

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125557Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: November 17, 2014
To: Administrative File, STN 125557/0
From: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OC/OMPQ/DGMPA/BMAB
Reyes Candau-Chacon, Ph.D., Biologist CDER/OC/OMPQ/DGMPA/BMAB
Endorsed: Patricia Hughes, Ph.D. Team Leader CDER/OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Application
US License: 1080
Applicant: Amgen, Inc.
Facility: DP: (b)(4) (FEI # (b)(4))
Product: Blincyto® (blinatumomab)
Dosage: Lyophilized powder for solution; reconstituted for intravenous injection (b)(4) mcg
mg/vial)
Indication: For the treatment of adult patients with Philadelphia chromosome-negative
relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)
Due date: December 5, 2014

Recommendation: BLA 125557, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

1. To conduct an (b)(4)
The results from these studies will be used to support the proposed (b)(4)
2. To develop a reliable endotoxin detection method for release of drug substance (DS), drug product (DP), and intravenous stabilizing solution (IVSS) not subject to low endotoxin recovery.
3. To conduct a risk assessment to ensure microbial control and mitigate risk of endotoxin contamination during the drug substance (DS), drug product (DP), and intravenous solution stabilizer (IVSS) manufacturing processes. Risk assessment mitigating actions should include endotoxin limits of input materials.
4. To assess the pyrogenic response in rabbits of drug product (DP) and intravenous stabilizing solution (IVSS) spiked with control standard endotoxin. If the

pyrogenic response is positive, the rabbit pyrogen test should be used as an interim test until a reliable endotoxin detection method is developed.

REVIEW SUMMARY

Amgen Inc. has submitted BLA 125557 in eCTD format on 19-Sep-2014 to license blinatumomab for treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL). Blinatumomab is a single chain antibody construct of the bi-specific T-cell engager (BiTE®) class. The drug substance (DS) is manufactured at (b) (4)

This review covers the product quality microbiology of the drug product (DP) and the IV stabilizer solution (IVSS) as presented in BLA section 3.2.P. Section 3.2.P.5 and the product quality microbiology review for the DS (Section 3.2.S) was completed by Reyes Candau-Chacon, Ph.D.

DRUG PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Amendments Reviewed For Drug Product Quality Microbiology

- Amendment 0005 - Response to information request sent 29-Sep-14
- Amendment 0016 - Response to information request sent 23-Oct-14
- Amendment 0017 - Response to information request sent 28-Oct-14
- Amendment 0018 – Response to information request sent 10-Nov-14
- Amendment not officially submitted by the end of the review, send by e-mail on 17-Nov-14; Response received 18-Nov-14

Reviewer comment: The sponsor has updated BLA Section 3.2.P.3.5 to include qualification/validation information provided in Amendments 0005 and 0017.

LABELING

1.14.1.1 Draft Labeling

2.5 Reconstitution and Preparation of Solution

Blinatumomab drug product is reconstituted with 3 mL of preservative-free Sterile Water for Injection, USP. It is then transferred to an IV bag containing 0.9% sodium chloride and intravenous stabilizer solution (IVSS). IV tubing is attached to the bag with a sterile 0.2 µm filter. The prepared solution is then stored at 2-8°C. The Blinatumomab solution is administered by continuous infusion using an infusion pump and the bags are changed at least every 24 to 48 hours. The Blinatumomab solution is discarded at the end of infusion.

Storage Requirements

The storage requirements for the Blinatumomab drug product and IVSS are summarized in the table below.

Table 1. Storage Requirements for BLINCYTO and IV Solution Stabilizer

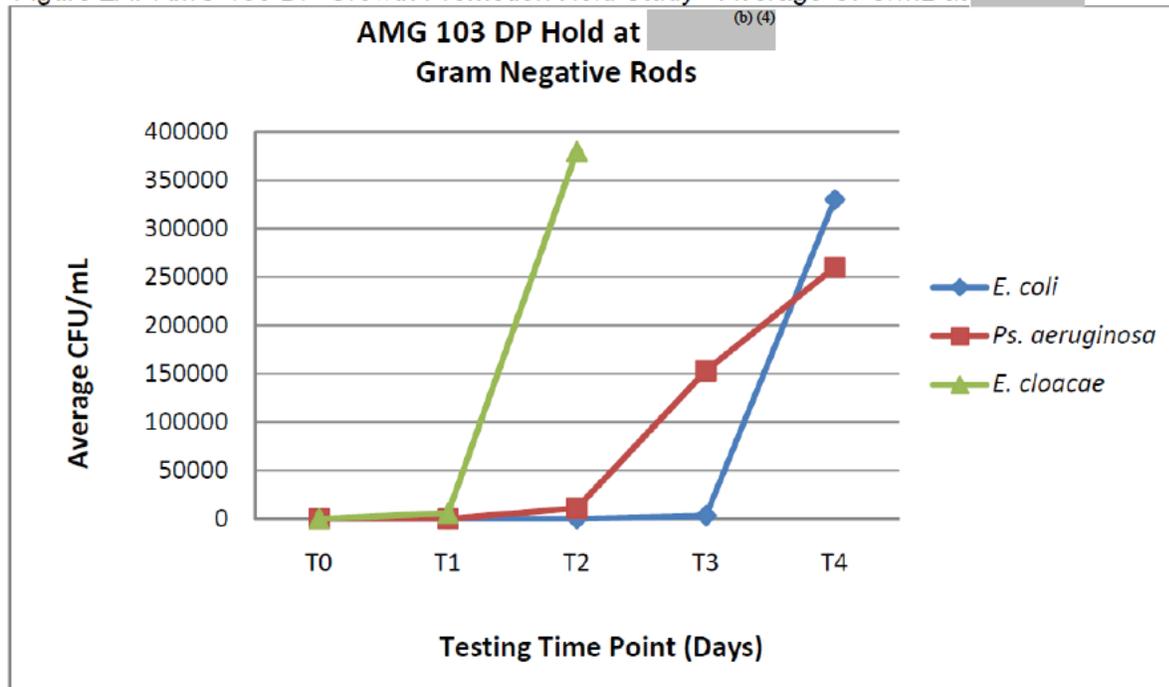
| (b)(4) | Maximum storage time of reconstituted BLINCYTO vial* | | Maximum storage time of prepared IV bag containing BLINCYTO Solution for Infusion | |
|--------|--|--|---|--|
| | Room Temperature 23°C to 27°C (73°F to 81°F) | Refrigerated 2°C to 8°C (36°F to 46°F) | Room Temperature 23°C to 27°C (73°F to 81°F) | Refrigerated 2°C to 8°C (36°F to 46°F) |
| | 4 hours | 24 hours | 48 hours [†] | 8 days |

* While stored, protect BLINCYTO and IV Solution Stabilizer vials from light.

[†] Storage time includes infusion time. If IV bag containing BLINCYTO solution for infusion is not administered within the timeframes and temperatures indicated, it must be discarded; it should not be refrigerated again.

Growth promotion studies were completed (RPT-049413, Report of Blinatumomab (AMG103) Microbial Growth Promotion Study to Support Storage and Administration Time in IV bag). When the blinatumomab drug product with IVSS in an IV bag containing saline solution was held for (b)(4) results show that *E. cloacae* had a >0.5 log increase in growth at Day 1 (24 hours) and subsequently at Day 2. In addition, on Day 2 *Ps. aeruginosa* showed similar results with a >0.5 log increase in growth on Days 2 and 3. Figure 2A from the report is provided below.

Figure 2A: AMG 103 DP Growth Promotion Hold Study - Average CFU/mL at (b)(4)



Reviewer comment: Storage times over 4 hours typically must be supported by microbial data. Adequate supporting microbial data is available for storage times at 2-8°C. The 48 hour storage time limit at Room Temperature for the prepared IV bag containing BLINCYTO for Infusion is not supported by microbial data. However, this storage time includes the 24-48 hour infusion time which cannot be limited due to the administration regime. During infusion, the drug is administered to the patient through an in line 0.2 micron filter which may mitigate some microbial contamination risks. However, potential contamination risks resulting from in home use cannot be fully mitigated.

SATISFACTORY



SIGNATURES

Candace Y. Gomez-
broughton -S

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ou=People,
0.9.2342.19200300.100.1.1=2000640207,
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Food and Drug Administration
Center for Drug Evaluation and Research
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Silver Spring, MD 20993

Date: November 10, 2014
To: Administrative File, STN 125557/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1080
Applicant: Amgen Inc.
Facilities: [REDACTED] (b) (4)
(FEI [REDACTED] (b) (4))
Product: BLINCYTO (blinatumomab, AMG103, MT103)
Dosage: Sterile lyophilized powder in 4-ml vials for reconstitution with 3 mL SWFI and further dilution with IV stabilizer into an infusion bag containing saline solution for intravenous administration; blinatumomab is provided with a separated vial of IV stabilizer that prevents its adsorption to surfaces of administration materials
Indication: Breakthrough therapy for the Treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)
Due date: Planned action date December 3, 2014

Recommendation for Approvability: The drug substance part of BLA 125557 is recommended for approval from a microbial control and microbiology product quality perspective with the following post-marketing commitments:

1. To conduct maximum hold time validation of [REDACTED] (b) (4) for two additional batches (for a total of three batches)
2. To conduct bioburden qualification of [REDACTED] (b) (4) to conduct endotoxin method qualification of [REDACTED] (b) (4)

Review Summary

Amgen Inc. has submitted BLA 125557 to license blinatumomab drug substance and drug product and their manufacturing processes.

BLA 125557 was submitted in eCTD on September 19, 2014. This review contains the assessment of the manufacturing process of blinatumomab bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Candace Gomez-Broughton.

Amendments Reviewed for Drug Substance Quality

| Information Request date | Question numbers | Amendment sequence | Amendment date |
|--------------------------|--|--------------------|-------------------|
| October 10, 2014 | 1 to 10 | 0010 | October 21, 2014 |
| October 29, 2014 | 3a, 3d, 4a, 4b, 5b, 5c, 7b, 8a, 9a, 9c | 0017 | November 6, 2014 |
| November 10, 2010 | 9c | n.a. (e-mail) | November 11, 2014 |

Review Narrative

(b) (4)



Maria D.
Candauchacon -S

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ou=People, 0.9.2342.19200300.100.1.1=2000639745,
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Date: 2014.11.17 09:45:34 -05'00'

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**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 12557 Applicant: Amgen, Inc. Stamp Date: 19 Sep 2014
Established/Proper Name: BLA/NDA Type: Priority
blinatumomab

On **initial** overview of the BLA/NDA application for filing:

| CTD Module 1 Contents | Present? | If not, justification, action & status |
|---|-----------------|---|
| Cover Letter | Y | |
| Form 356h completed | Y | |
| <input type="checkbox"/> including list of all establishment sites and their registration numbers | Y | |
| Comprehensive Table of Contents | Y | |
| Environmental assessment or request for categorical exclusion (21 CFR Part 25) | Y | |
| Labeling: | Y | |
| <input type="checkbox"/> PI –non-annotated | Y N | |
| <input type="checkbox"/> PI –annotated | Y N | |
| <input type="checkbox"/> PI (electronic) | Y N | |
| <input type="checkbox"/> Medication Guide | Y N | |
| <input type="checkbox"/> Patient Insert | Y N | |
| <input type="checkbox"/> package and container | Y N | |
| <input type="checkbox"/> diluent | Y N | |
| <input type="checkbox"/> other components | Y N | |
| <input type="checkbox"/> established name (e.g. USAN) | Y N | |
| <input type="checkbox"/> proprietary name (for review) | Y N | |

| Examples of Filing Issues | Yes? | If not, justification, action & status |
|---|-------------|---|
| Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: | Y | |
| <input type="checkbox"/> legible | Y | |
| <input type="checkbox"/> English (or translated into English) | Y | |
| <input type="checkbox"/> compatible file formats | Y | |
| <input type="checkbox"/> navigable hyper-links | Y | |
| <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays | Y | |
| <input type="checkbox"/> summary reports reference the location of individual data and records | Y | |
| <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance) | Y | |
| Companion application received if a | Y N | N/A |

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

| Examples of Filing Issues | Yes? | If not, justification, action & status |
|---|-------------|---|
| shared or divided manufacturing arrangement | | |

| CTD Module 2 Contents | Present? | If not, justification, action & status |
|--|-----------------|---|
| Overall CTD Table of Contents [2.1] | Y | |
| Introduction to the summary documents (1 page) [2.2] | Y | |
| Quality overall summary [2.3] | Y | |
| <input type="checkbox"/> Drug Substance | Y | |
| <input type="checkbox"/> Drug Product | Y | |
| <input type="checkbox"/> Facilities and Equipment | Y | |
| <input type="checkbox"/> Adventitious Agents Safety Evaluation | Y N | Defer to OBP |
| <input type="checkbox"/> Novel Excipients | Y N | Defer to OBP |
| <input type="checkbox"/> Executed Batch Records | N | In Module 3 |
| <input type="checkbox"/> Method Validation Package | N | In Module 3 |
| <input type="checkbox"/> Comparability Protocols | Y N | NA |

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|-----------------|---|
| Module Table of Contents [3.1] | Y N | |
| Drug Substance [3.2.S] | | |
| <input type="checkbox"/> general info | Y N | Defer to OBP |
| <input type="checkbox"/> nomenclature | | |
| <input type="checkbox"/> structure (e.g. sequence, glycosylation sites) | | |
| <input type="checkbox"/> properties | | |
| <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) | Y | |
| <input type="checkbox"/> description of manufacturing process and process control | Y | Description of manufacturing process is adequate from a microbial control perspective |
| <input type="checkbox"/> batch numbering and pooling scheme | | |
| <input type="checkbox"/> cell culture and harvest | | |
| <input type="checkbox"/> purification | | |
| <input type="checkbox"/> filling, storage and shipping | | |
| <input type="checkbox"/> control of materials | Y N | Defer to OBP |
| <input type="checkbox"/> raw materials and reagents | | |
| <input type="checkbox"/> biological source and starting materials | | |
| <input type="checkbox"/> cell substrate: source, history, and generation | | |
| <input type="checkbox"/> cell banking system, characterization, and testing | | |

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|-----------------|---|
| including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) | | |
| <input type="checkbox"/> controls of critical steps and intermediates | Y | |
| <input type="checkbox"/> process validation including aseptic processing & sterility assurance: | Y | |
| <input type="checkbox"/> Filter validation | Y | |
| <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation | N | Information requested 9/29/2014 |
| <input type="checkbox"/> Validation of aseptic processing (media simulations) | Y | N |
| <input type="checkbox"/> Environmental Monitoring Program | N | Information requested 9/29/2014 |
| <input type="checkbox"/> Lyophilizer sterilization validation | N | Information requested 9/29/2014 |
| <input type="checkbox"/> Other needed validation data (hold times) | | |
| <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) | Y | N |
| <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) | Y | N |
| <input type="checkbox"/> reference standards | Y | N |
| <input type="checkbox"/> container closure system | Y | |
| <input type="checkbox"/> specifications (vial, elastomer, drawings) | | |
| <input type="checkbox"/> availability of DMF & LOAs | | |
| <input type="checkbox"/> stability | Y | |
| <input type="checkbox"/> summary | | |
| <input type="checkbox"/> post-approval protocol and commitment | | |
| <input type="checkbox"/> pre-approval | | |
| <input type="checkbox"/> protocol | | |
| <input type="checkbox"/> results | | |
| Other components to be marketed (full description and supporting data, as listed above): | | N/A |

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|----------|--|
| <input type="checkbox"/> other devices | Y N | |
| <input type="checkbox"/> other marketed chemicals (e.g. part of kit) | Y N | |
| Appendices for Biotech Products [3.2.A] | | |
| <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination | Y | |
| <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production | Y N | Defer to OBP |
| <input type="checkbox"/> novel excipients | Y N | Defer to OBP |
| USA Regional Information [3.2.R] | | |
| <input type="checkbox"/> executed batch records | Y | |
| <input type="checkbox"/> method validation package | Y | |
| <input type="checkbox"/> comparability protocols | N | N/A |
| Literature references and copies [3.3] | Y N | Defer to OBP |

| Examples of Filing Issues | Yes? | If not, justification, action & status |
|--|-------|--|
| 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) | Y | |
| Includes data demonstrating consistency of manufacture | Y | |
| Includes complete description of product lots and manufacturing process utilized for clinical studies | Y N | Defer to OBP |
| Describes changes in the manufacturing process, from material used in clinical | Y N | Defer to OBP |

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

| Examples of Filing Issues | Yes? | If not, justification, action & status |
|---|----------------------|---|
| 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) | Y N | Defer to OBP |
| Certification that all facilities are ready for inspection | Y | |
| 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. | Y | |
| 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: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility | Y Y N Y | Defer to OPB |
| 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 | Y | |
| Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product | Y | |
| Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment | Y | |

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Product Quality Reviewer(s)

Date

Branch Chief/Team Leader/Supervisor

Date

Division Director

Date

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

/s/

REYES CANDAU-CHACON
10/01/2014

CANDACE GOMEZ-BROUGHTON
10/02/2014

PATRICIA F HUGHES TROOST
10/02/2014