSION:

Question 1: Does the Agency require any clarifications regarding the proposed nonclinical content in support of the BLA submission for PMO and HALT indications (see Section 6 and Appendix 1)?

DA Response: No, not at this time.

Meeting Discussion: No additional discussion

Question 2: Does the Agency agree that the clinical data from the 4 pivotal phase 3 studies, in addition to data summarized from the overall development program, provide an adequate basis for BLA submission in support of the PMO and HALT indications (see Section 7)?

FDA Response: The proposed clinical data from the four pivotal phase 3 studies, in addition to data summarized from the overall development program, appear adequate for BLA submission for the proposed PMO and HALT indications. As outlined in February 08 meeting, all available safety and efficacy data should be submitted for the supportive studies. Trial synopsis or abbreviated report will not be sufficient.

Meeting Discussion: Amgen confirms that all available safety and efficacy data from supportive studies will be included in the BLA. The Agency requested that information regarding the study design (e.g., eligibility criteria) be present in the synopsis CSRs. Amgen replied that the protocol would be appended to each synopsis CSR. The Agency also requested that key demographic information be added to each synopsis CSR. Amgen agreed to provide this information for Studies 20060289 and 20060232. Amgen replied that it may be difficult to obtain this information for Study 20050209, since the database is not housed at Amgen.

FDA reconfirmed agreement with Amgen's proposed data cut-off date of 31 May 2008, as previously agreed during the 05 February 2008 Type C meeting.

DA Response: Studies 20040138 and 20040135, intended to support licensure for the HALT indications are ongoing, and will not complete the follow up phase until 2010 and 2011. FDA expects complete, cleaned and verified safety data up to the date of the data cut-off to be submitted with the BLA, and a final study report to be submitted upon completion of the trials.

Meeting Discussion: Amgen will provide in the BLA, full, complete clinical study reports from the treatment phases of studies 20040135 (month 24) and 20040138 (month 36) with data cut-off points of the Month 24 visit or the Month 36 visit, respectively. Amgen agreed to submit a final study report upon completion of both studies, including results from the safety follow-up phases of these studies. Final CSRs will be available in Q4 2009 and Q4 2010 for studies 20040135 and 20040138, respectively.

- **Study 20040135 2-year Safety Follow up: This 2 year follow up study to the two year treatment phase of the 20040135 will complete March 2009. In this extension, subjects are no longer receiving denosumab and limited data are collected via every 6 month phone or clinic contact (AE and concomitant medication). Interim data up to December 2nd, 2008 will be provided in the 120 day safety update (see Question 5).**
- **Study 20040138 2-year Safety Follow up: This 2-year follow up study to the 3-year treatment phase of the 20040138 will complete April 2010. In this extension, subjects are no longer receiving denosumab and limited data are collected via every 6 month phone or clinic contact (AE and concomitant medication). Interim data up to December 2nd, 2008 will be provided in the 120 day safety update (see Question 5).**

Question 3: Does the Agency require any clarifications regarding Amgen's approach for inclusion of information from completed and ongoing studies in the BLA submission as described in Section 7.1?

FDA Response: We do not require any clarification. Please refer to the answer to Question 2.

Meeting Discussion: No additional discussion.

Question 4: Does the Agency require any clarifications regarding Amgen's approach for overall safety evaluation as described in Section 7.6.2?

FDA Response: Your submission should include the charters, procedures and meeting minutes for any of the adjudication committees used in evaluation of the denosumab safety data. At a minimum, the information should include: the date the committees were appointed, a roster of committee members, what criteria were used for query of the safety databases and selection of events forwarded for committee review, criteria used for adjudication for each condition, procedures used to resolve differences of opinion among committee members. Please include minutes from all DMC meetings and minutes of classification meetings with detailed descriptions of analysis populations. Similarly, describe the data safety monitoring procedures in detail.

Meeting Response: Amgen confirmed that the BLA will contain the requested information.

FDA Response: In studies of denosumab therapy for treatment of rheumatoid arthritis, a concern has been raised about an apparent dose-dependent prolongation of the QT interval at month 12. One patient with QTc prolongation > 60 msec developed intermittent left bundle branch block. A complete analysis of all EKG data from all trials should be included in the BLA submission. If concern regarding QT prolongation remains, a thorough QT study may be necessary. Please clarify if the investigator's overall interpretation of ECG results as "normal", "abnormal, but not clinically significant" or "abnormal, clinically significant" as noted on the case report forms in several studies [see page 126] were sent to the Cardiovascular Events Adjudication Committee. Ultimately, the safety determination regarding QT prolongation is a review issue and therefore a definitive answer regarding a requirement for a thorough QT study can not be provided at this time.

Meeting Discussion: Amgen acknowledged the Agency's comment regarding QT prolongation and confirms that the BLA will contain a complete analysis of all ECG data from studies for which this information was collected, including Studies 20030148, 20030180, 20040245, 20050146, 20050227, 20060446, 20060286, 20010223, 20040132, 20050172, and 20040144. Additionally, for Studies 20010223 and 20040132, ECGs were also read by a central reader and results are described in the study reports.

None of these studies included CV adjudication (CV adjudication was performed in pivotal phase 3 studies 20040138 and 20030216). Therefore, none of these events were sent for adjudication.

FDA requested that Amgen include hyperlinked CRFs for all subjects with "abnormal, clinically significant" ECG results (using the investigator's interpretation) in the BLA submission. Amgen agreed to provide these CRFs in the BLA.

DA Response: Regarding bone quality, we are concerned that up to 35% of bone biopsy samples showed either a single tetracycline label or no label on the cortical and trabecular bone surface. Please

clarify the number of bone histomorphometry samples obtained, and what percent were adequate for valuation.

Meeting Discussion: Bone biopsy samples have been collected from studies of treatment naïve women treated with denosumab (20010223 and 20030216) and women who had previously received alendronate and were transitioned to denosumab (20050234). Amgen noted the Agency's concern with regard to the lack of label in some bone biopsy samples, and Amgen committed to provide a detailed explanation of this observation in the BLA to address this concern.

FDA Response: Adverse events of interest

- a. Hypersensitivity reactions: the analysis should also examine any injection or infusion site reactions. Also, please review any subjects with lags in therapy/reintroduction of therapy in case these subjects are more at risk for hypersensitivity reactions.
- b. Hypocalcemia: provide a listing of all subjects who received intravenous calcium replacement.
- c. Infections: present and evaluate the infection data over time – e.g. present the SOC categories for Year 1, Year 2, etc. then microbial types for Year 1, Year 2, etc. Also, evaluate infections in subjects receiving concomitant immunosuppressant therapy (e.g. systemic corticosteroids, methotrexate, azathioprine, etc.)

Meeting Discussion: For items a and b, Amgen confirmed that these analyses will be included in the assessment of these adverse events of interest.

For item c, Amgen recognized the Agency's interest in identifying subpopulations of subjects at higher risk of infection.

Study 20040144 (a phase 2 dose-ranging study in rheumatoid arthritis) provides the opportunity to explore the risk for infection in subjects receiving concomitant immunosuppressant therapy (e.g., systemic corticosteroids, methotrexate, azathioprine, etc.), where immunosuppressant therapy was used in all subjects. These analyses will be provided in the BLA.

In addition, Amgen will evaluate the utility of performing analyses of concomitant immunosuppressant therapy from the pivotal PMO and HALT studies.

FDA requested that Amgen include a comprehensive evaluation of infections across all studies, including phase 1 studies, in the BLA.

Question 5: Does the Agency agree with the proposed content and analysis for the 120-day safety update as described in Section 7.10?

FDA Response: No. A more complete safety update at 120 days is required. The 120 day safety update should include complete, cleaned and source verified safety data. In addition, the 120-day safety update should be accompanied by any new and updated narratives and case report forms for all deaths, as well as for all patients with serious adverse events, those terminating study drug prematurely, and those categorized as other, lost to follow up, physician decision, or subject decision. In addition, please provide an updated comprehensive evaluation of the adverse events of interest identified in section 7.6.4.

Meeting Discussion: Amgen confirmed that it will provide a complete safety update (including cleaned and source verified safety data) for the following PMO and HALT studies for the 120-day safety update:

- **Data from the safety follow up phase of Studies 20040135 and 20040138 up to the cut-off of December 2, 2008**
- **BMD and safety data from the off-treatment phase of Study 20040132 up to the final study visit (month 48) in January 2009**
- **Final clinical study report (including 12 months of safety and immunogenicity data) from Study 20060237 (vial vs. PFS study)**
- **Interim analysis of Study 20060289 (open-label extension phase to study 20030216) up to the cut-off of December 2, 2008**

Amgen will also provide new and updated safety narratives from these studies and case report forms as specified above.

Amgen is not planning to provide clean, source verified safety data from the other ongoing studies, since these studies are not anticipated to provide additional significant information for the safety evaluation of denosumab in these indications. These studies include:

- **Study 20050233: 4-year open label safety extension to the phase 2 dose ranging study (20010223)**
Study 20060232: 2-year open label adherence, preference, and satisfaction study
- **Study 20040114: phase 2 open-label, active-controlled study in subjects with advanced cancer currently being treated with intravenous bisphosphonates**
- **Study 20050134: phase 2 open label multiple myeloma study**
- **Study 20050209: ABCSG Cooperative Group breast cancer study in postmenopausal women with nonmetastatic breast cancer undergoing aromatase inhibitor therapy**

Amgen would like confirmation of the Agency's agreement with this proposal.

Based on this incremental data set, Amgen will provide a comprehensive evaluation of the adverse events of interest in the 120-day update for the studies being submitted.

FDA stated that this proposal was acceptable but requested that Amgen provide a complete safety update (including cleaned and source verified safety data) for Study 20050233 in the 120-day safety update. Amgen agreed to provide this information.

FDA Response: We note the precipitous decrease in bone density once denosumab treatment was discontinued in study 20040132 (page 92, 93). This raises concern about a possible negative rebound effect. The last patient last visit for study 2004132 is in January 2009. Therefore, the 120 day safety update must include 48 month BMD data from study 2004132.

Meeting Discussion: Amgen will provide the 48-month BMD data from Study 20040132 in the 120-day update.

In addition, Amgen will provide in the BLA BMD results, bone turnover, and safety data, from the 2-year period following discontinuation of denosumab treatment from Study 20010223 (phase 2 dose ranging study in PMO). The results for lumbar spine and total hip BMD in this study demonstrate that BMD declines to approximately pre-treatment levels in the first year after discontinuation of treatment. No further declines in BMD are observed in the second year after discontinuation from treatment.

Amgen presented the results indicated above from Study 20010223, showing changes in lumbar spine BMD for the 2-year period after discontinuation of denosumab treatment, demonstrating the lack of further declines in BMD in the 2nd year of off-treatment. In addition, the similar changes in lumbar spine BMD after denosumab discontinuation for two different dose regimens were presented. These data will be provided in the BLA.

Question 6: As described in Section 4.3, Amgen considers that the criteria for priority review are met for denosumab in the treatment and prevention of PMO and in the treatment of bone loss associated with HALT in patients with breast cancer and prostate cancer. A formal request for priority review will be included in the BLA. Does the Agency have any comments on this proposal?

FDA Response: The status of the application will be determined once it is submitted for review. However, DRUP does not believe that denosumab meets the criteria for priority review for the PMO indication as there are multiple safe and effective therapies available, including medications administered once yearly.

Meeting Discussion: Amgen acknowledged that the status of the application will be determined after submission of the BLA, and we look forward to receiving the Agency's response to Amgen's request for priority review.

Additional Clinical Comments:

Please include following in the BLA submission:

- summary tables of the incidence of adverse events based on the cumulative dose and the average dose of Denosumab administered,
- a dataset that describes all prior therapies.
- a discussion and justification of the clinical utility of measuring BMD at a one month time point.

Meeting Discussion:

Bullet 1

The same dose and dosing frequency was used in all phase 2 and phase 3 studies to support the proposed indications (60 mg SC Q6M), except for the phase 2 Study 20010223 dose finding study. Therefore adverse event analyses using categories of average dose and total dose received would contain nearly the same information. Any analysis based on cumulative dose or average dose would also be nearly identical to grouping studies based on duration (1 year, 2 year, and 3 year studies) because of high compliance.

Amgen will provide exposure-adjusted (using time on study), and by-year-of-study incidences of adverse events and serious adverse events, in the individual clinical study reports for Studies 20030216 and 20040138 as well as in the integrated safety datasets in the BLA.

Amgen believes that these analyses will satisfy the Agency's request for incidence of adverse events based upon cumulative and average dose.

Bullet 2

In Study 20030216, Amgen will provide in the BLA, a dataset that describes all prior therapies affecting bone metabolism. For HALT Studies 20040135 and 20040138, information regarding prior bisphosphonate therapy will be provided.

Study 20050234 evaluated the safety and efficacy of denosumab in subjects who had previously received bisphosphonate therapy compared to subjects continuing on bisphosphonate therapy. A final full clinical study report will be provided in the BLA.

Bullet 3

Amgen will provide a discussion and justification of the relevance of measuring BMD at early time points in clinical studies of denosumab.

FDA stated that these proposals were acceptable.

FDA Response: Amgen's proposal for providing training to FDA staff on their CDISC submission is acceptable. However, a 2 hour presentation is preferable to the 3 hour and 50 minute agenda proposed.

Meeting Discussion: *Amgen will follow-up with the FDA following the submission of the BLA to coordinate this meeting. An abbreviated agenda for this meeting will be provided.*

Additional Clinical Pharmacology Comments:

- In addition to the biopharmaceutics and clinical pharmacology findings summary, we recommend including the following information in your BLA submission to facilitate the review:
 - A table listing all the studies with respect to the drug substance and product used in Section 2.7.1.
 - Summary of bioanalytical methods for pharmacokinetic, pharmacodynamic, and immunogenicity assessments in Section 2.7.1.
 - Summary of immunogenicity assessment results in Section 2.7.2.

Meeting Discussion: *Amgen confirmed that this information will be included in the BLA.*

Additional CMC Comments:

- In follow-up to the CMC preBLA meeting of July 8, 2008 and the subsequent telecon of July 29, 2008, we have the following comment regarding Amgen's proposed validation strategy for licensure of the 60 mg/ml vial. In order to license the 60 mg/ml vial, a comprehensive data package, including complete validation and stability data for the 60 mg/ml vial manufactured at AML, will need to be included in a BLA submission.

Please submit the planned denosumab manufacturing schedule prior to the submission of the BLA, so that pre-approval inspections for each intended manufacturing site can be scheduled to conform to the GRP review timeline.

Meeting Discussion: Process validation, consisting of 3 consecutive drug product lots of the 60 mg/mL vial manufactured at Amgen Manufacturing Limited (AML), was performed in September 2008. Validation data, including 1 month of stability data will be submitted in the BLA. Additional stability data up to 3 months for these lots will be available during the review period, approximately 120 days after the BLA submission.

A comparability assessment for the site transfer from the clinical to the commercial site, AML, for the 60 mg/mL vial will also be provided in the BLA. This will include an assessment against historical ranges for lot release testing.

Amgen will submit a manufacturing schedule for both commercial drug substance manufacturing sites, BI Pharma and Amgen Colorado, and for the commercial drug product site, AML, prior to submission of the BLA.

Amgen requested an Agency point of contact to facilitate coordination of these inspections.

FDA stated that these proposals were acceptable. In addition, FDA recommended that Amgen coordinate with the regulatory project manager to provide manufacturing schedule details.

Additional Division of Biologic Oncology Products (DBOP) Comments:

DBOP has the following general comments regarding the content and organization of a BLA.

I Information Required for Review

A. The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, DBOP requests you provide analyses, and the supporting ADaM datasets as applicable, that will address the items in the template, including:

1. Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Exposure-Response Relationships - important exposure-response assessments.
3. Less common adverse events (between 0.1% and 1%).
4. Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Marked outliers and dropouts for laboratory abnormalities.
7. Analysis of vital signs focused on measures of central tendencies.

8. Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Overdose experience.
12. Explorations for dose dependency for adverse findings.
13. Explorations for time dependency for adverse findings.
14. Explorations for drug-demographic interactions.
15. Explorations for drug-disease interactions.
16. Explorations for drug-drug interactions.
17. Dosing considerations for important drug-drug interactions.
18. Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Meeting Discussion to Items 1 – 18:

Amgen confirmed that the requested analyses, and the supporting ADaM datasets as applicable, will be included in the BLA. This information will be summarized in the clinical summary documents contained in Module 2 of the CTD and applicable clinical study reports.

In addition, DBOP requests the following:

1. For the submitted datasets:
 - a. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration. The integrated safety dataset should include the following fields/variables:
 - A unique patient identifier
 - Study/protocol number
 - Patient's treatment assignment
 - Demographic characteristics, including gender, chronological age (not date of birth), and race
 - Dosing at time of adverse event
 - Dosing prior to event (if different)
 - Duration of event (or start and stop dates)
 - Days on study drug at time of event
 - Outcome of event (e.g. ongoing, resolved, led to discontinuation)
 - Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - Marker for serious adverse events
 - Verbatim term

Meeting Discussion: Amgen will provide the requested dataset, and confirmed that this integrated safety dataset applies to all phase 2 and phase 3 PMO and HALT studies for completed studies or studies for which the treatment phase is complete only and will exclude studies outside the proposed indications (i.e., advanced cancer and rheumatoid arthritis) due to differences in patient populations.

FDA stated that this proposal was acceptable but recommended that we follow-up with DBOP to ensure agreement on this proposal.

2. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.

Meeting Discussion: Amgen will provide the requested dataset.

3. Please see the mock adverse event data set following this section that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.

Meeting Discussion: Amgen commits to providing the requested dataset.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

Meeting Discussion: Amgen will provide the requested dataset.

5. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

Meeting Discussion: Amgen will provide the requested information.

6. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related renal disorders – comprehensive search SMQ. Also, please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

Meeting Discussion: Amgen will provide the requested information.

7. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

Meeting Discussion: Amgen confirmed that this formatting will be performed as requested.

8. *Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.*

Meeting Discussion: Amgen will provide the requested information.

9. *In every dataset, all dates should be formatted as ISO date format.*

Meeting Discussion: Amgen will provide the requested information.

C. Provide a comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities. Also, provide a list of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The BLA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

Meeting Discussion: Amgen confirmed that data from patients with potentially clinically significant laboratory or vital sign abnormalities will be provided in the Summary of Clinical Safety ADaM datasets. Amgen confirmed that patients reporting adverse events involving abnormalities of laboratory values or vital signs will be tabulated. Analyses of laboratory values will include assessments of changes from baseline to worst values.

D. For all HALT pivotal trials, CRFs for all deaths occurring within 3 months of a denosumab dose, all serious adverse events, and all withdrawals will be required. In addition, CRFs for all patients with cardiovascular adverse events should be submitted. Any change in the CRF documents should be hyperlinked to the query or documentation from which the change resulted.

Meeting Discussion: As agreed during the Type C meeting of February 2008, Amgen will provide CRFs for all deaths occurring within 3 months of a denosumab dose, all serious adverse events, cardiovascular adverse events, and all withdrawals due to adverse events.

E. For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

Meeting Discussion: Amgen confirmed that its data management procedures include a review of reasons for discontinuation to confirm whether the appropriate reason for discontinuation has been selected by the investigator. Amgen tabulates the study disposition table according to the reason for discontinuation provided by the investigator.

F. If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions

with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

Meeting Discussion: Amgen acknowledged the Agency's comment and will engage in these discussions as necessary.

II Information Regarding Submission of Electronic Data Sets

A. Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org) .

At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: FDA Guidance to Industry: Pre-Marketing Risk Assessment, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- b. Safety endpoints for Adverse Events of Special Interest (AERI)
- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the QSAP may be amended.

Meeting Discussion: Although Amgen does not have a QSAP, the requested items a – g above will be included in the BLA, including an integrated SAP for the Summary of Clinical Safety, the define.xml document, and adjudication and DMC charters.

FDA stated that this proposal was acceptable.

Amgen inquired as to whether a QSAP will be a requirement for future submissions, and if guidance will be provided. There is no regulatory requirement for the submission of a separate QSAP. It is expected that there is an expanded section of the current Statistical Analysis Plan(SAP) that provide details on adverse events of special interest, the data structure, analysis, etc. Future guidance on this will be provided.

B. Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) should be followed carefully. Refer to the SDTMIG section on Conformance (3.2.3)

Meeting Discussion: Amgen confirms that they are following SDTMIG 3.1.1.

2. Domains

- a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - (DV) Protocol deviations
 - (DA) Drug Accountability
 - (PC, PP) Pharmacokinetics
 - (MB, MS) Microbiology
 - (CF) Clinical Findings

Meeting Discussion: Amgen confirmed that they are using DV, DA, PC, PP, and CF (named DF in their datasets) domains. Data for the PC and PP domains will be provided for the phase 2 and 3 studies and phase 1 Study 20040245.

- b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - Imaging Data
 - Complex Inclusion/Exclusion Criteria

Meeting Discussion: Amgen confirmed that they have created custom domains following SDTM guidance. It is highly desirable that Amgen follow the CDISC recommendations and it would be very helpful for the sponsor to provide details on these domains and their quality checks to show that they are CDISC compliant.

3. Variables

- a. All required variables are to be included.

Meeting Discussion: Amgen confirmed that all required variables will be included.

- b. All expected variables should be included in all SDTM datasets.

Meeting Discussion: Amgen confirmed that all required variables will be included.

- c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.

Meeting Discussion: Amgen has explicitly stated in the CRT reviewer's guide the variables (expected or permissible) for which no values will be submitted. Variables

will have no values for one of 2 reasons, either the data was not explicitly collected on the CRF or the data point was conditional and no occurrence was encountered in the study. This approach is consistent with the published CDISC SDTM Implementation Guide.

FDA stated that this proposal was acceptable but requested that Amgen include this information in the Define.xml file in addition to the CRT Reviewers Guide.

- d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.

Meeting Discussion: Amgen has excluded a permissible variable from a domain only when data was not explicitly collected on the CRF for that variable. They have not made subjective decisions on which permissible variables to include or exclude this decision is purely data driven. This approach is consistent with the published CDISC SDTM Implementation Guide. Amgen has not indicated which permissible variables have been included or excluded from each domain.

FDA stated that this proposal was acceptable.

- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.

Meeting Discussion: Amgen confirms that this information is included in the define.xml file.

- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG. :

Meeting Response: Amgen confirms that all datasets are compliant with the SDTMIG.

4. Specific issues of note:

- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.

Meeting Discussion: Amgen confirmed that SDTM formatted datasets do not provide replication of core variables.

- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.

Meeting Discussion: Amgen confirms that we will include MedDRA hierarchy variables in the SUPPQUAL dataset.

- c. These issues can be addressed through the request for ADaM datasets

Meeting Discussion: No further discussion.

C. Analysis Data Model (ADaM) Issues

1. Specify which ADaM datasets you intend to submit.

Meeting Discussion: The specific ADaM datasets that Amgen will submit are listed in the define.xml file and in the CRT reviewer's guide which was agreed during the Type C meeting of February 2008.

2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.

Meeting Discussion: The specific variables in the ADaM datasets that Amgen will submit are listed in the define.xml file.

3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.

Meeting Discussion: Amgen plans to be consistent with the dataset structures agreed upon during the Type C meeting of February 2008.

4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.

Meeting Discussion: Amgen confirms that this information will be included in the dataset.

5. Indicate which core variables will be replicated across the different datasets, if any.

Meeting Discussion: Amgen will indicate which core variables will be replicated across the different datasets in the CRT Reviewers Guide.

6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

Meeting Discussion: Amgen confirms that these identifiers will be retained.

D. General Items

1. Controlled terminology issues
 - a. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire BLA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for

individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

Meeting Discussion: Amgen has used different MedDRA dictionaries, and will provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another.

Amgen requests clarification regarding the Agency's preferred format for this table and the eCTD location for this table.

FDA stated that this proposal was acceptable but did not specify a preferred format or eCTD location for the table. FDA agreed with Amgen's suggestion to include this table in the Summary of Clinical Safety.

- b. For the concomitant medication dataset, the standard nomenclature and spellings from the WHO Drug dictionary, including the numeric code in addition to the ATC code/decode, are recommended.

Meeting Discussion: Amgen will not provide numeric codes in the concomitant medications dataset. They will provide the character decodes for the preferred terms.

FDA stated that this proposal was acceptable. Amgen will explore the possibility of providing the numeric codes as requested.

- c. Please refer to the CDISC terminology for lab test names.

Meeting Discussion: CDISC controlled terminology for lab test names was not in place when we began our CDISC implementation. Therefore, Amgen uses Amgen-defined lab test names.

FDA stated that this proposal was acceptable.

- d. Issues regarding ranges for laboratory measurements should be addressed. Provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from a local lab or central lab. Also, the variable for the laboratory result should be in numeric format.

Meeting Discussion: Amgen will provide an indication whether the lab result was from a local lab or central lab.

III Label in the Physician Labeling Rule (PLR) Format

A. Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

8. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
9. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
10. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]

11. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
12. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
13. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

B. Contents (Table of Contents):

14. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
15. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
16. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
17. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
18. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

19. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:
 - “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

C. Full Prescribing Information (FPI):

20. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

21. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
22. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
23. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
24. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
25. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
26. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
27. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
28. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
29. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.

30. If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
31. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
32. Refer to the Institute of Safe Medication Practices' website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

Meeting Discussion: Amgen acknowledged the Agency's comments regarding labeling (Section III above) and will submit the proposed labeling for denosumab in accordance with the Physician Labeling Rule (PLR) format per the PLR-related regulations and guidance documents.

During the labeling review process, Amgen proposes to provide both a 'tracked changes' version and a 'clean' version of the label to FDA. To facilitate this process and alleviate issues associated with version control, Amgen requests that the FDA reviewers provide their comments and changes in 'tracked changes' to the 'clean' version of the label.

Amgen inquired about the possibility of an Advisory Committee meeting, and FDA stated that an Advisory Committee meeting will almost certainly be required for denosumab, but no further details were available. Further details on whether this will be a joint Advisory Committee will be discussed following submission of the BLA.

In addition to the meeting responses above, Amgen provided the following summary of agreements and action items from the meeting:

1. ***The proposed clinical data from the four pivotal phase 3 studies, in addition to data summarized from the overall development program, appear adequate for BLA submission for the proposed PMO and HALT indications. Amgen's proposed responses to the Agency's pre-meeting comments are considered generally acceptable; there are a few additional considerations from today's discussion. It is understood that all safety and efficacy data will be provided irrespective of the type of report, and that the provision of the proposed reports is considered appropriate. Amgen will follow up with DBOP to ensure agreement with Amgen's responses.***
2. ***For synopsis reports, a copy of the protocol will be included to provide information regarding the study design (e.g., eligibility criteria). In addition, key demographic information will be added to each synopsis CSR, recognizing this information may be limited in some cases.***

3. *Final agreements on Amgen's proposals to provide clean, source verified safety data from Studies 20040135 and 20040138 in the 120-day safety update and full CSR's upon study completion will be provided by DBOP.*
4. *Amgen will provide all CRFs for those cases of ECGs considered "abnormal, clinically significant".*
5. *Amgen will provide a comprehensive evaluation of bone biopsy data in the BLA and look forward to further discussion with the FDA on this subject during BLA review once these data have been assessed.*
6. *Amgen will provide clean, source verified data from the open-label extension Study 20050233 in the 120-day safety report.*
7. *Amgen will seek to have a face-to-face meeting to discuss CDISC aspects shortly.*
8. *Amgen will liaise with Celia Peacock, the DRUP Regulator Project Manager to schedule inspections.*
9. *Amgen will ensure that appropriate comments are provided in Define.xml file to provide sufficient direction to reviewers on what is provided in the data sets.*
10. *Amgen will include a table mapping MedDRA codes for the integrated analysis in the Summary of Clinical Safety unless otherwise instructed to locate elsewhere in the CTD by FDA.*
11. *FDA would appreciate the inclusion of numerical codes in addition to ATC. Amgen will explore the possibility of providing this information.*

ACTION ITEMS;

Finalize meeting minutes within 30 days.

ATTACHMENTS/HANDOUTS:

Amgen Slides.

41 pages(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BB IND 9837

Amgen, Inc
Attention: John J. Bergan
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-9978

Dear Mr. Bergan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for denosumab.

We also refer to the meeting between representatives of your firm and the FDA on July 8, 2008. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Control issues.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Celia R. Hayes, MPH, RD
Captain, U.S. Public Health Service
Regulatory Project Manager
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 8, 2008

TIME: 1:00 p.m. – 2:30 p.m.

LOCATION: FDA, White Oak Campus

APPLICATION: BB IND 9837

DRUG NAME: Denosumab

TYPE OF MEETING: Type B

MEETING CHAIR: Chana Fuchs, Ph.D.

MEETING RECORDER: Celia Hayes, M.P.H., R.D.

FDA ATTENDEES:

Celia Hayes, MPH, RD	Regulatory Project Manager	Division of Reproductive and Urologic Products
George Benson, M.D.	Acting Deputy Director	Division of Reproductive and Urologic Products
Gerald Willett, M.D.	Medical Officer	Division of Reproductive and Urologic Products
Adrienne Rothstein, Pharm.D.	Clinical Analyst	Division of Reproductive and Urologic Products
Margaret Kober, R.Ph., MPA	Chief, Project Management Staff	Division of Reproductive and Urologic Products
Myong-Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader	Office of Clinical Pharmacology
Kimberly Hatfield, Ph.D.	Pharmacologist	Division of Reproductive and Urologic Products
Theresa Kehoe, M.D.	Medical Team Leader	Division of Metabolism and Endocrinology Products
Patricia Hughes, Ph.D.	Microbiologist	Division of Manufacturing and Product Quality
Jang-Ike Lee	Clinical Pharmacologist	Office of Translational Science
Jeffery Summers M.D.	Medical Team Leader	Division of Biologic Oncology Products
Patrick Swann, Ph.D.	Deputy Director	Division of Monoclonal Antibodies
Chana Fuchs, Ph.D.	CMC Team Leader	Division of Monoclonal Antibodies

Sarah Kennett, Ph.D.	Biologist	Division of Monoclonal Antibodies
Hong Zhao, Ph.D.	Pharmacology Reviewer	Office of Translational Sciences

EXTERNAL CONSTITUENT ATTENDEES:

Lorena Barrón, PhD	Principal Scientist, Drug Product and Device Development	Amgen
John Bergan	Senior Manager, Regulatory Affairs CMC	Amgen
Laura Bloss, PhD	Executive Director, Clinical Development	Amgen
Mike Moxness, Ph D	Principal Scientist, Clinical Immunology	Amgen
David Feigal, MD	Vice President, Global Regulatory Affairs	Amgen
Bradley Glasscock, Pharm D	Senior Manager, Regulatory Affairs	Amgen
Simon Hotchin	Senior Manager, Regulatory Affairs CMC	Amgen
Christopher Johnson	Director, Product Quality	Amgen
Rick Lit	Executive Director, Regulatory Affairs CMC	Amgen
Jennifer Mercer	Director, Regulatory Affairs CMC	Amgen
Tony Mire-Sluis, PhD	Executive Director, Corporate Quality	Amgen
Athena Nagi, PhD	Principal Scientist, Analytical Sciences	Amgen
Gregg Nyberg, PhD	Principal Scientist, Process Development	Amgen
Margaret Ricci, PhD	Director, Formulation Analytical Resources	Amgen
Wen Ryan, PhD	Executive Director, Global Operations	Amgen
Javier San Martin, MD	Executive Director, Clinical Development	Amgen

BACKGROUND:

On April 22, 2008, Amgen submitted a request and a subsequent briefing package, on May 29, 2008, for a Type B meeting to discuss Chemistry, Manufacturing, and Control issues. The package contained the questions listed below. DRUP's responses to the questions were conveyed to the sponsor on July 7th, 2008, and are also included below. Additional meeting discussion is shown in bold italicized font after each response.

QUESTIONS, RESPONSES, AND FURTHER DISCUSSION:

Question 1: The overall strategy for demonstration of drug substance and drug product comparability between clinical and commercial production was discussed during a Type C meeting held 08 December 2006. Subsequent to this meeting, analytical comparability for the transfer of the commercial drug substance process from Amgen Colorado (ACO) to Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma) has been completed and the results of this study were submitted to BB-IND 9837 on 07 December 2007 (SN 0406). Further characterization studies have been completed in order to assess the analytical differences in charge and size profile noted between drug substance manufactured at ACO and drug substance manufactured at BI Pharma.

- a) Does the FDA agree that the additional drug substance characterization data demonstrate that the observed differences between drug substance manufactured at ACO and BI Pharma are understood, and when combined with the results of the bioequivalence study, will provide sufficient evidence to conclude that the materials are comparable?

FDA's Response: Final conclusions on comparability are a BLA review issue. The analyses provided support biochemical similarity and, with associated bioequivalence study results, these data may be sufficient to demonstrate comparability between the ACO and BIP manufactured DS.

Greater detail is needed regarding the distribution and activity of (b) (4) structural isoforms¹. You state in Table 24 on page 126 that structural isoforms are present at levels of between (b) (4) and that all structures were equally potent. Results in the cited literature indicate that the (b) (4) isoform can have diminished activity.

Regarding both comparability and specifications, please include in the BLA line item data for release and stability testing for each referenced lot. Please provide good quality reproductions of representative gels and chromatographs for our assessment.

We note that there is a small difference in the results of host cell DNA, host cell protein, and Protein A testing for ATO/ACO vs. BI Pharma. In the BLA, please clarify if this is due to the testing procedure (e.g., testing at different locations or with different protocols) and reporting, or due to the different manufacturing processes.

¹ Dillon et al, JBC, Published online March 12, 2008; Wypych et al, JBC, Published online March 13, 2008.

Please clarify which reference material (ATO or ACO) is being used in the clinical comparability study (20060286)

Meeting Discussion: Amgen stated that they have isolated and tested the potency of the (b) (4) variants of denosumab by the various potency methods and have shown them to be equivalent. This information will be presented in the BLA. Marginal differences have been observed in the levels of CHOP in the in-process pools at ACO and BI Pharma. However, the purification process at both sites has similar clearance capabilities and reduces the levels of CHOP in DS to the LOD at both sites. The same methodology is used at both sites and the apparent differences in Protein A, DNA and CHOP at the DS stage are due to rounding and reporting differences between sites. Amgen acknowledged the Agency's concern regarding any process related differences and confirmed that any differences detected between sites will be evaluated for other underlying differences which are not part of normal monitoring/testing. Amgen confirmed that ATO material was the reference material used in Study 20060286. FDA indicated that chromatograms shown in the comparability reports were shown in full scale and that any smaller peaks cannot be seen well at such scale; Amgen agreed to include expanded view chromatograms in the BLA.

- b) Does the FDA agree that the overall plan for submission of comparability data in the BLA is sufficient for product registration including drug substance manufactured at ACO and BI Pharma and for the drug product presentations (vials and prefilled syringes) manufactured at AML?

FDA's Response: No. Comparability analyses between drug products manufactured at AML and ATO, for both the PFS and the 60mg/mL vial, should be finalized, and a full comparability data package should be included in the BLA submission.

From a clinical pharmacology standpoint, your proposed plan of submitting the clinical comparability data from studies 20050227, 20050146, 20060446, and 20060286 appear to be adequate to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) comparability for the transfer of drug substance manufacturing sites and for the different drug product presentations. However, the drug product manufacturing site change from ATO to AML may need an additional PK and PD comparability study in humans if the analytical comparability assessments detect a potential for PK or PD difference. A conclusive determination of the comparability is a BLA review issue.

Meeting Discussion: Amgen stated that the ATO to AML process comparability will be presented in the BLA, highlighting the high degree of similarity in process and equipment between sites. Where process or equipment differences exist, process characterization studies have been performed to show that the process differences do not impact process performance or product quality. These data will be provided in the BLA. Site-to-site comparability data has been generated for the 60 mg/mL PFS and the final report will be presented in the BLA. Site-to-site comparability data has been generated for the 70 mg/mL vial and the final report will be presented in the BLA. Amgen considers that the site-to-site comparability data generated on the 70 mg/mL vial may be appropriately extrapolated to the 60 mg/mL vial to support approval of this presentation, based on the high degree of

similarity between the 60 mg/mL and 70 mg/mL vial processes, and will justify this approach in the BLA.

The FDA indicated that insufficient information is provided to make an assessment regarding the site-to-site comparability at this time, and this proposal would need to be subject to a complete review of the data, including process validation and a comparability study from the commercial manufacturing site in order to make a final determination.

Amgen stated that based on experience from other commercial products and the results of the technical transfer of the denosumab fill process between the clinical and commercial sites (including execution of an engineering run for the 60 mg/mL vial), the technology transfer of the 60 mg/mL vial process from ATO to AML was not expected to adversely impact product quality. The strategy developed for denosumab was based on this historical precedence as well the data obtained from the 70 mg/mL vial. Amgen indicated that the 70 mg/mL vial was manufactured with the same equipment, process scale, and container closure system with only a difference in the fill volume and protein concentration.

The FDA stated that decisions could not be made prior to reviewing the data, however, should there be a problem, and the necessary data not be available on time, the 60 mg/mL vial may be reviewed as a supplement to the license post approval. Amgen suggested that a comparability protocol may be an option if the Agency would agree to further discussions.

The FDA stated that licensing both the 60 mg/mL and 70 mg/mL vial could led to medication errors and inquired as to whether or not the 70 mg/mL vial was intended for multiple doses. Amgen responded that all presentations of denosumab are intended for single use and that there is no intention to develop a multidose product. The FDA agreed to a follow up discussion with Amgen in an attempt to reach agreement on this strategy.

Question 2: Amgen will propose drug substance and drug product release specifications in the BLA based on an assessment of the critical quality attributes of denosumab and statistical analysis of data generated from clinical and commercial lots, including data generated during ongoing primary, commercial and supportive stability studies. Does the Agency agree that the selection of tests proposed for inclusion in the release specifications is adequate to control the quality of denosumab drug substance and drug product?

FDA Response: No. We have the following preliminary comments.

- a. A binding assay is not adequate for use as the sole potency assay for licensure of this product, and a validated bioassay assay that reflects the proposed mechanism of action should be included for release and stability testing of DS and DP.
- b. In the BLA, please provide data for all CE-HPLC peaks. The inclusion of only main peak in the acceptance criteria will be a BLA review issue.
- c. We note that SDS-PAGE is being replaced by CE-SDS. In the BLA, please discuss the amount of CE-SDS data that is available and the overlap in data between CE-SDS and SDS-PAGE. Any changes in the CE-SDS method should also be discussed in the BLA.

- d. In the BLA, please discuss the reason for proposing the appearance acceptance criteria (b) (4) instead of (b) (4)
- e. An upper limit for volume should be included in the DP specification.
- f. When reporting lot release results, the numerical values obtained for subvisible particulates testing should be included. Please also include these data for the lots presented in the BLA.
- g. From Table 25 on page 134, there is no proposed acceptance criterion for osmolality. If osmolality is not to be included under footnote "a," an acceptance criterion should have been provided.
- h. Please note that if host cell DNA, host cell protein, and Protein A are not included in the release specifications, validation of removal by the manufacturing process at both ACO and BI Pharma should be included in the BLA. Please assure that process validation also includes assessment of CHOP and DNA removal on appropriately aged resins. A discussion of the critical process parameters and monitoring that are in place to assure removal and the controls of these impurities should be presented in the BLA.

The acceptability of the specifications and associated acceptance criteria will be a BLA review issue. Final concurrence will require review of historical data based on independent calculation, our understanding of the assays based on review of the SOPs and validation sections, and of the product critical quality attributes. Please provide statistical analyses of all data regarding the proposed acceptance criteria. Please include separate analyses of drug substance and drug product, and both separate and integrated analyses of materials manufactured at the different sites. The BLA should include tables with all lot release data, and if possible, these should be provided in a format that can be accessed by the FDA reviewers for internal statistical analysis using programs such as JMP.

Acceptability of the proposal to not monitor or limit additional product related substances will be a BLA review issue. Please provide data and a comprehensive discussion in the BLA.

Meeting Discussion: Regarding the potency assay, the FDA had questions regarding the cell associated RANK ligand. Amgen proposed to consider this and requested a follow up meeting to discuss this issue prior to finalizing the meeting minutes. Amgen acknowledges the comments presented in 2b, 2c, 2d, 2e, and 2f and intends to address each comment within the BLA. For item "g", an acceptance criteria for osmolality will be proposed in the BLA. Regarding item "h", FDA noted that if host cell DNA, host cell protein, and Protein A are not included in the release specifications, validation of removal by the manufacturing process at both ACO and BI Pharma should be included in the BLA. Process validation should also include assessment of CHOP and DNA removal on appropriately aged resins. A discussion of the critical process parameters and monitoring that are in place to assure removal and the controls of these impurities should be presented in the BLA. Amgen agreed to provide all of

these requested data/justifications in the BLA. For those limits based on statistical analyses, Amgen agreed to conduct the analyses as requested. The datasets used for the statistical analyses will be provided to the Agency upon request. A detailed discussion and justification of the proposal to not routinely monitor product related substances will be provided in the BLA.

Question 3: Following a risk-based assessment of the drug substance manufacturing process to identify the potential points of introduction and removal of bioburden, Amgen is proposing to establish in-process controls for bioburden with associated reject limits at the production bioreactor and bulk drug substance fill stages. Other in-process steps will also be monitored for bioburden with action limits rather than reject limits. Does the FDA agree that this approach provides adequate control of bioburden in the denosumab drug substance manufacturing process?

FDA's Response: A risk based approach is appropriate; however, we have the following comments:

- a. The cell culture is expected to be free of bioburden. A bioreactor (b) (4) bioburden action limit (b) (4) and rejection limits (b) (4) are too high. Please consider lowering the bioburden limit. Using (b) (4) would allow for increase in the volume of sample tested for bioburden.
- b. The in-process bioburden action limits (b) (4) (b) (4) steps are not acceptable. The high bioburden limits pose a risk to the product intermediates. In addition, please consider using (b) (4) method for bioburden testing of the in-process samples, where sample volumes can be larger. The bioburden limits should reflect the sample volumes used.
- c. Please provide data demonstrating that the proposed bioburden limits at hold steps would not adversely impact product quality for the time and temperature at which the product would be stored.

Meeting Discussion: Amgen acknowledges the FDA's comments and the acceptance that a risk based approach is appropriate. Amgen will address each of these comments in detail within the BLA. The FDA indicated that the bioburden limits are also linked to the facility controls. FDA questioned why the limits were so high and enquired as to whether this was necessary to accommodate the limits at both DS manufacturing facilities. Amgen indicated that this was not the case, and the Agency indicated that the justification of the proposed bioburden limits would be discussed at the pre-approval inspection.

Question 4: Validation of the 60 mg/mL PFS has been successfully executed at a (b) (4) scale at Amgen Manufacturing, Limited (AML). Amgen intends to increase the scale to approximately (b) (4) prior to launch. There will be no significant changes to the manufacturing process or changes in the container closure. Amgen is proposing to submit a validation plan for the (b) (4) prefilled syringe scale-up in the BLA with predefined acceptance criteria.

Additionally, Amgen has conducted the appropriate pre-validation studies to support the introduction of a 60 mg/mL vial presentation into AML and is executing the 70 mg/mL (1.7 mL) vial validation in May 2008. The results of this 70 mg/mL (1.7 mL) process validation study will be provided in the BLA, together with a validation plan for the 60 mg/mL vial presentation.

Does the Agency agree with Amgen's denosumab drug product validation strategy for the 60 mg/mL PFS scale-up and 60 mg/mL vial drug product process validation plans for licensure for the PMO and HALT indications in the initial BLA along with the proposed reporting requirements?

FDA's Response: No. The final validated process should be in place prior to licensure to assure that a marketable Denosomab is available upon approval. For the 60 mg/kg vial, Amgen has not provided scientific rationale as to why the 70 mg/kg vial process validation is fully supportive of the 60mg/kg vial manufacturing process at AML. This should include information for the full manufacturing process as well as for the microbiological validation. For the PFS process, Amgen states that validation of the of the (b) (4) process will be included in the BLA on submission, with validation of the (b) (4) PFS process to be completed and available for review during the PAI (page 157). We would be willing to accept the updated validation for the (b) (4) process as an amendment to the BLA during the review cycle so long as we have an agreed upon date by which it will be submitted, and that it is submitted prior to the PAI.

Meeting Discussion: Amgen will provide detailed justification for the extrapolation of the 70 mg/mL vial process validation data to the 60 mg/mL vial in the BLA, and also agreed to provide an estimate for the submission date for the (b) (4) scale-up data once the schedule has been confirmed for this activity. Amgen noted that process development studies have been conducted at bench scale to characterize the hydrodynamic environment resulting from the mixing, filtration, and filling process. Full-scale (e.g., engineering runs) manufacturing data have been generated for the 60 mg/mL vial, 70mg/mL (1.7 mL) vial, and 60 mg/mL PFS, confirming that the transfer to AML does not impact product quality attributes. Process validation has been completed for the 70mg/mL (1.7 mL) vial and 60 mg/mL PFS. The results from the validation lots confirmed no impact on product quality with the change in site and fill volume as predicted from the process characterization and engineering run. It is believed that data generated on the 70 mg/mL vial is predictive of process performance and product quality for the 60 mg/mL vial and support approval of the 60 mg/mL vial. FDA acknowledged that data for the (b) (4) scale of 60 mg/mL PFS will be in the BLA and requested the dates and timing when the (b) (4) scale-up data will be available. FDA requested that Amgen communicate these dates prior to submission of the BLA and requested that the data be available prior to the pre-approval inspection.

Question 5: Based on available data, Amgen intends to apply for a 30 month expiration period for all drug product presentations.

a) Does the FDA agree with the strategy to establish expiration dating for the drug product?

FDA's Response: No, the stability data for each presentation to be licensed should include data from DP manufactured at AML from DS produced at ACO and BI Pharma, in addition to the

supporting data from fill at ATO. At this time it appears that Amgen does not intend to provide stability data for the 60 mg/mL vials manufactured at AML. Acceptance of data exclusively from the ATO fill in support of expiration dating for DP manufactured at AML may be appropriate based on the following caveats: ICH Q1a (www.ich.org) defines pilot scale batch as a batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. Amgen should provide a detailed description of each manufacturing process and a comprehensive list of differences between the ATO processes and the AML processes for both the PFS and the 60mg/mL vial. The applicability of the data from the ATO process would depend upon a comparison of the pilot process to the to-be-marketed process.

Additionally, from Q1a, if significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

Final assessment of appropriateness will have to be based on review of a complete data package. Please provide results of stability evaluation as described in ICH Q1e (e.g., graphical presentation with confidence intervals where appropriate).

b) Does the FDA agree with Amgen's proposal for submission of stability updates during review of the marketing application?

FDA's Response: Yes.

Meeting Discussion: Amgen acknowledges the comments of the FDA and will provide the necessary justifications in the BLA.

Question 6: Module 3 of the BLA will contain information to support licensure of the drug substance manufacturing sites at Amgen Colorado (ACO) and Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma). The process operated at both sites is essentially identical with the exception of process scale and minor differences necessary to achieve facility fit. Amgen therefore proposes to provide information regarding the manufacturing process operated at both sites in a single drug substance section (Section 3.2.S), with the exception of the process validation data for each site, which will be presented in separate Sections 3.2.S.2.5 (Process Validation and/or Evaluation).

Does the FDA agree with Amgen's proposal for a single drug substance manufacturing process description which covers both BI Pharma and ACO?

FDA's Response: Yes. Please clearly differentiate the portions that are identical to both from those that apply solely to ACO or to BI Pharma. For ease of reviewing this complicated BLA, it would be useful if different colors of font are associated with each site for which there are differences, for example, use blue font for ACO-specific items, green font for BI Pharma-specific items, and use black font for items that apply to both ACO and BI Pharma. The use of color coding was very helpful in enabling a quick review and understanding of figure 2 on page

32 in the meeting package. In addition, please assure that detailed links to the appropriate validation data (preferably to the specific item, not just the whole validation section) are included. For submission to the BLA, separate statistical analyses should be performed for materials manufactured at ACO and for materials manufactured at BI Pharma, and the same analyses should be performed for datasets containing all materials.

In the characterization section, it would be helpful if the lots used for each data section are identified, including the site and process of manufacture.

Meeting Discussion: Amgen acknowledged the comments of the FDA regarding the potential complexity of the file. As stated in the briefing document, the processes operated at ACO and BI Pharma are highly similar and differ only in terms of scale and minor differences necessary to achieve facility fit. Amgen will assure that facility specific aspects of the process description will be clearly delineated in the BLA using separate headings, or color coding as suggested. Amgen anticipates that the identified differences will be few in number.

As requested, data generated on ACO and BI Pharma DS will be analyzed separately and together in those sections where such analyses are appropriate, e.g., Justification of Specifications.

The FDA requested that release and stability data generated from lots manufactured at ACO and BIP are presented independently to allow for an independent comparative statistical analysis. The Agency expressed concern about how Amgen will monitor manufacturing from both facilities to assess process drift. Amgen stated that Quality systems were in place to manage process monitoring and change control from the contract manufacturing site. The FDA emphasized this as a concern, given that the contract site is not under direct control of Amgen. Amgen indicated that the process manufactured at both facilities uses the same controls and proven acceptable ranges.

Question 7: There will be 3 stand-alone quality drug product (3.2.P Module) sections to be electronically submitted to the BLA in eCTD format in the same PMO/HALT application for the 60 mg/mL PFS, 60 mg/mL Vial and 70 mg/mL (1.7 mL) vial. Amgen intends to include CMC information for all 3 drug product presentations in the initial BLA for the PMO and HALT indications. Amgen plans to cross reference and submit supporting CMC information in the initial BLA for the 70 mg/mL (1.7 mL) vial drug product presentation. Amgen does not intend to request approval of the 70 mg/mL (1.7 mL) vial presentation in the PMO/HALT application.

Does the Agency agree with Amgen's proposal to include information for the 70 mg/mL (1.7 mL) vial presentation in the BLA on the basis that it is only provided for the purposes of supporting approval of the 60 mg/mL vial and 60 mg/mL PFS presentations?

FDA's Response: Yes. Three stand alone DP quality sections are appropriate, though the applicability of the 70 mg/mL (1.7 mL) presentation to this BLA remains to be demonstrated. Please ensure that detailed links to the appropriate data (preferably to the specific item, not just the whole other quality section) are included. For the supporting 70 mg/mL DP presentation, please include only information that could be supportive of the 60 mg/ml presentations, as this presentation will not be reviewed for approval in this BLA. A complete information package in support of the 70 mg/ml (1.7 ml) vial presentation will need to be submitted in the BLA in which it is intended for marketing approval.

Meeting Discussion: Amgen acknowledged the comments of the FDA and will structure the BLA accordingly.

Question 8: The denosumab drug product manufacturing operations will be conducted at Amgen Manufacturing Limited, located in Juncos, Puerto Rico. (b) (4) processing, facility and equipment information will be provided in the initial filing through a cross-reference to the applicable information of the Amgen Manufacturing Limited (AML) Type V Drug Master File (DMF) No. (b) (4)

Does the FDA agree with Amgen's proposal to provide (b) (4) processing, facilities and equipment information for AML via cross-reference to Type V Drug Master File (DMF) No. (b) (4)?

FDA's Response: We prefer to have summary validation information for (b) (4) processing and equipment specific validation data and information for this product provided under Section 3.2.P.3.5 in the BLA. The provided information should follow 1994 "Guidance for industry for the submission documentation for sterilization process validation in applications for human and veterinary drug products" and 2004 "Guidance for Industry, sterile drug products produced by (b) (4) processing - current Good Manufacturing Practice".

Additionally, any information in support of the ATO procedure being fully representative of, and simulating the AML full production scale manufacturing process should be included in the BLA.

If the Type V DMF is cross-referenced, the information provided in the DMF should be specific for this product and be updated. The location of this information in the DMF should be specified.

Meeting Discussion: Amgen will cross-reference the electronic DMF (b) (4) within the BLA, but also provide the (b) (4) process and product specific equipment validation data in Section 3.2.P.3.5. of the BLA, as requested by the Agency. AML is a multiproduct facility and reference to the DMF would facilitate maintenance of the facility information, including (b) (4) process validation and equipment validation data. Following approval, Amgen proposes to maintain these data using the DMF. Detailed process and equipment comparisons conducted as part of comparability assessment will be provided in Section 3.2.P.2.3 (Process Development). The FDA indicated that it would be easier if the data could be provided in the BLA. The FDA agreed that following approval, data could be managed in a DMF as long as it is appropriately managed by ensuring that product specific information is clearly indicated.

Linked Applications

Sponsor Name

Drug Name

IND 9837

AMGEN INC

Human Monoclonal Antibody (AMG
162)(CHO Cells, Amgen) to
Osteoprotegerin Ligand (RANKL)

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

/s/

CELIA R HAYES
08/07/2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 125320	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Prolia Established/Proper Name: denosumab Dosage Form: subcutaneous injection		Applicant: Amgen, Inc. Agent for Applicant (if applicable):
RPM: Celia Peacock, M.P.H., R.D. – 1 st review cycle Nenita Crisostomo, R.N. – 2 nd review cycle		Division: Division of Reproductive and Urologic Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>July 23, 2010</u> • Action Date: <u>June 1, 2010</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None <input checked="" type="checkbox"/> CR, October 16, 2009
❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain: Not an accelerated approval		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch</p> <p><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch</p> <p><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E</p> <p><input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41)</p> <p><input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H</p> <p><input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR</p> <p><input type="checkbox"/> Submitted in response to a PMC</p> <p><input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input checked="" type="checkbox"/> Yes, date <u>May 20, 2010</u>
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
<p>❖ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ³	<input checked="" type="checkbox"/>
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	<input checked="" type="checkbox"/> Approval: June 1, 2010 <input checked="" type="checkbox"/> Comp Resp: October 16, 2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Final Label	May 28, 2010, agreement by email
• Original applicant-proposed labeling	December 19, 2008
• Example of class labeling, if applicable	N/A

³ Fill in blanks with dates of reviews, letters, etc.

<p>Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent labeling. 	<p>May 12, 2010, agreement by email</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>September 11, 2009</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p>N/A</p>
<p>❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> March 25, 2010 <input checked="" type="checkbox"/> May 7, 2010
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	<input checked="" type="checkbox"/> May 20, 2009, granted letter <input checked="" type="checkbox"/> April 7, 2010, granted letter <input checked="" type="checkbox"/> April 7, 2009, review <input checked="" type="checkbox"/> March 26, 2010, review
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<input checked="" type="checkbox"/> DMEPA, container 5/20/10 <input checked="" type="checkbox"/> OBP, container 5/13/10 <input checked="" type="checkbox"/> DRISK, MG 4/8/10 <input checked="" type="checkbox"/> DMEPA, container 4/5/10 <input checked="" type="checkbox"/> DDMAC, MG 4/5/10 <input checked="" type="checkbox"/> OBP 3/30/10 <input checked="" type="checkbox"/> DDMAC, PI 3/18/10 <input checked="" type="checkbox"/> SEALD 12/15/09 <input checked="" type="checkbox"/> PharmTox 10/30/09 <input checked="" type="checkbox"/> DMEPA 9/24/09 <input checked="" type="checkbox"/> PMHT 9/11/09 <input checked="" type="checkbox"/> RPM 3/3/09
<p>Administrative / Regulatory Documents</p>	
<p>❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</p>	<input checked="" type="checkbox"/> RPM, February 17, 2009
<p>❖ 505(b)(2) Assessment (<i>indicate date</i>)</p>	<input checked="" type="checkbox"/> Not a (b)(2)
<p>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</p>	<p>N/A</p>
<p>❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
 Version: 5/14/10

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>June 3, 2009</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	<input checked="" type="checkbox"/>
❖ Internal memoranda, telecons, etc.	<input checked="" type="checkbox"/>
❖ Minutes of Meetings <ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Other: CMC (<i>indicate dates of mtgs</i>) 	<input type="checkbox"/> No mtg <input type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> October 21, 2008 <input checked="" type="checkbox"/> June 3, 2009 <input checked="" type="checkbox"/> July 8, 2008
Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) • FR Notice of Advisory Committee Meeting • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	<input type="checkbox"/> No AC meeting <input checked="" type="checkbox"/> August 13, 2009 <input checked="" type="checkbox"/> May 18, 2009
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> June 1, 2010 <input checked="" type="checkbox"/> October 16, 2009
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> May 28, 2010 <input checked="" type="checkbox"/> October 16, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> May 28, 2010 <input checked="" type="checkbox"/> October 14, 2009
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> 7 Templates
Clinical Information⁵	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical reviews (<i>indicate date for each review</i>) • Clinical Filing Checklist 	<input checked="" type="checkbox"/> see CDTL memos for May 28, 2010 and October 14, 2009 <input checked="" type="checkbox"/> October 6, 2009 April 26, 2010 <input checked="" type="checkbox"/> January 29, 2008

⁵ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<p>Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i></p>	<input checked="" type="checkbox"/> See Clinical Review, dated April 26, 2010, page 27
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> <ul style="list-style-type: none"> • Division of Dermatology and Dental Products: Skin/Soft Tissue Reactions • Division of Dermatology and Dental Products: ONJ • Division of Cardiovascular and Renal Products: Cardiac Safety • Division of Anti-Infective and Ophthalmology Products: Possible increased risk of infections • Division of Cardiovascular and Renal Products: QT-IRT 	<input checked="" type="checkbox"/> July 24, 2009, DDDDP <input checked="" type="checkbox"/> June 24, 2009, DDDDP <input checked="" type="checkbox"/> June 12, 2009, DCRP <input checked="" type="checkbox"/> June 10, 2009, DAIOP <input checked="" type="checkbox"/> May 20, 2009, DCRP
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Review: addendum • REMS Review • REMS DOCUMENT • REMS Supporting Documents <i>(indicate date(s) of submission(s))</i> <ul style="list-style-type: none"> • Dear Healthcare Provider • Web Page • REMS Memo(s) • REMS letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> <ul style="list-style-type: none"> ➤ Pediatric-Maternal Health Team: Review of Pregnancy Registry Protocol ➤ Division of Epidemiology: Review of Postmarketing studies ➤ Pediatric-Maternal Health Team: Review of Pregnancy Registry Protocol ➤ Pediatric-Maternal Health Team: Review of Pregnancy Registry Protocol ➤ Division of Epidemiology: Review of Postmarketing studies ➤ Division of Risk Management: Review of Risk Management Plan 	<input checked="" type="checkbox"/> May 28, 2010 <input checked="" type="checkbox"/> May 19, 2010 <input checked="" type="checkbox"/> June 1, 2010 <input checked="" type="checkbox"/> June 1, 2010 <input checked="" type="checkbox"/> October 2, 2009 <input checked="" type="checkbox"/> September 1, 2009 <input checked="" type="checkbox"/> May 10, 2010 <input checked="" type="checkbox"/> May 4, 2010 <input checked="" type="checkbox"/> March 16, 2010 <input checked="" type="checkbox"/> October 14, 2009 <input checked="" type="checkbox"/> October 5, 2009 <input checked="" type="checkbox"/> September 4, 2009

DSI Clinical Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input checked="" type="checkbox"/> August 27, 2009
<ul style="list-style-type: none"> • DSI letter: Dr. Grattan Woodson • DSI letter to Dr. Christine Teglbjaerg 	<input checked="" type="checkbox"/> August 17, 2009 <input checked="" type="checkbox"/> August 12, 2009
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	
<ul style="list-style-type: none"> • Statistical Reviews: Safety • Statistical Review: Efficacy • Statistical Filing Review: Efficacy • Statistical Reviews: Safety • Statistical Filing Review: Safety • Statistical Consultative Reviews <ul style="list-style-type: none"> ➤ Division of Biometrics 7: QSPG-Infections ➤ Division of Biometrics 6: QSPG-cardiovascular events ➤ Division of Biometrics 7: QSPG-Hypocalcemia ➤ Division of Biometrics 7: QSPG-hypersensitivity and Immunology 	<input checked="" type="checkbox"/> April 29, 2010 <input checked="" type="checkbox"/> March 15, 2010 <input checked="" type="checkbox"/> August 19, 2009 <input checked="" type="checkbox"/> August 10, 2009 <input checked="" type="checkbox"/> January 28, 2009 <input checked="" type="checkbox"/> September 14, 2009 <input checked="" type="checkbox"/> August 21, 2009 <input checked="" type="checkbox"/> July 30, 2009 <input checked="" type="checkbox"/> July 28, 2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> April 28, 2010 <input checked="" type="checkbox"/> August 25, 2009
Clinical Pharmacology Filing review	<input checked="" type="checkbox"/> January 28, 2009
Clinical Pharmacology Pharmacometric Review	<input checked="" type="checkbox"/> August 21, 2009
Division of Monoclonal Antibodies: ClinPharm consult for Bioanalytical Method	<input checked="" type="checkbox"/> September 16, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> October 7, 2009

<p>Environmental Assessment (check one) (original and supplemental applications)</p>	
<p><input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</p>	<p><input checked="" type="checkbox"/> See Chemist's review, dated October 1, 2009, page 7</p>
<p><input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)</p>	
<p><input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)</p>	
<p>❖ Facilities Review/Inspection</p>	
<p><input checked="" type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)</p> <p><input checked="" type="checkbox"/> Facility Information Sheet</p> <p><input checked="" type="checkbox"/> Manufacturing Facility Filing Review</p>	<p>Date completed: September 2, 2009</p> <p><input checked="" type="checkbox"/> Acceptable</p> <p><input checked="" type="checkbox"/></p> <p><input checked="" type="checkbox"/> January 26, 2009</p>