# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125557Orig1s000

# CHEMISTRY REVIEW(S)

**First Approval for Indication**
**Breakthrough and Priority Review**

**Recommendation: Approval**

# BLA 125557
## Review # 01

**Date:** November 18, 2014

**From:** Rashmi Rawat, Ph.D.
Team Leader, DMA/OBP

Rashmi Rawat -S
Digitally signed by Rashmi Rawat -S
DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Rashmi Rawat -S
0 9 2342 19200300 100 1 1=0014137532
Date: 2014 11 19 08:22:50 05'00'

**Through:** Sarah Kennett, Ph.D.
Review Chief, DMA/OBP

Sarah B. Kennett -S
Digitally signed by Sarah B. Kennett -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000597165, cn=Sarah B. Kennett -S
Date: 2014.11.19 08:30:23 -05'00'

Kathleen Clouse, Ph.D.
Director, DMA/OBP

Kathleen A. Clouse Strebel -S
Digitally signed by Kathleen A. Clouse Strebel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054511, cn=Kathleen A. Clouse Strebel -S
Date: 2014.11.19 15:28:38 -05'00'

| | |
|---|---|
| **Drug Name/Dosage Form** | **Blincyto/For Injection** |
| **Strength/Potency** | **35 µg/vial** |
| **Route of Administration** | **Intravenous** |
| **Rx/OTC Dispensed** | **Rx** |
| **Indication** | **Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)** |
| **Applicant/Sponsor** | **Amgen** |

| Communication/Document | Date |
|---|---|
| Information Request #01(IR#01) | Sep 27, 2014 |
| Information Request #02 (IR#02) | Oct 7, 2014 |
| Information Request #03 (IR#03) | Oct 20, 2014 |
| Information Request #04 (IR#04) | Oct 30, 2014 |
| Information Request #05 (IR#05) | Nov 4, 2014 |
| Information Request #06 (IR#06) | Nov. 11, 2014 |

| Submission | Date Received | Review Completed (Yes/No) |
|---|---|---|
| Response to FDA IR#01 (eCTD seq. #0008) | Oct 16, 2014 | Yes |

| | | |
|---|---|---|
| Response to FDA IR#02 (eCTD seq. #0009) | Oct 17, 2014 | Yes |
| Response to FDA IR#03 (eCTD seq. #0012) | Oct 30, 2014 | Yes |
| Response to FDA IR#04 (eCTD seq. #0017) | Nov 6, 2014 | Yes |
| Response to FDA IR#05 received by email | Nov 7, 2014 | Yes |
| Response to FDA IR#06 received by email | Nov 13, 2014 | Yes |

**Quality Review Team**

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Qing Zhou | DMA/OBP/OPS |
| Drug Product | Deborah Schmiel | DMA/ OBP/OPS |
| Immunogenicity | Laura F. Salazar<br>Susan Kirshner (Team Leader) | DTP/OBP/OPS |
| Biologics Manufacturing and Assessment Branch | Candace G. Broughton (DP)<br>Reyes Candau-Chacon (DS)<br>Patricia Hughes (Team Leader) | OC/OMPQ/DGMPA/BMAB |
| Labeling | Jibril Abdus-Samad | OBP/OPS |
| Secondary Reviewer | Rashmi Rawat | OBP/DMA |
| Tertiary Reviewer | Sarah Kennett | OBP/DMA |

**Multidisciplinary Review Team**

| DISCIPLINE | REVIEWER | OFFICE/DIVISION |
|---|---|---|
| RPM | Krisopher Kolibab | DOPI/OHOP/CDER |
| Cross-disciplinary Team Lead | Albert Deisseroth | DOPI/OHOP/CDER |
| Medical Officer | Donna Przepiorka | DOPI/OHOP/CDER |
| Pharm/Tox | Brenda Gehrke, Haw-Jyh, Chiu, Tiffany Ricks | CDER/OND/OHOP/DHOT |
| Clinical Pharmacology | Pengfei Song, Nitin Mehrotra | CDER/OTS/OCP |
| Biometrics | Ko Chia-Wen | CDER/OB/DBV |

*Quality Review Data Sheet*

## 1. LEGAL BASIS FOR SUBMISSION: 351(a)

## 2. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

| DMF # | HOLDER | ITEM REFERENCED | Letter of Cross-Reference | COMMENTS (STATUS) |
|---|---|---|---|---|
| [redacted] (b) (4) | | | Provided in the BLA | Sufficient information was provided in the BLA for its intended use. |
| | | | Provided in the BLA | Type III<br>Sufficient information was provided in the BLA for its intended use. |
| | | | Provided in the BLA | Type V<br>Sufficient information was provided in the BLA for its purpose. |
| | | | Provided in the BLA | Type III<br>[redacted] (b) (4) Sufficient information was provided in the BLA for their intended use. |
| | | | Provided in the BLA | Sufficient information was provided in the BLA for their intended use. |
| | | | Provided in the BLA | Type III<br>Sufficient information was provided in the BLA to support their intended use. |

**B. Other Documents:** *None*

## 3. CONSULTS: *None*

*Executive Summary*

# I. Recommendations

## A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125557 for Blincyto manufactured by Amgen pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Bincyto is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

b. Action letter language

- Manufacturing location:
  - Drug substance
    (b) (4)

    Drug product
    (b) (4)
- Fill size and dosage form – 35 µg single dose vial
- Dating period:
  - Drug product, Blincyto: 36 months; 2-8 ºC
  - Drug Product, Intravenous solution stabilizer: 60 months; 2-8 ºC
  - Drug substance: (b) (4) months: (b) (4) ºC
  - Stability option
    - For stability protocols:
      - We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes
  - Rationale if exempted – specified product
    - Note: We exempt specified products according to 601.2a

c. Benefit/Risk Considerations

Blincyto is indicated to treat adult Philadelphia chromosome negative B-precursor relapsed/refractory adult acute lymphocytic leukemia. The dosage regimen includes treatment cycles of 4 weeks of continuous infusion separated by 2 week intervals. The starting dose is 9 µg/day for one week followed by 28 µg/day from week 2 through week 4. All subsequent cycles are dosed at 28 µg/day. Due to blinatumomab's high cytotoxic activity and ability to

stimulate T-cells, the adverse events and consequent warnings for this drug include cytokine release syndrome and neurologic events; medication errors frequently related to the administration/infusion pump settings have the potential to exacerbate risks. Because of the narrow therapeutic window and safety risk to the patients due to cytotoxicity, it is important to have appropriately tight control over the product's potency and protein content to ensure that patients are not underdosed or overdosed. The initially proposed potency acceptance criterion ([redacted] (b) (4) %) and drug product (DP) protein content acceptance criterion ([redacted] (b) (4) %) for blinatumomab drug substance (DS) and DP release and stability were determined to be too wide and not supported by clinical/historical data or the manufacturing and analytical capabilities for the control of these attributes. Due to the risks stated above, the proposed range of potency and protein content in vial, which directly impacts the administered dose (µg protein), would result in under or overdosing that could affect the risk benefit ratio of this product. Therefore, the sponsor was asked to tighten the potency and protein content acceptance criteria. The sponsor revised the acceptance criteria for potency to [redacted] (b) (4) % and protein content to [redacted] (b) (4) %, based on the clinical experience and the manufacturing capabilities. The revised acceptance criteria were deemed sufficient with respect to the risk benefit ratio. As was discussed with the sponsor, the potency acceptance criterion may be re-evaluated if appropriate data are collected from future clinical studies.

[redacted] (b) (4)

Leachables studies for the commercial DS and DP container closure system (CCS) are not yet complete. The toxicological risk evaluation of the leachables and extractables from the [redacted] (b) (4) and the commercial DS and DP provided in the BLA showed little or no risk from the leachables/extractables detected in the [redacted] (b) (4) DS and DP. Based on the results of the extractable studies and leachables studies to date, the sponsor was asked to perform real time leachable studies for the DS and DP stored in commercial CCS through the end of DS and DP expiry periods as post marketing commitments.

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

1. To perform real-time drug substance storage container leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of the dating period. The results of this study and the toxicology risk evaluation for the levels of leachates present in the drug substance will be provided in the final study report.

2. To perform real-time drug product storage container leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the (b) (4) end of the dating period. The results of this study and the toxicology risk evaluation for the levels of leachates present in the drug product will be provided in the final study report.

3. To re-evaluate blinatumomab drug substance lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

4. To re-evaluate blinatumomab drug product lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

## II. Summary of Quality Assessments

(b) (4)



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# BLA STN 125557

**Blincyto (Blinatumomab)**

**Amgen Inc.**

**Drug Substance Reviewer: Qing Zhou, Ph.D.**
**Drug Product Reviewer: Deborah Schmiel, Ph.D.**

**Product Quality TL: Rashmi Rawat, Ph.D.**

**Division of Monoclonal Antibodies**

**Immunogenicity Reviewer: Laura Salazar-Fontana, Ph.D.**
**Immunogenicity TL: Susan Kirshner, Ph.D.**

**Division of Therapeutic Proteins**

## OBP CMC Review Data Sheet

1. **BLA#:** STN 125557

2. **REVIEW DATE:** Nov 10, 2014

3. **PRIMARY REVIEW TEAM:**
**Medical Officer:** Donna Przepiorka, Albert Deisseroth
**Pharm/Tox:** Brenda Gehrke, Haw-Jyh, Chiu, Haleh Saber
**Product Quality Team:** Qing Zhou, Deborah Schmiel, Rashmi Rawat, Laura Salazar-Fontana, Susan Kirshner
**BMT or Facilities:** Candace Gomez-Broughton, Maria Candauchacon, Patricia Hughes
**Clinical Pharmacology:** Penfei Song, Liu Qi, Lian Ma, Nitin Mehrotra
**Statistics:** Chia-Wen Ko, Lei Nie
**OBP Labeling:** Jibril Abdus-Samad
**RPM:** Kristopher Kolibab

4. **MAJOR 21st Century Review DEADLINES**
**Filing Meeting:** Oct 1, 2014
**Mid-Cycle Meeting:** Oct 16, 2014
**Late-Cycle Meeting:** Oct 30, 2014
**Wrap-Up Meeting:** Nov 10, 2014
**Primary Review Due:** Nov 10, 2014
**Secondary Review Due:** Nov 17, 2014
**CDTL Memo Due:** Nov 24, 2014
**PDUFA Action Date:** March 19, 2015

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

| Communication/Document | Date |
|---|---|
| Information Resquest-1 | 9-27-2014 |
| Filling Review Memo | 9-29-2014 |
| Information Resquest-2 | 10-7-2014 |
| Mid-Cycle Communication | 10-17-2014 |
| Information Resquest-3 | 10-20-2014 |
| Information Resquest-4 | 10-31-2014 |
| Information Resquest-5 | 11-4-2014 |
| Teleconference-1 | 11-6-2014 |
| Late Cycle Communication | 11-7-2014 |

6. **SUBMISSION(S) REVIEWED:**

| Submission | Date Received | Review Completed (Yes/No) |
|---|---|---|
| STN **125557/0** (BLA Original Submission) | 9-19-2014 | Yes |
| STN **125557/0008** (Sponsor's response to IR-1) | 10-16-2014 | Yes |
| STN **125557/0009** (Sponsor's response to IR-2) | 10-17-2014 | Yes |

| | | |
|---|---|---|
| STN **125557/0012** (Sponsor's response to IR-3) | 10-30-2014 | Yes |
| STN **125557/0017** (Sponsor's response to IR-4) | 11-6-2014 | Yes |
| STN **125557/via email** (Sponsor's response to IR-5) | 11-7-2014 | Yes |

**7. DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name: Blincyto
b. Trade Name: Blincyto
c. Non-Proprietary/USAN: Blinatumomab
d. CAS name: 853426-35-4
e. Common name: AMG-103
f. INN Name: Blinatumomab
g. Compendial Name: N/A
h. OBP systematic name: [redacted] (b) (4)
[AMG-103]
i. Other Names: AMG-103

**8. PHARMACOLOGICAL CATEGORY:** bispecific CD19 directed CD3 T-cell engager

**9. DOSAGE FORM:** For Injection

**10. STRENGTH/POTENCY:**

- The Blincyto (blinatumomab) Drug Product is supplied at 35 µg/vial in a 4 ml vial.
- Potency is defined as the percent activity relative to the reference standard, using a cell based cytotoxicity assay [redacted] (b) (4) .
- The dating period for vialed drug product is 36 months when stored at 5 ± 3°C and protected from light.

**11. ROUTE OF ADMINISTRATION:** Intravenous infusion

**12. REFERENCED MASTER FILES:**

| DMF # | HOLDER | ITEM REFERENCED | Letter of Cross-Reference | COMMENTS (STATUS) |
|---|---|---|---|---|
| [redacted] | | (b) (4) | Provided in the BLA | Sufficient information was provided in the BLA for its intended use. |
| | | | Provided in the BLA | Type III<br>Sufficient information was provided in the BLA for its intended use. |
| | | | Provided in the BLA | Type V<br>Sufficient information was provided in the BLA for its purpose. |
| | | | Provided in the BLA | Type III<br>[redacted] (b) (4)<br>(b) (4) Sufficient information was provided in the |

| | | | | |
|---|---|---|---|---|
| | | | | BLA for their intended use. |
| | | (b) (4) | Provided in the BLA | Sufficient information was provided in the BLA for their intended use. |
| | | | Provided in the BLA | Type III<br>Sufficient information was provided in the BLA to support their intended use. |

## 13. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the biologics drug substance manufacturing facility was conducted following a request by the Biotech Manufacturing Team, Office of Compliance, CDER, under FEI No. (b) (4) The inspection covered the manufacturing operations for the blinatumomab drug substance at (b) (4) under BLA STN 125557/0. The inspection was conducted on (b) (4) by BMAB reviewer, (b) (4) and OBP product quality reviewer (b) (4) in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of blinatumomab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

A five-item 483 was issued; the 483 issues were related to water quality, hold time validation, sample storage, control of cross-contamination of bioburden samples, and pest control. The recommendation for the classification of the inspection is VAI.

The requirement for conducting a PLI for the drug product manufacturing facility was waived.

## 14. CONSULTS REQUESTED BY OBP: NONE

## 15. QUALITY BY DESIGN ELEMENTS

| | |
|---|---|
| | Design Space |
| X | Design of Experiments |
| X | Formal Risk Assessment / Risk Management |
| | Multivariate Statistical Process Control |
| | Process Analytical Technology |
| | Expanded Change Protocol |

## 16. PRECEDENTS: NONE

## 17. ADMINISTRATIVE

**Signature Block**

Primary Reviewers: Qing Zhou, Ph.D. Qing Zhou -S

Deborah Schmiel, Ph.D. Deborah Schmiel -A

OBP/Division of Monoclonal Antibodies

Team Leader: Rashmi Rawat, Ph.D. Rashmi Rawat -S

OBP/Division of Monoclonal Antibodies

Review Chief: Sarah Kennett, Ph.D. Sarah Kennett 11/10/14

OBP/Division of Monoclonal Antibodies

Susan Kirshner, Ph.D. Susan L. Kirshner -S

OBP/Division of Therapeutic Proteins

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# PRODUCT QUALITY (Biotechnology)
## FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

| **BLA/NDA Number:** | **Applicant:** | **Stamp Date:** |
|---|---|---|
| STN 125557/0 | Amgen Inc. | 9/19/2014 |
| **Established/Proper Name:** Blinatumomab | **BLA/NDA Type:** Break Through, Original BLA | |

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 | | |
| ❑ 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 | | |
| ❑ PI –non-annotated | Y | | |
| ❑ PI –annotated | Y | | |
| ❑ PI (electronic) | Y | | |
| ❑ Medication Guide | Y | N | Defer to clinical reviewer |
| ❑ Patient Insert | Y | N | Defer to clinical reviewer |
| ❑ package and container | Y | | |
| ❑ diluent | | N | Not applicable |
| ❑ other components | Y | | IVSS label |
| ❑ established name (e.g. USAN) | Y | | |
| ❑ proprietary name (for review) | | N | Not found |

| 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 | | |
| ❑ legible | Y | | |
| ❑ English (or translated into English) | Y | | |
| ❑ compatible file formats | Y | | |
| ❑ navigable hyper-links | Y | | |
| ❑ interpretable data tabulations (line listings) & graphical displays | Y | | |
| ❑ summary reports reference the location of individual data and records | Y | | |
| ❑ all electronic submission components usable (e.g. conforms to published guidance) | Y | | |
| Companion application received if a shared or divided manufacturing arrangement | Y | N | Not applicable |



Reference ID: 3636437

# PRODUCT QUALITY (Biotechnology)
## FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

| CTD Module 2 Contents | Present? | If not, justification, action & status |
|---|---|---|
| Overall CTD Table of Contents [2.1] | N | |
| Introduction to the summary documents (1 page) [2.2] | Y | |
| Quality overall summary [2.3] | Y | |
| ❑ Drug Substance | Y | |
| ❑ Drug Product | Y | |
| ❑ Facilities and Equipment | Y | |
| ❑ Adventitious Agents Safety Evaluation | Y | |
| ❑ Novel Excipients | N | Not applicable |
| ❑ Executed Batch Records | Y | Provided in 3.2.R |
| ❑ Method Validation Package | Y | Provided in 3.2.R |
| ❑ Comparability Protocols | N | Not applicable |

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|---|---|
| Module Table of Contents [3.1] | N | |
| Drug Substance [3.2.S] | | |
| ❑ general info | Y | |
| ○ nomenclature | | |
| ○ structure (e.g. sequence, glycosylation sites) | | |
| ○ properties | | |
| ❑ manufacturers (names, locations, and responsibilities of all sites involved) | Y | |
| ❑ description of manufacturing process and process control | Y | |
| ○ batch numbering and pooling scheme | | |
| ○ cell culture and harvest | | |
| ○ purification | | |
| ○ filling, storage and shipping | | |
| ❑ control of materials | Y | |
| ○ raw materials and reagents | | |
| ○ biological source and starting materials | | |
| ○ cell substrate: source, history, and generation | | |
| ○ cell banking system, characterization, and testing | | |
| ❑ control of critical steps and intermediates | Y | |
| ○ justification of specifications | | |
| ○ stability | | |
| ❑ process validation (prospective plan, results, analysis, and conclusions) | Y | |
| ❑ manufacturing process development | Y | |



Reference ID: 3636437

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|---|---|
| (describe changes during non-clinical and clinical development; justification for changes) | | |
| ❑ characterization of drug substance | Y | |
| ❑ control of drug substance | Y | |
| ○ specifications | | |
| ○ Justification of specs. | | |
| ○ analytical procedures | | |
| ○ analytical method validation | | |
| ○ batch analyses | | |
| ❑ reference standards | Y | Provided in Section 3.2.P.6 |
| ❑ container closure system | Y | |
| ❑ stability | Y | |
| ❑ summary | | |
| ❑ post-approval protocol and commitment | | |
| ❑ pre-approval | | |
| ○ protocol | | |
| ○ results | | |
| ○ method validation | | |
| Drug Product [3.2.P] [Dosage Form] | | |
| ❑ description and composition | Y | |
| ❑ pharmaceutical development | Y | |
| ○ preservative effectiveness | N | Not applicable |
| ○ container-closure integrity | Y | |
| ❑ manufacturers (names, locations, and responsibilities of all sites involved) | Y | |
| ❑ batch formula | Y | |
| ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) | Y | |
| ❑ controls of critical steps and intermediates | Y | |
| ❑ process validation including aseptic processing & sterility assurance: | Y | Review of process validation for aseptic processing and sterility assurance is deferred to BMAB |
| ○ Filter validation | | |
| ○ Component, container, closure depyrogenation and sterilization validation | | |
| ○ Validation of aseptic processing (media simulations) | | |
| ○ Environmental Monitoring Program | | |



Reference ID: 3636437

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|---|---|
| ○ Lyophilizer validation<br>○ Other needed validation data (hold times) | | |
| ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) | Y | |
| ❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) | Y | |
| ❑ reference standards or materials | Y | |
| ❑ container closure system [3.2.P.7] | Y | |
| ○ specifications (vial, elastomer, drawings) | Y | |
| ○ availability of DMF & LOAs | | |
| ○ administration device(s) | N | Not applicable |
| ❑ stability<br>❑ summary<br>❑ post-approval protocol and commitment<br>❑ pre-approval<br>○ protocol<br>○ results<br>○ method validation | Y | |
| Diluent (vials or filled syringes) [3.2P′] | | IVSS |
| ❑ description and composition of diluent | Y | |
| ❑ pharmaceutical development | Y | |
| ○ preservative effectiveness | N | No preservative is used. Not applicable |
| ○ container-closure integrity | | |
| ❑ manufacturers (names, locations, and responsibilities of all sites involved) | Y | |
| ❑ batch formula | Y | |
| ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) | Y | |
| ❑ controls of critical steps and intermediates | Y | |
| ❑ process validation including aseptic processing & sterility assurance: | Y | Review of process validation for aseptic processing and sterility assurance is deferred to BMAB |
| ○ Filter validation | Y N | |
| ○ Component, container, closure depyrogenation | | |



Reference ID: 3636437

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|---|---|
| and sterilization validation | Y N | |
| ○ Validation of aseptic processing (media simulations) | Y N | |
| ○ Environmental Monitoring Program | Y N | |
| ○ Lyophilizer sterilization validation | | |
| ○ Other needed validation data (hold times) | | |
| ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) | Y | |
| ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) | | |
| ❑ reference standards | N | No reference standard for IVSS. Not applicable |
| ❑ container closure system | Y | |
| ○ specifications (vial, elastomer, drawings) | | |
| ○ availability of DMF & LOAs | | |
| ❑ stability | Y | |
| ❑ summary | | |
| ❑ post-approval protocol and commitment | | |
| ❑ pre-approval | | |
| ○ protocol | | |
| ○ results | | |
| Other components to be marketed (full description and supporting data, as listed above): | Y N | See IVSS above |
| ❑ other devices | N | Not applicable |
| ❑ other marketed chemicals (e.g. part of kit) | N | Not applicable |
| Appendices for Biotech Products [3.2.A] | | |
| ❑ facilities and equipment | Y N | Defer to BMAB |
| ○ manufacturing flow; adjacent areas | | |
| ○ other products in facility | | |
| ○ equipment dedication, preparation, sterilization and storage | | |
| ○ procedures and design features | | |



Reference ID: 3636437

| CTD Module 3 Contents | Present? | If not, justification, action & status |
|---|---|---|
| to prevent contamination and cross-contamination<br>❑ adventitious agents safety evaluation (viral and non-viral) e.g.:<br>○ avoidance and control procedures<br>○ cell line qualification<br>○ other materials of biological origin<br>○ viral testing of unprocessed bulk<br>○ viral clearance studies<br>○ testing at appropriate stages of production<br>❑ novel excipients | Y<br><br><br><br><br><br><br><br><br>Y N | <br><br><br><br><br><br><br><br><br>There are no novel excipients therefore it is not applicable |
| USA Regional Information [3.2.R]<br>❑ executed batch records<br>❑ method validation package<br>❑ comparability protocols | <br>Y<br>Y<br>N | <br><br><br>No comparability protocols are proposed |
| Literature references and copies [3.3] | Y | |

| 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 | |
| Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots | Y | |
| 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 | |
| Certification that all facilities are ready for inspection | Y N | Defer to BMAB |
| 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 | Y | |



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| Examples of Filing Issues | Yes? | If not, justification, action & status |
|---|---|---|
| regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:<br>❑ LAL instead of rabbit pyrogen<br>❑ mycoplasma<br>❑ sterility | <br><br><br>Y N<br>Y<br>Y N | <br><br><br>Rabbit pyrogen and sterility tests defer to BMAB |
| 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 N | Not applicable |
| Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product | Y N | Defer to BMAB |
| Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment | Y N | Defer to BMAB |

**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?** (Yes) ~~No~~

**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.**

No issue to be sent at this time.



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/s/

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QING ZHOU
09/29/2014

DEBORAH H SCHMIEL
09/29/2014

RASHMI RAWAT
09/29/2014