

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125557Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be reviewed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

BLA # 125557
Product Name: blinatumomab

PMR Description: Complete the trial and submit the final report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00103311, a Phase 3 randomized, open-label, active-controlled trial comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph-negative B-cell precursor acute lymphoblastic leukemia (ALL). Enrollment of approximately 400 patients is expected, and the primary endpoint is overall survival.

PMR Schedule Milestones:	Completed:	08/2014
	Trial Completion:	08/2016
	Final Report Submission:	06/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This is a PMR to fulfill subpart E approval. Relapsed or refractory ALL is an immediately life-threatening condition. Depending on the treatment history, complete remissions (CR) can be induced with intensive combination chemotherapy in 17-44%, but remissions are generally short, and median overall survival is 3-6 months. Single agent Marqibo, the only drug approved for this indication in recent history, has a 5% CR rate as a single agent with a median duration of response of 56 days.

In the single-arm trial MT103-211, the applicant reported a CR rate of 33% using single-agent blinatumomab in patients with relapsed or refractory ALL, and the median duration of CR was 10 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has previously accepted overall response rates supported by duration of response from a single arm trial as a basis for accelerated approval for acute leukemia therapies.

The goal of this PMR is to obtain long term efficacy outcomes including overall survival from a randomized controlled clinical trial. Time to event endpoints cannot be adequately interpreted in single arm clinical trials due to confounding effects of the heterogeneity of the patient population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☒ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the complete final study report and data showing clinical efficacy and safety from Protocol 00103311, a Phase 3 randomized, open-label, active-controlled study comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph-negative B-precursor acute lymphoblastic leukemia (ALL).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☒ Other (provide explanation)

Confirmatory clinical trial under 21 CFR 601.40-46

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

____RCK____
(signature line for BLAs)

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

/s/

KRISTOPHER KOLIBAB
12/02/2014

ROBERT C KANE
12/02/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review Microbiologist from BMAB and included for each type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125557
Product Name: BLINCYTO (blinatumomab)

PMC #1 Description: To conduct maximum hold time validation of (b) (4) for two additional batches (for a total of three batches).

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2016
	Other:	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.* USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE***

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
☒ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☐ Improvements to methods
☐ Theoretical concern
☐ Manufacturing process analysis
☐ Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4) may be at risk for a microbial contamination; therefore, maximum hold times (b) (4) should be validated at scale from a microbial quality point of view. Validation is usually demonstrated by the completion of at least three lots for consistency.

The proposed study will include microbial quality results (bioburden and endotoxin) from two validation lots of all (b) (4) to establish a maximum validated hold time. Results from one lot from all (b) (4) except (b) (4) are included in the BLA.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

The study will be executed under an approved protocol and documented in a protocol report. The report will contain microbial quality results (bioburden and endotoxin) from a maximum hold time validation study from two lots of each (b) (4) (3 lots for (b) (4)).

5. To be completed by ONDQA/OBP/BMAB Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #2 Description: To conduct bioburden qualification of (b) (4) and to conduct endotoxin method qualification of (b) (4)

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	04/30/2015
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
☒ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☐ Improvements to methods
☐ Theoretical concern
☐ Manufacturing process analysis
☐ Other

Bioburden method qualification has not been conducted for (b) (4); endotoxin method qualification has not been conducted for (b) (4). However, both methods were qualified for (b) (4) therefore, the risk of impact to product quality is deemed low.

2. Describe the particular review issue and the goal of the study.

Bioburden and endotoxin method qualification is necessary to ensure that samples do not exhibit inhibitory properties that may interfere with bioburden or endotoxin detection. The study will include bioburden and endotoxin method qualifications for the (b) (4) that were not qualified at the time of the BLA approval.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
☐ Assay
☐ Sterility
☐ Potency
☐ Product delivery
☐ Drug substance characterization
☐ Intermediates characterization
☐ Impurity characterization

- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

The study will include bioburden method qualification of (b) (4) and endotoxin method qualification of (b) (4)

5. To be completed by ONDQA/OBP?BMAB Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #3 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>10/31/2015</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The endotoxin detection method currently used for drug substance, drug product, and intravenous solution stabilizer samples may not be reliable. However, several controls are in place to minimize the risk of endotoxin contamination in those samples and to detect potential endotoxin contamination in the final injectable products.

2. Describe the particular review issue and the goal of the study.

Drug substance, drug product, and intravenous solution stabilizer samples exhibit low endotoxin recovery when spiked with control standard endotoxin; as a consequence, the endotoxin detection method currently used may not be reliable and presence of endotoxin in drug substance, drug product, and intravenous solution stabilizer samples may be undetected. The study will develop a reliable endotoxin detection method not subject to low endotoxin recovery.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization

- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

The study will explore alternative endotoxin detection methods for drug substance, drug product, and intravenous solution stabilizer samples that are not subject to low endotoxin recovery.

5. To be completed by ONDQA/OBP/BMAB Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #4 Description: To conduct a risk assessment to ensure microbial control and mitigate risks of endotoxin contamination during drug substance (DS), drug product (DP), and intravenous solution stabilizer (IVSS) manufacturing. Risk mitigating actions should include establishment of endotoxin limits on appropriate input materials as determined by the risk assessment.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

Several controls are currently in place to minimize the risk of endotoxin contamination of drug sample, drug product, and intravenous solution stabilizer. These controls include (b) (4)

2. Describe the particular review issue and the goal of the study.

The study will assess additional controls to lower further the risk of endotoxin contamination of drug substance, drug product, and intravenous solution stabilizer during the manufacturing. These controls include but are not limited to endotoxin limits of input material.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery

- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

A risk assessment will be conducted to ensure microbial control and to mitigate potential risks of endotoxin contamination during drug substance, drug product, and intravenous solution stabilizer manufacturing. The risk assessment will include endotoxin limit of input material.

5. To be completed by ONDQA/OBP/BMAB Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #5 Description: To assess the pyrogenic response in rabbits to drug product (DP) and to 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.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>02/28/2015</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

The endotoxin detection method currently used for drug product and intravenous solution stabilizer samples may not be reliable. However, additional controls are currently in place to mitigate the risk of endotoxin contamination of drug product and intravenous solution stabilizer samples. These controls include (b) (4)

2. Describe the particular review issue and the goal of the study.

According to 21 FCR. 610.13 (b) "Each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances..." Bacterial endotoxin is the most common pyrogenic substance introduced during product manufacture; therefore, contamination of the final injectable product with pyrogenic substances is routinely monitored using a bacterial endotoxin detection method. Drug product (DP) and intravenous solution stabilizer (IVSS) samples exhibit low endotoxin recovery (LER) when spiked with control standard endotoxin; as a consequence, the endotoxin detection method currently used may not detect possible pyrogenic endotoxin contaminations. The sponsor is currently designing a study to assess if DP and IVSS endotoxin-spiked samples result in a pyrogenic response when injected in rabbits; the study is planning to start on December 2014. If the pyrogenic response in rabbits is positive, a rabbit pyrogenic test will be used as an interim test until a reliable bacterial endotoxin detection method is developed.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

The study will assess the pyrogenic response in rabbits injected with drug product and intravenous solution stabilizer spiked with control standard endotoxin. If the pyrogenic response in rabbits is positive, a rabbit pyrogenic test will be used as an interim test until a reliable bacterial endotoxin detection method is developed.

5. To be completed by ONDQA/OBP/BMAB Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #6 Description: To conduct (b) (4)
The results from
these studies will be used to support the proposed (b) (4)
as supported by currently
available microbial data.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	12/31/2015
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
☒ Long-term data needed (e.g., stability data)
☐ Only feasible to conduct post-approval
☐ Improvements to methods
☐ Theoretical concern
☐ Manufacturing process analysis
☐ Other

The proposed (b) (4) are not supported by microbial data, however, the sponsor will adhere to (b) (4) that are supported by microbial data. The (b) (4) until the studies are complete.

2. Describe the particular review issue and the goal of the study.

(b) (4) must be justified with microbial data.
(b) (4) should be validated at manufacturing scale (b) (4)
Validation is usually demonstrated by the completion of at least three runs for consistency.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
☐ Assay

- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

The study will be completed according to an approved protocol and documented in a protocol report. The report will contain microbial quality results (bioburden and endotoxin) from a (b) (4) validation study done at commercial scale.

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

KRISTOPHER KOLIBAB
12/02/2014

PATRICIA F HUGHES TROOST
12/02/2014



Department of Health and Human Services Division of Monoclonal Antibodies
Food and Drug Administration Office of Biotechnology Products
Center for Drug Evaluation and Research

FINAL LABEL AND LABELING REVIEW

Date: November 20, 2014

Reviewer: Jibril Abdus-Samad, PharmD, Labeling Reviewer
Division of Monoclonal Antibodies

Jibril Abdus-samad -S
Digitally signed by Jibril Abdus-samad -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S
Date: 2014.11.20 14:29:42 -05'00'

Through: Deborah Schmiel, PhD, Product Quality Reviewer
Division of Monoclonal Antibodies

Deborah Schmiel -A
Digitally signed by Deborah Schmiel -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001319460, cn=Deborah Schmiel -A
Date: 2014.11.20 14:34:28 -05'00'

Sarah Kennett, PhD, Review Chief
Division of Monoclonal Antibodies

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: 2014.11.20 14:37:38 -05'00'

Application: BLA 125557/0

Product: Blincyto (blinatumomab)

Applicant: Amgen Inc.

Submission Dates: September 19; November 5, 6, and 19, 2014

Executive Summary

The container labels and carton labeling for Blincyto (blinatumomab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia [8/1/2014 – 11/30/2014] USP 37/NF 32. The initial labeling deficiencies were identified, mitigated, and resolved. The labels and labeling submitted via email on November 19, 2014 in advance of the official submission are acceptable.

Background and Summary Description

BLA 125557 Blincyto (blinatumomab) has a proposed indication for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Blincyto (blinatumomab) is supplied in a carton containing a single-dose vial of blinatumomab as a 35 mcg of lyophilized powder and a single-dose vial of Intravenous Solution Stabilizer (IVSS). The recommended dose is 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for the first cycle. For subsequent cycles, the dosage is 28 mcg/day on Days 1-28. Blincyto is administered as 24 hour or 48 hour infusions. Blincyto requires the healthcare practitioner to follow detailed preparation instructions, which required a Human Factors study that was evaluated by the Division of Medication Error Prevention and Analysis to assess the potential for medication errors.

Materials Reviewed:

Blincyto Container Vial Label
IV Solution Stabilizer Vial Label
Carton Labeling

Start of Sponsor Material

Blincyto Container Vial Label

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

Partial label: If the container is capable of bearing only a partial label, the container shall show as a minimum:

1. name (expressed either as the proper or common name); Blincyto Vial *conforms*. IVSS vial conforms but OBP recommends revising. OBP Request: Revise the name from "IV Solution Stabilizer for Trade Name" to appear as "**Intravenous Solution Stabilizer** for Blincyto". Note Intravenous Solution Stabilizer is the most prominent and "Blincyto" is less prominent. *Applicant revised as requested.*
2. lot number or other lot identification; *conforms*.
3. name of the manufacturer; conforms, but OBP recommends revising.
OBP Request: Revise the manufacturer information
(b) (4) to read
"Amgen Inc. US Lic No 1080". *Applicant revised as requested.*
4. for multiple dose containers, the recommended individual dose. *Not applicable.*
5. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Conforms.*
 - (a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label; *not applicable.*
 - (b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable.*
 - (c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which

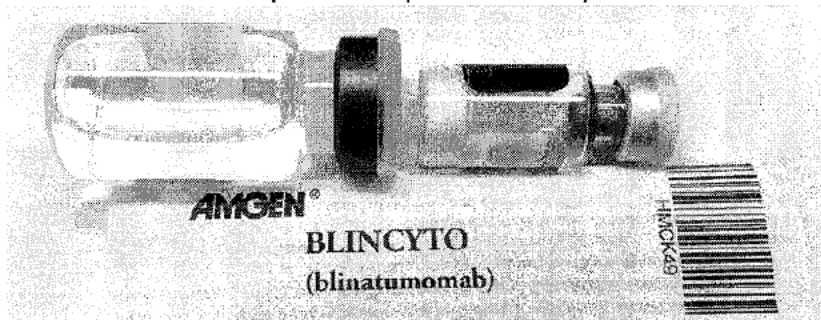
bears all the items required for a package label. *See Partial Label comments above.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

FDA Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

The Applicant confirmed the labeling for both vials allows for uncovered area to permit inspection. *Acceptable.*



B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *does not conform.*

OBP Request: Assign the Blincyto vial and IV Solution Stabilizer vial a different NDC by revising the different product codes/second segment of the NDC. *Applicant revised as requested.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *Blincyto vial - Not applicable. Stabilizer Vial – we concur with DMEPA's recommendations.*

Revise the current statement of "[REDACTED] (b) (4)" to "NOT FOR DIRECT RECONSTITUTION OF TRADE NAME" to make the instructions clear and direct. *Applicant revised as requested.*

Remove the statement " (b) (4) since IVSS is not for intravenous infusion and is only used to increase the stability of the infusion bag during preparation of blinatumomab. Please consider revising the label as follows:

IV Solution Stabilizer for BLINCYTO
NOT FOR DIRECT RECONSTITUTION OF TRADE NAME
Applicant revised as requested.

D. 21 CFR 201.6 Drugs; misleading statements; *Not applicable.*

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]; *not applicable.*

F. 21 CFR 201.15 Drugs; prominence of required label statements;
Blinicyto vial - Not applicable. Stabilizer Vial – does not conform.

OBP Request: Revise the name from "IV Solution Stabilizer for Trade Name" to appear as "**IV Solution Stabilizer** for Blincyto".

Note **IV Solution Stabilizer** is the most prominent and "Blincyto" is less prominent. *Applicant revised as requested.* Additionally, DMEPA finds it acceptable to use "IV" in this case.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*

H. 21 CFR 201.25 Bar code; *conforms.*

I. 21 CFR 201.50 Statement of identity; *conforms.*

J. 21 CFR 201.51 Declaration of net quantity of contents; does not conform.

OBP Requests:

Revise Blincyto strength to 35 mcg/vial. *Applicant revised as requested.*

Add the volume of the stabilizer solution. *Applicant revised as requested.*

K. 21 CFR 201.55 Statement of dosage; *not applicable.*

L. 21 CFR 201.100 Prescription drugs for human use; *does not conform.*
See comments on declaration of net quantity above.

Start of Sponsor Material

Carton Labeling

(b) (4)




End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label


a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. *Conforms.*

b) The name, addresses, and license number of manufacturer; *does not conform.* Manufacturer is listed as " (b) (4) rather than "Manufactured by."

FDA Requests:

Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t). Thus the manufacturer information should appear as "Manufactured by:" or "Manufacturer:" Applicant *revised as requested.*

Relocate manufacturer information to appear with the US License Number. For example:

Manufacturer:
Amgen, Inc. Thousand Oaks, CA 91320 USA
US Lic No 1080
Product of  (b) (4)

Applicant Response: Applicant revised country of origin to United Kingdom. *Acceptable.*

c) The lot number or other lot identification; *conforms.*

d) The expiration date; *conforms.*

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms.*

f) The number of containers, if more than one; *conforms.*

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as

needed for an accurate description of the contents, whichever is applicable; does not conform.

OBP Request: Revise Blincyto strength to 35 mcg/vial.
Applicant revised as requested.

- h) The recommended storage temperature; *conforms.*
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; Do Not Shake reconstituted solution. *Conforms.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.*
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *Not applicable.*
- m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*
- o) The adjuvant, if present; *not applicable.*
- p) The source of the product when a factor in safe administration; *not applicable.*
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable.*
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms.*

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Does not conform*.

FDA Request: Add the medication Guide statement.
Dispense the enclosed Medication Guide to each patient. *Applicant revised as requested*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Blincyto is exempt because it is a therapeutic recombinant DNA-derived product*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. *Not applicable*.

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; *conforms*.

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35]; *does not conform*.

OBP Request: Assign the Blincyto vial and IV Solution Stabilizer vial a different NDC by revising the different product codes/second segment of the NDC. *Applicant revised as requested*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] does not conform.

OBP Requests:

Per USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients, please list the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). Thus, the statement of ingredients should appear as:

Each vial of Blincyto contains blinatumomab (35 mcg), citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), and trehalose dihydrate (95.5 mg) with a pH of 7.0. After reconstitution with 3 mL of preservative free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

Note the deletion of “µg” and the trailing zero from “(b) (4) mg”.

Each vial of Stabilizer for Blincyto Intravenous Solution contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), and Sterile Water for Injection, USP with a pH of 7.0.

J. 21 CFR 201.15 Drugs; prominence of required label statements; does not conform.

OBP Request: Change the font color of the statement “See Package Insert for complete instructions on preparation and administration” from black to red. *Applicant revised as requested.*

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; does not conform.

OBP Request: Revise the Blincyto strength from (b) (4) mcg/vial to 35 mcg/vial to comply with 21 CFR 201.51(g) and United States Pharmacopeia (USP) standards for excess volume (USP, 8/1/2014 – 11/30/2014, USP 37/NF 32, General Chapters: <1151> Pharmaceutical Dosage Forms). Your extractable volume studies of reconstituted Blincyto solution (12.5 mcg/mL concentration) state (b) (4) mL is the withdrawable volume, which is equivalent to 35 mcg of Blincyto. Generally, the overfill should not be declared in labeling. The slight excess lyophilized powder (b) (4) mcg) and volume after reconstitution (b) (4) mL) allows the end-user to withdraw what we request as the revised labeled strength (35 mcg/vial). See Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, Draft Guidance. *Applicant revised as requested.*

O. 21 CFR 201.55 Statement of dosage; conforms.

P. 21 CFR 201.100 Prescription drugs for human use; does not conform. See comments above regarding declaration of net contents and statement of ingredients.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant revised as requested unless noted otherwise.

A. General Comment

1. Comment on if there is any text on the ferrule and cap overseal of both Blincyto and Stabilizer vials to comply with a revised USP standard [USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1> Injections/General Requirements] that went into effect on December 1, 2010. We refer you to the following address:
http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

The Applicant confirmed there is no text on the top of the ferrule and cap overseal. *Acceptable.*

B. Blincyto Vial Container Label

We consider the Container Label a partial label due to its small size. Our recommendations below aim to provide the required and recommended information on the label and remove less important information to provide more white space and improve readability.

1. Consider capitalizing the first letter of the proprietary name followed by lower case letters (i.e., "Blincyto" instead of "BLINCYTO") as discussed in Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. Draft Guidance.
2. Revise the dosage form (b) (4) to "For Injection" per USP [8/1/2014 – 11/30/2014 USP 37/NF 32, General Chapter, Injection <1>, Nomenclature and Definitions.
3. Express the strength presentation of this lyophilized powder in terms of the amount of drug per vial "35 mcg/vial". Consider deleting the duplicate strength presentations.
4. Improve the color contrast between the (b) (4) font color and the orange circular background color of the strength statement. The color contrast appears acceptable on the carton labeling; however the smaller font size may contribute to the poor readability on the small container label. For consistency, consider revising the color contrast of strength statement on the carton labeling as well.
5. For biologic products, the preferred CDER format is to include the dosage form "for Injection" on the line below the proper name "(blinatumomab)". However if space is limited, you may omit the dosage form from this small container label. Thus, the principal display panel (PDP) should appear as:

Trade Name
(blinatumomab)
35 mcg/vial
For Intravenous Infusion Only
Amgen Inc. US Lic No 1080 Rx Only

or

Trade Name
(blinatumomab)
for Injection
35 mcg/vial
For Intravenous Infusion Only
Amgen Inc. US Lic No 1080 Rx Only

C. Stabilizer Container Label

1. Place a volume statement on the label.

D. Carton Labeling

1. Consider capitalizing the first letter of the proprietary name followed by lower case letters (i.e., "Blincyto" instead of "BLINCYTO") as discussed in Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design Minimize Medication Errors. Draft Guidance.
2. Move the following statement "Single Use Vial. Discard Unused Portion" to the PDP under "No Preservative." This recommendation is made to ensure users clearly understand that the vial is for a one time use only.

Conclusions

Labeling deficiencies were identified, mitigated, and resolved. The labels and labeling submitted via email on November 19, 2014 in advance of the official submission are acceptable.

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

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: November 17, 2014

From: Candace Gomez-Broughton, Ph.D., OC/OMPQ/DGMP/BMAB
Deborah Schmiel, Ph.D., OPS/OBP/DMA

To: BLA File, STN 125557/0

Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

Subject: Biological License Application (BLA)

Applicant: Amgen, Inc.

Facility: (b) (4) (FEI# (b) (4))

Product: Blincyto™ (blinatumomab)

Dosage: lyophilized powder for solution

Indication: For the treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that (b) (4) (b) (4) has been approved to manufacture multiple licensed products using the same manufacturing process, we recommend that the pre-approval inspection of the (b) (4) drug product manufacturing facility in (b) (4) (FEI: (b) (4)) be waived for STN 125557/0.

Summary

BLA 125557/0 is for blinatumomab (proposed name: Blincyto™) indicated for treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL). Blinatumomab drug product is supplied as a sterile powder for injection, for intravenous administration in USP Type 1 (b) (4) glass vials. The vials contain (b) (4) mcg of the drug product that is reconstituted with sterile water for injection (WFI). Blinatumomab is supplied with an intravenous stabilizer solution which is filled into Type 1 glass vials as well.

Blinatumomab drug substance is manufactured at (b) (4) and shipped to (b) (4) at (b) (4). The drug substance is stored at (b) (4). The blinatumomab manufacturing process consists of the following unit operations:

(b) (4)

The blinatumomab drug product is packaged with an intravenous stabilizer solution (IVSS) which is also aseptically manufactured at (b) (4). The IVSS is aseptically added to an infusion bag containing saline prior to adding reconstituted blinatumomab drug product.

Facility Information
Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

- a. (b) (4) (FEI# (b) (4)) will manufacture blintumomab drug product which is the subject of BLA 125557 that is currently under review at the Agency.
- b. (b) (4) is approved for manufacturing licensed biological products

2. *FDA has not inspected the establishment in the last 2 years.*
FDA has been inspected the establishment in the past 2 years.

Inspection Dates	Inspection conclusions
(b) (4)	Inspected by IOG. The following profile classes were covered: CBI, CHG, SVL, SVS, and TRP. The inspection was classified VAI and the firm has acceptable GMP status.
(b) (4)	Inspected by IOG. The following profile classes were covered: (b) (4), TRP, SVP, SVL, SVS, (b) (4), and (b) (4). The inspection was classified NAI and final GMP status was acceptable.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The site has acceptable compliance status.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.* (b) (4) facility is approved to manufacture multiple products using aseptic processing. The previous two inspections covered biological products. Both the inspections covered TRP, and SVL profiles.

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*
Point to consider:

The manufacturing process for this BLA is substantially equivalent to other parenteral products manufactured in the same facility.

Signatures:

Candace Y. Gomez-
broughton -S

Digitally signed by Candace Y. Gomez-
broughton -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000640207,
cn=Candace Y. Gomez-broughton -S
Date: 2014.11.19 08:58:03 -05'00'

Patricia F.
Hughestroost
-S

Digitally signed by Patricia F.
Hughestroost -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
096547, cn=Patricia F.
Hughestroost -S
Date: 2014.11.19 10:21:30 -05'00'

Deborah
Schmiel -A

Digitally signed by Deborah Schmiel -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2001319460,
cn=Deborah Schmiel -A
Date: 2014.11.19 11:04:34 -05'00'

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=20005971
65, cn=Sarah B. Kennett -S
Date: 2014.11.19 13:07:04 -05'00'

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 17, 2014

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Robert Kane, MD
Deputy Director for Safety
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adam George, PharmD.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name),
Dosage Form and
Route: BLINCYTO (blinatumomab)
for injection, for intravenous use

Application
Type/Number: BLA 125557

Applicant: Amgen Inc.

1 INTRODUCTION

On September 19, 2014, Amgen Inc. submitted for the Agency's review a Biologics License Application (BLA 125557) for BLINCYTO (blinatumomab) for injection, for intravenous use, with the proposed indication for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on October 3, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for BLINCYTO (blinatumomab) for injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft BLINCYTO (blinatumomab) for injection, for intravenous use MG received on September 19, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2014.
- Draft BLINCYTO (blinatumomab) for injection, for intravenous use Prescribing Information (PI) received on September 19, 2014, further revised by the Applicant and resubmitted to the Agency on October 15, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 5, 2014 and November 14, 2014.
- Approved KEYTRUDA (pembrolizumab) comparator labeling dated September 4, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

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

/s/

MORGAN A WALKER
11/17/2014

ADAM N GEORGE
11/17/2014

BARBARA A FULLER
11/17/2014

LASHAWN M GRIFFITHS
11/17/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 14, 2014

To: Kris Kolibab, PhD.
Regulatory Project Manager
Division of Hematology Products (DHP)

From: Adam George, PharmD. Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Acting Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for BLA# 125557
Blincyto[™] (blinatumomab) for injection, or intravenous use

In response to your consult dated October 3, 2014, we have reviewed the draft prescribing information (PI) for Blincyto[™] (blinatumomab) for injection, for intravenous use provided in an email on November 11, 2014 and have no comments at this time. OPDP's comments on previous versions of the proposed labeling have been addressed during labeling meetings with the Division.

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

/s/

ADAM N GEORGE
11/17/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125557/Blincyto (blinatumomab)

Product Name:

PMC #1 Description: To perform real-time drug substance commercial container closure system 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 shelf life. The results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug substance will be provided in the final study report.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	04/2015
	Other:	MM/DD/YYYY

NDA/BLA # 125557/Blincyto (blinatumomab)

Product Name:

PMC #2 Description: To perform real-time drug product commercial container closure system 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 shelf life. The results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	08/2016
	Other:	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods

- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The preliminary results from extractables and leachables studies indicate that the presence of leachates from the blinatumomab commercial container closure systems during drug substance and drug product storage does not appear to be a safety issue. However, the real-time leachate studies were not performed to the end of the drug substance and drug product shelf life. A real-time leachable study through the end of drug substance and drug product expiry period would provide a comprehensive assessment of the levels of leachates that can be introduced into the drug substance and drug product under recommended storage conditions.

2. Describe the particular review issue and the goal of the study.

Leachable studies for blinatumomab drug substance and drug product using the commercial container closure systems are currently incomplete. The performance of real-time leachable studies to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of the drug substance and drug product shelf life and a toxicological evaluation of the levels of leachates detected in the drug substance and drug product would provide a better assessment of the risk to patients from any leachates that are potentially present in the drug substance and drug product by the end of the expiry period.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

Conducting real-time drug substance and drug product commercial container closure system 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 shelf life and performing a toxicology risk evaluation for the levels of leachates detected in blinatumomab drug substance and drug product.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
 - ☒ Are the objectives clear from the description of the PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125557/Blincyto (blinatumomab)

Product Name:

PMC #3 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	01/2021
	Other:	MM/DD/YYYY

NDA/BLA # 125557/Blincyto (blinatumomab)

Product Name:

PMC #4 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	10/2018
	Other:	MM/DD/YYYY

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis

☐ Other

Blinatumomab drug substance and drug product release and stability specifications approved under the BLA are sufficient to ensure adequate quality and safety of blinatumomab for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate an improved control strategy.

2. Describe the particular review issue and the goal of the study.

Blinatumomab drug substance and drug product release and stability specifications are based on the clinical and manufacturing experience provided in the BLA. However, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that can be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

Statistical analysis of blinatumomab drug substance and drug product release data acquired following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?

- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(Signature line for BLAs only)

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

/s/

QING ZHOU
11/14/2014

DEBORAH H SCHMIEL
11/14/2014

RASHMI RAWAT
11/15/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 125557

Application Type: NME BLA

Name of Drug/Dosage Form: Blincyto (blinatumomab) and (b) (4) mcg

Applicant: Amgen, Inc.

Receipt Date: September 19, 2014

Goal Date: May 19, 2015

1. Regulatory History and Applicant's Main Proposals

Amgen submitted a biologics license application on September 19, 2014 under section 351(a) of the Public Health Service Act to market blinatumomab, a novel single-chain antibody construct of the bispecific T-cell engager (BiTE®) class, designed to target CD19 expressed on malignant B cells. Amgen is seeking to market blinatumomab as a single agent for the treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL). This indication was granted Breakthrough Therapy designation on June 30, 2014.

Amgen considers that blinatumomab meets the qualifying criteria for priority review designation for the treatment of Philadelphia chromosome-negative relapsed or refractory B-precursor ALL and, therefore, requested for priority review designation. Amgen received priority review on October 6, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit** year.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

KRISTOPHER KOLIBAB
11/06/2014

AMY C BAIRD
11/06/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: October 20, 2014

TO: Kris Kolibab, PhD., Regulatory Project Manager
Donna Przepiorka, M.D., Ph.D., Medical Officer
Albert Deisseroth, M.D., Ph.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125557 (IND 100135)

APPLICANT: Amgen

DRUG: blinatumomab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: breakthrough therapy

INDICATION: Treatment of adult patients with chromosome-negative or refractory B-precursor acute lymphoblastic leukemia

CONSULTATION REQUEST DATE:	July 22, 2014
INSPECTION SUMMARY GOAL DATE (original):	October 20, 2014
DIVISION ACTION GOAL DATE (original)	December 1, 2014
Division Action GOAL DATE (revised)	December 3, 2014
PDUFA DATE:	March 19, 2015

I. BACKGROUND:

Relapsed or refractory B-precursor acute lymphoblastic leukemia in adult patients is an aggressive malignant disease with dismal prognosis. Blinatumomab is a bispecific T cell engager (BITE[®]), designed to direct T cells towards target cells. The resulting target cell specific cytotoxicity closely resembles standard cytotoxic T cell activation and is the reason for the therapeutic action of blinatumomab.

A single adequate and well-controlled clinical trial was submitted in support of the applicant's BLA. Three domestic clinical study sites were selected for audit. These clinical study sites had an unexpectedly high response and also had the highest accrual of the enrolled study sites.

Protocol MT103-211

Study MT103-211 was an open label, single-arm, multicenter Phase 2 study to evaluate the safety and efficacy of the bispecific T cell engager antibody, blinatumomab, in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL) using a Simon-2 stage design. Treatment consisted of up to five cycles of blinatumomab. Patients who discontinued treatment prematurely entered the efficacy and/or survival follow-up period.

Patients with Ph-negative B-precursor ALL were eligible to participate in the study. The patient population included (1) relapsed or refractory patients with first remission duration less than or equal to 12 months in the first salvage, (2) relapsed or refractory patients after the first salvage therapy, or (3) relapsed or refractory patients within 12 months or allogeneic hematopoietic stem cell transplantation (HSCT). The primary efficacy endpoint was complete response or remission (CR) and complete response or remission with partial recovery of peripheral blood counts (CRh*) within two cycles of treatment with blinatumomab.

II. RESULTS:

Name of CI Location	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Anthony Stein, M.D. City of Hope 1500 East Duarte Road Duarte, CA 92010	MT 103-211/ Site #2306 N=27	August 19-28, 2014	NAI
Hagop Kantarjian, M.D. MD Anderson Cancer Center 1515 Holcombe Blvd, Unit 428 Houston, TX 77030	MT 103-211/ Site #2309 N=27	September 12-17, 2014	Preliminary: NAI
Richard Larson, M.D. University of Chicago 5841 South Maryland Avenue, MC 2115 Chicago, IL 60637	MT 103-211/ Site #2311 N=6	September 1-5, 2014	Preliminary: VAI
Amgen One Amgen Center Drive Mail Stop 17-2-A Thousand Oaks, CA 91320-1799	Sponsor of Study Protocol MT103-211	September 8-17, 2014	Preliminary: NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Anthony Stein, M.D./Protocol MT 103-211/Site 2306

Duarte, CA 92010

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from August 19-28, 2014. A total of 48 subjects were screened and 30 subjects were enrolled. Of the 30 enrolled subjects, 20 discontinued (15 due to disease progression and 5 due to adverse events). Thus, 10 subjects completed the study.

An audit of 13 subjects' records was conducted for subject eligibility criteria. An audit of six enrolled subjects' records was conducted for adverse events, concomitant therapies, and the primary efficacy raw data. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for these enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Hagop Kantarjian, M.D./Protocol MT 103-211/Site 2309

Houston, TX

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from September 12-17, 2014. A total of 53 subjects were screened and 30 subjects were enrolled. Two patients died. Seven subjects still on long term follow-up and three were lost to follow-up. Thus, 18 patients completed the study. An audit of 10 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for these enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Richard Larson, M.D./ Protocol MIT 103-211/Site 2311
Chicago, IL

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from September 1-5, 2014. A total of thirteen subjects were screened and seven subjects were enrolled. Two enrolled patients, who are alive, are still in follow-up in this ongoing study. The other five study subjects who were enrolled died. An audit of the six enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for these enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A one-item Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection, due to failure to follow the investigational plan. Specifically,

- i. Informed Consent:
 - a. Informed consent was obtained from two of seven subjects (Subject #2311-003 and 2311-003) by site personnel not designated on the Authorized Personnel Form to perform informed consent.
 - b. Dr. Larson failed to re-consent three of seven subjects with updated versions of the informed consent form containing substantial new safety information.
- ii. Serious Adverse Events and Non-serious Adverse Events: The protocol requires the investigator to report SAEs to the sponsor within 24 hours of awareness. Additionally, the site did not report the following untoward medical occurrences as adverse events to sponsor.

- a. Subject 2311-001 had febrile neutropenia and acute liver enzyme elevations on 3/27/2012. These adverse events were documented and reported to the sponsor. The same subject experienced febrile neutropenia on 3/30/2012, prolonging his discharge to (b) (6). This SAE was not reported to the sponsor.
 - b. Subject 2311-003 had febrile neutropenia on 9/16/2012, which was documented in source records on 9/26/2012. For the same subject, the site was aware of SAE of neutropenia on 10/5/2012, but reported it to the sponsor on 10/16/2012.
 - c. For Subject 2311-004, the site was aware of SAE of upper limb tremors on 11/9/2012, but reported it to the sponsor on 11/14/2012.
 - d. Subject 2311-005 had increased LDH and risk for tumor lysis/cytokine release syndrome on 11/27/2012, which was documented in source records on 11/29/2012.
 - e. For Subject 2311-008, the site was aware of a steroid-induced myopathy affecting the lower extremities on 4/22/2013, but reported it to the sponsor on 7/2/2013. The site was aware of profound lower extremity weakness on 4/26/2013 and progressive ALL leading to death on (b) (6), but the events were reported to the sponsor on 7/2/2013.
- iii. Inclusion/exclusion criteria: Protocol exclusion criterion #17d excludes subjects with screening hemoglobin values 9 g/dL or less from study participation.
- a. Subject 2311-003 had hemoglobin values of 8.2 to 8.7 g/dL from 9/15/2012 to 9/18/2012. The subject was determined to be eligible for the study on 9/18/2012.
 - b. Subject 2311-008 had screening hemoglobin value of 8.9 g/dL on 2/13/2013. The subject was determined to be eligible for the study on 2/18/2013.

At the clinical site close out meeting, the following items were also discussed: (a) financial disclosure forms for Sub-Investigators were not submitted concurrently with their participation in the trial, (b) serious adverse events were not submitted to the (b) (4) IRB, and (c) training for 10 of 14 Sub-Investigators was not documented.

OSI Comment:

For Site 2311, the field investigator did note that the sponsor had the central laboratory re-analyze screening visit bone marrows aspirate examination results for some subjects in November of 2013 (up to 14 months after the test) and asked the clinical investigator to change percentage of blast cells information on the e-CRF for at least two subjects.

Given that these baseline values were used in determining primary efficacy endpoint, this could have an impact on the endpoint. However, per study protocol, "Section 8.2 Assessment of Efficacy 8.2.1 Bone Marrow Aspiration/Biopsy," stated that ".....for evaluation of baseline and response, the result of the central laboratory will prevail....." OSI informed and discussed this matter with DHP. DHP noted that they are addressing the issue with the bone marrow study reports, reporting and assessment methods, efficacy assessment nuances in Protocol MT 103-211, and evaluating any impact on the primary efficacy endpoint.

The inspectional observations listed by the ORA investigator dealt primarily with safety-related issues. There was late or under-reporting of adverse events as noted above. The events that were reported late or not reported (i.e. febrile neutropenia, increased LFTs, and increased LDH with risk for tumor lysis syndrome are conditions that occur frequently in the designated study population. The failure to exclude two subjects with borderline low hemoglobin issues would not seem to be of major concern, given that the difference in the hemoglobin values (i.e., eligibility criteria and hemoglobin study values at entry) was not clinical significant.

Dr. Larson responded adequately in writing to the List of Inspectional Observations (FDA Form 483) on October 2, 2014 and implemented staff training for future clinical studies. Two of three subjects not consented with the most recent version of the informed consent form are in follow-up (i.e. not on active treatment) and will be reconsented at their next clinic visit. The third subject who was not reconsented is deceased with cause of death listed as Acute Lymphoblastic Leukemia in the Clinical Study Report.

c. Assessment of data integrity:

Notwithstanding the regulatory deficiencies observed, data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

4. Amgen
Thousand Oaks, CA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from September 8-17, 2014. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors, or transfer of regulatory obligations.

b. General observations/commentary:

The sponsor generally maintained adequate oversight of the clinical trial. For the most part, monitoring of the investigator sites was adequate. There was no evidence of under-reporting of adverse events. The sponsor did not identify any noncompliant sites or clinical investigators.

A Form FDA 483 was not issued at the end of the sponsor inspection.

c. Assessment of data integrity:

Notwithstanding the regulatory deficiencies listed above, the sponsor monitoring of sites appeared to be reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical sites were inspected for this Phase 2, single-arm, open-label study submitted in support of this BLA. The sponsor was also inspected.

The final regulatory classification for Dr. Anthony Stein is No Action Indicated (NAI). The preliminary regulatory classification for Dr. Hagop Kantarjian and the sponsor is No Action Indicated (NAI). The preliminary regulatory classification of Dr. Richard Larson is Voluntary Action Indicated (VAI). The study data collected from these clinical sites appear reliable in support of the requested indication.

Note: The inspectional observations noted above for Drs. Kantarjian and Larson and for the sponsor, Amgen, are based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated, if conclusions on the current inspection report changes significantly, upon receipt of the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Oencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

ANTHONY J ORENCIA
10/20/2014

KASSA AYALEW
10/20/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125557	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Blincyto Established/Proper Name: blinatumomab Dosage Form: lyophilized powder for intravenous solution Strengths: (b)(4) mcg		
Applicant: Amgen, Inc. Agent for Applicant (if applicable):		
Date of Application: 9/19/2014 Date of Receipt: 9/19/2014 Date clock started after UN:		
PDUFA Goal Date: 5/19/2015		Action Goal Date (if different): 12/3/2014
Filing Date: 11/18/2014		Date of Filing Meeting: 10/1/2014
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

	<input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 100135				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Peds Page
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Med Guide was requested and due October 15, 2014
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT – IRT (Review Cardiac Summary Report, sent 9/23/2014)
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): May 4, 2010, March 25, 2013, and April 25, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 9, 2014 (CMC) and June 23, 2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 1, 2014

BLA: 125557

PROPRIETARY NAME: Blincyto

ESTABLISHED/PROPER NAME: blinatumomab

DOSAGE FORM/STRENGTH: lyophilized powder for solution, (b) (4) mcg

APPLICANT: Amgen, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)

BACKGROUND: Amgen, Inc. submitted a BLA under section 351(a) of the Public Health Service Act (PHS Act), BLA 125557, on September 19, 2014 and received on September 19, 2014. The proprietary name, Blincyto, is under review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kris Kolibab	Y
	CPMS/TL:	Amy Baird and Theresa Carioti	Y, Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Donna Przepiorka	Y
	TL:	Al Deisseroth	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Pengfei Song	Y
	TL:	Nitin Mehrotra Qi Liu	Y, Y
Biostatistics	Reviewer:	Chia-Wen Ko	Y
	TL:	Lei Nie	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brenda Gehrke, Tiffany Ricks, and Haw-Jhy Chiu	Y, N, N
	TL:	Haleh Saber and Christopher Sheth	N, Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	Reviewer:	Laura Salazar-Fontana	Y
	TL:	Susan Kirshner	N
Product Quality (CMC) - DMA	Reviewer:	Deborah Schmiel and Qing Zhou	Y, Y
	TL:	Rashmi Rawat	Y
BMAB - Micro	Reviewer:	Candace Gomez-Broughton and Maria Candauchaon	Y, Y
	TL:	Patricia Hughes	Y
CMC Labeling Review - OBP	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Rashmi Rawat	Y
Facility Review/Inspection	Reviewer:	Maria Candauchaon	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Neil Vora	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:	Naomi Reed	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orenca	N
	TL:	Janice Pohlman	N

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies): 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments List comments: 	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The clinical study design was acceptable and the application did not raise significant safety or efficacy issues.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Kris Kolibab, PhD, RPM Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): October 16, 2014 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

KRISTOPHER KOLIBAB
10/03/2014

AMY C BAIRD
10/03/2014