

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125320

MICROBIOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: September 9, 2009
To: Administrative Files, STN 125320, STN 125331, STN 125332, STN 125333
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT (PFH 9/10/09)
Subject: Team Leader Microbiology Product Quality review memo and assessment of Manufacturing Establishments
Applicant: Amgen, Inc.
US License: 1080
Facilities: Drug Substance:
1. Amgen Inc. (ACO) LakeCentre Facility, Boulder, CO 80301 (FEI = 3003072024)
2. Boehringer Ingelheim Pharma GmbH & Co. Kg Biberach an der Riss, Germany (FEI=3002806518)
Drug Product:
1. Amgen Manufacturing, Limited (AML), Juncos, Puerto Rico 00777 (FEI=1000110364)
Product: Prolia™ (Denosumab, AMD 162)
Dosage: Single-use, sterile preservative-free solution for subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial.
Indication: Treatment for prevention of osteoporosis in postmenopausal women (STN 125320)
Prevention of osteoporosis in postmenopausal women (STN 125331)
Treatment and prevention of bone loss associated with hormone ablation therapy with breast cancer (STN 125332) or prostate cancer (STN125333)
PDUFA date: 19 October 2009

RECOMMENDATION FOR BLA APPROVABILITY:

CMC Microbiology Product Quality Assessment:

BLA 125320, as amended, is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. Data and information supporting the recommendation for approval are presented in the review memos of Kalavati Suvarna, Ph.D., Ph.D., CDER/OC/DMPQ/BMT for the drug substance and Donald Obenhuber, Ph.D., CDER/OC/DMPQ/ NGDM for the drug product part of the application.

Establishment Assessment:

The manufacturing and testing facilities listed in the BLA have an acceptable compliance status.

1. Pre-approval inspections of the following drug substance manufacturing and testing sites were conducted by a team of investigators from OBP/DMA and OC/BMT during the review of this BLA:
 - a. Amgen Colorado LakeCentre facility, Boulder Colorado, FEI 3003072024
 - b. Boehringer ingelheim GmbH & Co, Biberach an der Riss, Germany, FEI= 3002806518

Both sites were found to be acceptable from a compliance perspective.

2. The drug product is manufactured at Amgen Manufacturing Limited (AML), Juncos, Puerto Rico (FEI=1000110364). This site was inspected by the district on January 8-12, 2007 and currently has an acceptable compliance status. A surveillance inspection of the AML site was conducted during the review of this BLA and is currently on-going.

Review Summary

Drug substance:

The drug substance is a fully human IgG2 monoclonal antibody that is expressed in Chinese Hamster Ovary (CHO) cells during cell culture at the (b) (4), bioreactor scale at the Amgen LakeCentre (ACO) manufacturing facility in Colorado, Boulder, and at the (b) (4), bioreactor scale at Boehringer Ingelheim Pharma in Biberach, Germany. Adequate in-process microbial controls, including endotoxin, are in place at various steps of the manufacturing process. In addition, in-process holds for intermediates and buffers, cleaning, sanitization and storage of purification (b) (4) are validated and microbial methods are qualified.

During the review cycle, the sponsor provided a calculation of the endotoxin limit based on worst-case minimal patient weight of 50 kg and the maximum single human dose for denosumab to determine the safety margin for the proposed endotoxin specification. The endotoxin drug substance specification is (b) (4), is well below the threshold of human pyrogenic response. The endotoxin results for batches manufactured at ACO site (b) (4) varied from that manufactured at BI Pharma (b) (4) due to the differences in testing methods (LAL turbidimetric at ACO versus chromogenic kinetic LAL method at BI Pharma). Both methods comply with USP <85> and Ph.Eur .2.6.14 compendial methods. The results from the two sites were within the acceptance criteria and well below the threshold of human pyrogenic response.

All drug substance review issues were resolved in the course of the review and six amendments were submitted to the BLA.

A pre-license inspection of the ACO establishment was conducted on June 8-12, 2009 by BMT and OPB reviewers (Kalavati Suvarna, Ph.D., Maan Abduldayem, and Sarah Kennett, Ph.D.) and by district inspectors (Nancy Schmidt and Kimberly Hoefen). The

inspection was classified as NAI and was acceptable from a compliance perspective. The BI Pharma facility was inspected by a BMT and OBP reviewers (Kalavati Suvarna, Ph.D., Chana Fuchs, Ph.D. and Sarah Kennett, Ph.D.) on May 11-19, 2009. The firm was cited with a one item 483 observation because (b) (4)

(b) (4) In response to the 483 observation, the firm indicated that (b) (4)

(b) (4) The response was also reviewed by the International Compliance Team in OC/DMPQ and was deemed acceptable.

Drug product:

The drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume. No issues that would prevent BLA recommendation for approval were identified by the primary microbiology reviewer. The drug product vials and pre-filled syringes are manufactured in AML (FEI=1000110364). This facility was inspected January 8-12, 2007 and classified VAI and currently has an acceptable compliance status. A surveillance inspection in progress during the review of this application revealed several complaints of broken syringes for other products of Amgen especially using auto injection device. This does not affect the recommendation for approval of this BLA since this application is for the vial and PFS final dosage form presentations.

Conclusion

- I. The BLA, as amended, is recommended for approval from a microbial control, sterility assurance and product quality microbiology perspective.
- II. Information and data in this submission not related to microbial control, sterility assurance and product quality microbiology should be evaluated by OBP reviewers.
- III. All establishments involved in the manufacture and testing of the drug substance and drug product have an acceptable compliance status.

Cc: WO51: Obenhuber
WO 51:Suvarna
WO51: Hughes
WO22: Peacock
WO:22 Pierce

WO51: eCTD Files (STN 125320, STN 125331, STN 125332, STN 125333)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: August 21, 2009
To: Administrative File, STN 125320, 125331, 125332, 125333
From: Donald C. Obenhuber, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *DCO 9/25/09*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *AL for PH 9/25/09*
Subject: New Biologic License Application (BLA)
Applicant: Amgen, Inc.
US License: 1080
Facility: Amgen Manufacturing, Limited (AML)
State Road 31, Kilometer 24.6 Juncos
Puerto Rico 00777 USA
FEI No. 1000110364
Product: Prolia (Denosumab)
Dosage: 60 mg (60 mg/mL), intervenus injection, vials and PFS
Indication: Treatment and prevention of osteoporosis in postmenopausal women and treatment and prevention of bone loss associated with HALT in patients with breast or prostate cancer
FA date: 19 October 2009

Recommendation: The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective. A separate evaluation of the drug product manufacture site at Amgen at Puerto Rico, will be conducted by the compliance officer at San Juan District Office.

Review Summary

Denosumab, a fully human IgG2 monoclonal antibody that inhibits receptor activator of nuclear factor kappa B ligand, for the 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. Denosumab drug product is supplied as a single-use, sterile, preservative-free solution intended for delivery by subcutaneous injection, supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial presentation with a 1.0 mL deliverable volume to support dosing of 60 mg every 6 months (Q6M). Each prefilled syringe contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, 0.01 % polysorbate 20, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2). Each vial contains: 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, sodium hydroxide for pH adjustment in Water for Injection, USP (pH of 5.2).

Assessment

Product

Description of the Composition of the Drug Product (3.2.P.1):

Batch Formula

The formula ingredients and amounts for different formulation batch sizes of the 60 mg/mL vial and PFS are shown below based on a batch scale range of (b) (4) for the PFS, and (b) (4) for the vial.

The vial and PFS presentations are produced using a protein concentration of 60 mg/mL and a minimum deliverable volume of 1.0 mL. Concentrations of active and inactive ingredients remain the same, regardless of the batch size. There are no formula overages in the drug product. (b) (4)

Qualitative and Quantitative Composition of Denosumab Drug Product Component	Grade	Function	Quantity / mL
Denosumab	In-house ^a	Active Ingredient	60 mg
Sorbitol	NF, PhEur, JP	(b) (4)	47 mg
Acetate	USP, PhEur, JP		1 mg
Polysorbate 20 ^b	NF, PhEur		0.1 mg
Sodium hydroxide	NF, PhEur, JP ^c		Titrate ^d
Water for Injection	USP, PhEur		Qs

qs = quantum sufficit

^a Tested to internal specifications (3.2.S.4.1, Specification).

^b Supplier tests sodium hydroxide pellets to NF, PhEur, and JP standards.

^c Sodium content is approximately 0.3 mg per dose.

Primary Container Closure Systems (Vial and PFS)

The prefilled syringe (PFS) is comprised of a type 1 glass barrel (1 mL) with a staked-in-place (integrated) needle ((b) (4) stainless steel). The plunger stopper is made of bromobutyl rubber ((b) (4) or equivalent), and is laminated with a (b) (4) on the product contact surface. The elastomeric needle shield is made from natural rubber (b) (4) (b) (4) or equivalent) and may be supplemented with an outer (b) (4) needle shield. The barrel is designed for minimal dead space to aid in a more consistent delivered dose. The interior of the barrel, the plunger, and the needle surface are coated with medical grade (b) (4) to support the functionality of the syringe system.

The (b) (4)^M syringe barrels are supplied to Amgen pre-washed and sterilized by (b) (4) (b) (4) by the manufacturer (b) (4). The (b) (4)^M plungers are supplied pre-washed and sterilized by gamma radiation. Sterility of syringe barrels and plungers is verified for each lot received by Amgen by certificate of conformity. Sterility is further verified during incoming inspection by visual examination for integrity of the outer packaging. Sterility of the components is tested according to USP <71>.

The vial presentation consists of a 3 cc Type 1 glass vial, elastomeric stopper (b) (4) (b) (4)), and aluminum seal with flip-off cap.

Formulation Buffer (60 mg/mL Vial and 60 mg/mL PFS)

The formula ingredients and amounts for the formulation buffer are shown in Table 7. The batch size for formulation buffer is (b) (4)

(b) (4)

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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: August 1, 2009
To: Administrative File, STN 125320/0, STN 125331/0, STN 125332/0,
STN 125333/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *KS 9/2/09*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PH 8/2/09*
Subject: Original BLA
US License: #1080
Applicant: Amgen, Inc.
Mfg Facility: For drug substance: Amgen Inc. (ACO) LakeCentre Facility
5550 Airport Boulevard, Boulder, CO 80301. USA.
FEI No. 3003072024

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

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

Product: Prolia™ (Denosumab, AMG 162)
Dosage: Single-use, sterile, preservative-free solution for subcutaneous injection,
supplied in either a 60 mg/mL prefilled syringe (PFS) or 60 mg/mL vial.
Indication: Treatment and prevention of osteoporosis in postmenopausal women.
Treatment and prevention of bone loss associated with hormone ablation
therapy with breast cancer or prostate cancer.
Due Date: October 19, 2009

Recommendation for Approvability: The drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective.

SUMMARY:

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico. The BLA was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the application from a microbiology product quality perspective. The following amendments to quality section of the submission were reviewed in addition to the original application: eCTD sequence number 0004 dated 1/22/2009 (new in process controls/specifications), eCTD sequence number 0006 dated 2/12/2009 (production schedule), eCTD sequence number 0007 dated 2/27/2009 (authorized representatives change), eCTD sequence number 0017 dated 4/15/2009 (stability conclusion for drug substance), eCTD sequence number 0018 dated 4/23/2009 (response to informational request), and eCTD sequence number 0021 dated 5/1/2009 (endotoxin assay and validation).

ASSESSMENT:

This is a new BLA requesting approval of denosumab (AMG 162), a fully human IgG2 monoclonal antibody that inhibits the receptor activator of the nuclear factor kappa B (RANK) ligand, for the 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. Denosumab is produced in the Chinese hamster ovary (CHO) cells. The application contains information to support commercial production of denosumab drug substance at Amgen Colorado (ACO) located in Boulder, Colorado, and Boehringer Ingelheim Pharma (BIP), located in Biberach an der Riss, Germany, as well as drug product manufacture at Amgen Manufacturing Limited (AML), Puerto Rico.

Denosumab drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous injection. Amgen is seeking approval of a 60 mg/mL vial and 60 mg/mL prefilled syringe (PFS) presentations. The only difference in the formulations for these presentations is the addition of 0.01% (w/v) polysorbate to the formulation used for the PFS. A 70 mg/mL (1.7 mL deliverable volume) vial is also being developed. Amgen is not seeking approval of the 70 mg/mL vial in this application.

This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Dr. Donald Obenhuber.

3.2.S. DRUG SUBSTANCE

3.2.S.1. GENERAL INFORMATION

Denosumab is a fully human IgG2 monoclonal antibody that inhibits the RANK ligand. It is derived from the Xeno-mouse™ technology and produced in CHO cells.

This section should be reviewed by OBP/DMA reviewer.

3.2.S.2. MANUFACTURE

3.2.S.2.1. MANUFACTURE(S)

The denosumab drug substance manufacturing process consists of (b) (4) stages. The denosumab drug substance manufacturing sites are (1) Amgen Inc. (ACO) located in Boulder, Colorado, and (2) Boehringer Ingelheim Pharma GmbH & Co. Kg (BIP) located in Biberach an der Riss, Germany.

The address and FEI numbers of the sites used for the manufacture of drug substance, raw material testing, storage of cell banks, contract testing laboratories, release and stability testing are listed below.

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

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

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

Storage of master cell bank, raw material testing and release, drug substance release and stability testing, and storage:

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

Storage of master cell bank, working cell bank, raw materials and drug substance.

Also, raw material testing and release:

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

Raw material testing and release, and drug substance storage, release and stability testing:

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



3.2.S.2.2. MANUFACTURING PROCESS AND PROCESS CONTROLS

The denosumab manufacturing process consists of (b) (4) (b) (4) stages. The BI Pharma and ACO sites use the same process except for facility specific differences. (b) (4)

(b) (4) The production bioreactor final working volume is approximately (b) (4) at ACO and (b) (4) at BI Pharma.

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