CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125320

CHEMISTRY REVIEW(S)

The Quality Team Leader's Executive Summary

From:	**Chana Fuchs, Ph.D., Team Leader, Division of Monoclonal Antibodies (DMA)**
Through:	**Patrick Swann, Ph.D. Deputy Director, DMA**
Through:	**Kathleen A. Clouse, Ph.D., Director, DMA**
To:	**Theresa Kehoe, M.D. CTDL, DRUP, ODEIII**
BLA Number:	**125320**
Product:	**Prolia (denosumab)**
Sponsor :	**Amgen**
Date of Review:	**April 30, 2010**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in the original Biologics License Application supported the conclusion that the manufacture of Prolia (denosumab) is well controlled and leads to a product that is pure, potent and sufficiently free from endogenous and adventitious infectious agents to meet the parameters recommended by FDA. DMA did not have any Complete Response items for the original BLA. The Drug Quality data submitted in the BLA amendments to the Complete Response letter continue to support approval based on the changes made to the Package Insert and in conjunction with the PMCs as described below. The Division of Monoclonal Antibodies recommends that Prolia™ (denosumab) be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments (PMC), Agreements (PMA), Requirements (PMR) and/or Risk Management Steps, if Approvable.

PMR:

PMCs:

- To perform stability testing annually on at least one marketed drug substance lot and one marketed drug product lot of both the 3 cc glass vial and the 1 ml glass syringe for each year in which respective drug substance and drug product are manufactured and for each site at which they are manufactured, using the post-approval stability protocols specified in the BLA. The first update will be included in an annual report to be submitted by February 28, 2011.

- 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.
- 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.
- 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.

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance

Full descriptions of the Drug Product and Drug Substance were provided in the TL memo for the original BLA submission review and will not be repeated in this memo. New information in the amendments in response to the CR letter includes:

- Breakloose and extrusion specification for pre-filled syringe (PFS) release testing: Breakloose and extrusion testing was not included in the original specifications for the PFS. Amgen was asked to add a specification for Breakloose and extrusion to release and stability testing of the PFS during the original BLA review submission timeline; Amgen committed to adding numerical acceptance criteria for breakloose and extrusion by the end of Q1 2010. Amendment 125320/0.57 contained an update to these release specifications and supporting data for the acceptance criteria set by Amgen based on "the maximum force associated with administering the dose" as determined using a human interface study. As the purpose for these criteria are to assess device performance in the context of the product injected, the proposed acceptance criteria were found inappropriate, and two PMCs were developed to assure that appropriate release and stability criteria are developed.

B. Description of How the Drug Product is Intended to be Used

Full descriptions were provided in the TL memo written in conjunction with the original BLA submission review, and will not be repeated in this memo. New information in the amendments in response to the CR includes:

- Stability data to support the package insert label: Section 16 of the package insert label allowed Prolia to be removed from refrigeration and stored at room temperature

(not to exceed 25°C/77°F) for up to ____ As conditions for storage outside of the GMP environment are not controlled to not exceed 25°C, and real use would be expected to exceed this temperature limit, the stability data provided was found to not be sufficient to support the extended storage (b) (4) at room temperature. The package insert label was amended to (b) (4) limit to 14 days.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

- Prolia (denosumab) is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Denosumab is manufactured consistently leading to a safe and effective product for the indications to be approved. Approval is recommended.

- Post marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

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

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N (b) (4)	Not necessary
Introduction to the summary documents (1 page) [2.2]		
Quality overall summary [2.3] ❑ Drug Substance ❑ Drug Product ❑ Facilities and Equipment ❑ Adventitious Agents Safety Evaluation ❑ Novel Excipients ❑ Executed Batch Records ❑ Method Validation Package ❑ Comparability Protocols		

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N (b) (4)	Not necessary
Drug Substance (API) [3.2.S] ❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties ❑ manufacturers o facility name o full address (street, city, state, country) o is facility registered with FDA o FEI number ❑ contact person o full name and title o telephone o fax o email ❑ Confirmation by applicant that each API facility, including contractors and subcontractors, understand their specific role in the manufacturing process as described in the application. ❑ Confirmation by written statement from each API facility that they are ready for inspection or the applicant identifies at what date the facility will be ready for inspection. *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.)		

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
❑ API processing product type: primary mode of deriving API o fermentation, bacterial host o fermentation, mammalian host o chemical synthesis o extraction/isolation, only o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping		
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping		
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability		
❑ process validation (prospective plan, results, analysis, and conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)		
❑ characterization of drug substance		
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots)		

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
○ justification of specs. ❑ reference standards ❑ container closure system ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation		
Drug Product [3.2.P] ❑ description and composition ❑ pharmaceutical development ❑ manufacturers ○ facility name ○ full address (street, city, state, country) ○ is facility registered with FDA ○ FEI number ❑ contact person ○ full name and title ○ telephone ○ fax ○ email ❑ Confirmation by the applicant that each facility, including contractors and subcontractors, understands their specific role in the manufacturing process as described in the application. ❑ Confirmation by written statement from each facility that they are ready for inspection or the applicant identifies at what date the facility will be ready for inspection. *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ finished drug processing: mixing/homogenizing components ○ dry powder mixing	(b) (4)	Not applicable

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
o granulation, wet o granulation, dry o granulation high/low shear o micro fluidization o emulsification o milling/micronization o sieving/particle sizing o spray drying o fluidized bed drying o tray drying o mixing, suspension o mixing, liquids not solution/suspension		
❑ finished drug processing: forming dosing/delivery unit o compression (compaction of a powder, slug, or granules by a press; includes multilayer tablets prepared by more than one compression cycle.) o molding (Forming a solid dosage other than by compaction, as in making suppository, lozenge, pill, soap, softgel, and gum.) o fabrication, inhalers liquid and gas cold fill o fabrication, inhalers dry powder o fabrication, transdermals o fabrication, pre-filled syringe o filling, powder/granule o extrusion (other than as used in granulation) o coating, color/taste only o coating delay/extend o release rate (includes coating tablets as well as granules, beads, or pellets) o filling, solution o filling suspension o filling, liquids not solution/suspension o filling, semi-solid		
❑ component and finished drug processing (b) (4) fill and sterilization o (b) (4) filling, manual process (including liquid and solid filling)		Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ (b) (4) filling, isolator process (enclosed environments for filling sterile drug, including blow-fill-seal, into which human intervention is not o expected or intended during process) o terminal sterilization (by any method, including steam, gas, dry heat, water, and radiation)	(b) (4)	Not applicable
❑ other operations o lyophilization o irradiation by cyclotron (positron emission tomography (PET) drugs o irradiation other (not intended to achieve sterility and not CYC) o not elsewhere classified (to be used infrequently and cautiously)		Not applicable
❑ finished drug processing: medical gas o gas separation (includes separation operations that also fill into vessels) o gas filling only		Not applicable
❑ controls of critical steps and intermediates		
❑ process validation including (b) (4) processing & sterility assurance: o 3 consecutive lots o other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)		
❑ control of drug product (justification of specifications; analytical method validation)		
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s)	(b) (4)	
❑ stability ❑ summary		

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation		
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including (b) (4) processing & sterility assurance: o 3 consecutive lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results		Not applicable

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)		Not applicable
Laboratory (Contractor) ❑ laboratories o facility name o full address (street, city, state, country) o FEI number ❑ contact person o full name and title o telephone o Fax o email ❑ Confirmation by applicant that each test facility, including contractors and subcontractors, understands their specific role in the testing process as described in the application. ❑ Confirmation by written statement from each testing facility that they are ready for inspection, or the applicant identifies at what date the facility will be ready for inspection *** (if the date is too late in the review timeline process, this would affect the PDUFA target date.) ❑ Each testing facility identified in the application and identification of the type of testing performed by the facility (if more than one type of testing is performed by a single facility, identify each type of testing.) o finished dosage o API o QC released testing/stability finished dosage or both o chemistry o microbiological **Appendices for Biotech Products [3.2.A]** ❑ facilities and equipment o manufacturing flow; adjacent areas		

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients		Not applicable
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols		
Literature references and copies [3.3]		

Examples of Filing Issues	Yes? (b) (4)	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable		
includes appropriate process validation data for the manufacturing process at the commercial production facility?		
includes production data on drug substance and drug product manufactured in the facility intended to be licensed		

Examples of Filing Issues	Yes?	If not, justification, action & status
(including pilot facilities) using the final production process(es)?	(b) (4)	
includes data demonstrating consistency of manufacture		
includes complete description of product lots and manufacturing process utilized for clinical studies		
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots		
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
certification that all facilities are ready for inspection		
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.		
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑		
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples		Not applicable
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product		
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment		
information and data supporting validity of sterilization processes for sterile products and (b) (4) manufacturing operations		
if this is a supplement for post-approval		Not applicable

Examples of Filing Issues	Yes?	If not, justification, action & status
manufacturing changes, is animal or clinical data needed? Was it submitted?		

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): File RTF

For Applications: Were any potential review issues identified for the day 74 letter? Yes No

Reviewer: Sarah Kennett_1-28-09_ Type (circle one): Product ~~(Chair)~~ Facility (DMPQ)

Concurrence:
Branch/Lab Chief: Chana Fuchs 1-28-09 Division. Director: Kathleen Clouse 1-28-09_

Part B – Product/CMC/Facility Reviewer(s)

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Overall CTD Table of Contents [2.1]		
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Quality overall summary [2.3] ❑ Drug Substance ❑ Drug Product ❑ Facilities and Equipment ❑ Adventitious Agents Safety Evaluation ❑ Novel Excipients ❑ Executed Batch Records ❑ Method Validation Package ❑ Comparability Protocols		No novel excipients

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
Module Table of Contents [3.1]		
Drug Substance [3.2.S] ❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties		OBP Lead
❑ manufacturers (names, locations, and responsibilities of all sites involved)		
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping		
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing		OBP Lead
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability		Bioburden and endotoxin controls present. Phone call received from company to say that bioburden information was incorrectly filed and will be amended.
❑ process validation (prospective plan, results, analysis, and conclusions)		OBP Lead

CTD Module 3 Contents	Present? (b) (4)	If not, justification, action & status
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)		OBP Lead
❑ characterization of drug substance		OBP Lead
❑ control of drug substance		OBP Lead; Bioburden and endotoxin specification, analytical procedures and validation included.
○ specification		
○ justification of specs.		
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
○ consistency (3 consecutive lots)		
○ justification of specs.		
❑ reference standards		OBP Lead
❑ container closure system		
❑ stability		OBP Lead
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P]	(b) (4)	
❑ description and composition		
❑ pharmaceutical development		
❑ manufacturers (names, locations, and responsibilities of all sites involved)		
❑ batch formula		
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates		
❑ process validation including (b) (processing & sterility assurance:		
○ 3 consecutive lots		
○ other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)		
❑ control of drug product		

CTD Module 3 Contents	Present?	If not, justification, action & status
(justification of specifications; analytical method validation) ❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	(b) (4)	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including (b) (4) processing & sterility assurance: o 3 consecutive lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings)	(b) (4)	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
○ availability of DMF ○ closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	(b) (4)	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)		Not applicable
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients		OBP Lead No novel excipients, OBP Lead
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols		OBP Lead
Literature references and copies [3.3]		

Examples of Filing Issues	Yes? (b) (4)	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable		
includes appropriate process validation data for the manufacturing process at the commercial production facility?		
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?		
includes data demonstrating consistency of manufacture		
includes complete description of product lots and manufacturing process utilized for clinical studies		OBP Lead
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots		OBP Lead
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		OBP Lead
certification that all facilities are ready for inspection		Drug substance manufacture at two sites: 1. Amgen Colorado facility (in operation early April 2009); 2. BI Pharma Germany (in operation early May 2009); Drug Product manufacture at Amgen, Juncos, Puerto Rico (in operation late April 2009).
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.		
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:		

Examples of Filing Issues		If not, justification, action & status
❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑		OBP Lead
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples		
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product		
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment		
information and data supporting validity of sterilization processes for sterile products and (b) (4) manufacturing operations		
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?		Not applicable

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Fileable

Recommendation (circle one): (File) RTF 1/22/09 01/22/09

Reviewer: Maan Abduldayem; Donald Obenhuber; Kalavati Suvarna, Bo Chi 01/22/09
(signature/ date)

Type (circle one): Product (Chair) (Facility (DMPQ))

Concurrence:
Branch/Lab Chief: 1/22/09 (signature/ date)

Division. Director: acting DD 1/26/2009 (signature/ date)