

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125557Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125557 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Hematology PDUFA Goal Date: _____ Stamp Date: 9/19/2014
3/19/2015

Proprietary Name: Blincyto

Established/Generic Name: blinatumomab

Dosage Form: lyophilized powder for solution

Applicant/Sponsor: Amgen, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

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

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 Disease/condition does not exist in children
 Too few children with disease/condition to study
 Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
09/29/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125557	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Blincyto Established/Proper Name: blinatumomab Dosage Form: lyophilized powder for solution		Applicant: Amgen, Inc. Agent for Applicant (if applicable): N/A
RPM: Kris Kolibab, PhD		Division: Division of Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 19, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|--|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other BURST
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval letter 12-3-2014
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 12-1-2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 9-19-2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 12-1-2014
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 10-16-2014
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 11-21-2014
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Acceptability letter 11-14-2014 Review 11-13-2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> 11-6-2014 DMEPA: <input checked="" type="checkbox"/> None DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 11-17-2014 OPDP: <input checked="" type="checkbox"/> 11-17-2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> OBP 11-20-2014
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	RPM Filing Review/Memo of Filing Meeting: 10/3/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Designation</u> 	Pediatric Page 9/29/2014
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	December 2, 1 (2), November 28, 26, 25 (2), 21 (2), 20, 18, 17 (2), 13, 11, 10 (2), 6, 5, 4, October 30 (2), 29, 28 (2), 24, 23 (3), 20, 19, 17 (3), 15, 14 (2), 10 (3), 9, 8, 7 (2), 6 (2), 2 (2), September 30 (2), 29 (2), 26, 23 (3), and 22 (3), 2014.
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	11-6-2014 TCON 10-23-2014 TCON 10-17-2014 TCON
❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg 6/23/2014 4/25/2013 10/17/2014 11/7/2014
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	12-3-2014
Division Director Summary Review (<i>indicate date for each review</i>)	12-2-2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11-24-2014
PMR/PMC Development Templates (<i>indicate total number</i>)	PMR - 1 PMC - 10
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	11-21-2014 review 11-21-2014 filing checklist 9-23-2014 <input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 18 clinical review 11-21-2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	reviews 12-3-2014, 11-26-2014, 11-23-2014, and 11-12-2014 <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	10-20-2014
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	11-17-2014 cosigned primary review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	11-17-2014 cosigned primary review
Statistical Review(s) (<i>indicate date for each review</i>)	Primary review 11-17-2014 Filing checklist 9-29-2014
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	11-17-2014 cosigned primary review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	11-17-2014 cosigned primary review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	Primary review 11-17-2014 Filing checklist 10-1-2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	11-10-2014
• Supervisory Review(s) (<i>indicate date for each review</i>)	11-9-2014
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	primary review 11-7-2014 filing checklist 9-30-2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review N/A
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	11-19-2014 OBP
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	OBP primary review 11-10-2014 Filing checklist 9-29-2014
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	BMAB primary review 11-19-2014 BMAB primary review 11-17-2014 Filing Checklist 10-2-2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 36 BMAB primary review 11-17-2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: 12-2-2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes N/A <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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
12/03/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, December 02, 2014 10:56 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/REMS Document IR/Immediate Response Requested
Attachments: REMS Doc Dec 2 FDA.doc

Importance: High

Hello Tai,

Please find attached the FDA revised version of the REMS document for your review for BLA 125557.

The BLINCYTO REMS Document (received by the Agency from the applicant via email on December 1, 2014 at 2:15 PM) requires minor changes to be acceptable to the Agency. See the following comments and the attached BLINCYTO REMS Document (that includes track changes):

BLINCYTO REMS Document includes the following minor changes:

- Rewording of the sequence of target providers with insertion of the text, “likely to administer BLINCYTO” following “infusion nurses”.
- Deletion of the use of (b) (4) in the REMS Document.
- Acceptance of the minor editorial change “the” before “BLINCYTO REMS website”.

Amgen is requested to accept the track changes in the attached BLINCYTO REMS Document and submit a clean WORD version of the BLINCYTO REMS Document to the Agency through the electronic Gateway by **12 Noon, (EDT), on December 2 ,2014.**

Please confirm receipt of this message via e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

3 Page(s) 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/

KRISTOPHER KOLIBAB
12/02/2014

Kolibab, Kristopher

From: Ramanadham, Mahesh
Sent: Tuesday, December 02, 2014 10:51 AM
To: Kolibab, Kristopher; Capacci-Daniel, Christina
Subject: RE: BLA 125557/TB EER
Attachments: Copy of Facility Report for BLA 125557.xls

Hi Kris

Attached is a facility recommendation report, modified from EES. This report captures the AC recommendations for all relevant sites.

Mahesh

From: Kolibab, Kristopher
Sent: Monday, December 01, 2014 11:29 AM
To: Ramanadham, Mahesh; Capacci-Daniel, Christina
Subject: RE: BLA 125557/TB EER

Hi Mahesh,

Thank you for your help in this matter. Please e-mail the TB EER when it comes available. I need it to complete the action package.

Thanks - Kris

From: Carioti, Theresa
Sent: Wednesday, November 26, 2014 3:54 PM
To: Ramanadham, Mahesh; Kolibab, Kristopher
Cc: Capacci-Daniel, Christina; Baird, Amy
Subject: RE: BLA 125557/TB EER

Great, thank you so much!

Can you have the final TBEER request uploaded into Panorama?

Theresa

From: Ramanadham, Mahesh
Sent: Wednesday, November 26, 2014 2:25 PM
To: Carioti, Theresa; Kolibab, Kristopher
Cc: Capacci-Daniel, Christina
Subject: RE: BLA 125557/TB EER

All good to go. Overall recommendation for inspection management is acceptable.

Mahesh

From: Carioti, Theresa
Sent: Tuesday, November 25, 2014 1:30 PM

Application	FEI	Establishment	Address	Country	Profile	Stage	Process	Last Milestone	Compliance Status	OAI Alert Status	EER Re-eval Date	Overall Recommendation
BLA 125557/000		(b) (4)	(b) (4)	(b) (4)	CBI	DRUG SUBSTANCE, FINISHED DOSAGE	MANUFACTURER, RELEASE TESTER	OC RECOMMENDATION	AC	"NONE"		ACCEPTABLE
BLA 125557/000		(b) (4)	(b) (4)		CTL	DRUG SUBSTANCE, FINISHED DOSAGE	RELEASE TESTER, STABILITY TESTER	OC RECOMMENDATION	AC	"NONE"	(b) (4)	ACCEPTABLE
BLA 125557/000		(b) (4)	(b) (4)		CBI	INTERMEDIATE	MANUFACTURER	NO FURTHER EVALUATION	NF	"NONE"		ACCEPTABLE
BLA 125557/000		(b) (4)	(b) (4)		CTL	DRUG SUBSTANCE	OTHER TESTER	OC RECOMMENDATION	AC	"NONE"		ACCEPTABLE
BLA 125557/000		(b) (4)	(b) (4)		SVS	FINISHED DOSAGE	MANUFACTURER, RELEASE TESTER	OC RECOMMENDATION	AC	"NONE"		ACCEPTABLE
BLA 125557/000	3003358885	AMGEN INC.	40 TECHNOLOGY WAY, RHODE ISLAND TECH SITE WEST GREENWICH RI 02817 USA	USA	CTL	DRUG SUBSTANCE, FINISHED DOSAGE	RELEASE TESTER, STABILITY TESTER	OC RECOMMENDATION	AC	"NONE"		ACCEPTABLE
BLA 125557/000	(b) (4)	(b) (4)	(b) (4)	(b) (4)	CTL	FINISHED DOSAGE	STERILITY TESTER	OC RECOMMENDATION	AC	"NONE"		ACCEPTABLE
BLA 125557/000	1000110364	AMGEN MANUFACTURING LIMITED, INC.	RD 31 KM 24.6 JUNCOS PR 00777 USA	USA	SVS	FINISHED DOSAGE	LABELER, PACKAGER	OC RECOMMENDATION	AC	"NONE"	3/28/2018	ACCEPTABLE
BLA 125557/000	2028154	AMGEN INC	1 AMGEN CENTER DR THOUSAND OAKS CA 91320-7599 USA	USA	CBI	INTERMEDIATE	MANUFACTURER	NO FURTHER EVALUATION	NF	"NONE"		ACCEPTABLE
BLA 125557/000	3002808497	AMGEN TECHNOLOGY IRELAND (FORMLY PFIZER IRELAND PHARMACEUTICALS)	POTTERY ROAD DUN LAOGHAIRE, DUBLIN / IRL POTTERY ROAD	IRL	CTL	FINISHED DOSAGE	STABILITY TESTER	OC RECOMMENDATION	AC	"NONE"	3/22/2016	ACCEPTABLE
BLA 125557/000	(b) (4)	(b) (4)	(b) (4)	(b) (4)	SVL	FINISHED DOSAGE	MANUFACTURER, RELEASE TESTER	OC RECOMMENDATION	AC	"NONE"	(b) (4)	ACCEPTABLE

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, December 01, 2014 11:39 AM
To: 'Yu, Tai'
Subject: BLA 125557/PI and Med Guide Acceptable/Official Submission

Importance: High

Hello Tai,

The Agency accepts the Med Guide and PI version received on November 26th, 2014 via e-mail. Please officially submit a clean version (PDF and word formats) of the Med Guide and PI to BLA 125557 as soon as possible.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [<mailto:tyu@amgen.com>]
Sent: Wednesday, November 26, 2014 6:53 PM
To: Kolibab, Kristopher; Chi, Amy H; Baird, Amy
Subject: RE: Correction - Response to BLA 125557/Revised PI/Due Nov 26

Hi Kris, Amy C, and Amy B.,

In review the PI, Amgen noticed that in the 2nd sentence of Section 6.1 the percentages for peripheral edema and febrile neutropenia are incorrect (see below). In the attached version (tracked changes and clean), this has been corrected to reflect the actual percentage in Table 2 Adverse Reactions With $\geq 10\%$ Incidence for Any Grade or $\geq 5\%$ Incidence for Grade 3 or Higher (N = 212) clean).

- Tracked changes version: S-blinatumomab-US-PI-v0.8-Initial USPI-AR 2014-1126
- Clean version: S-blinatumomab-US-PI-v0.8-Initial USPI-C 2014-1126

The most common adverse reactions ($\geq 20\%$) were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), and constipation (20%).

Serious adverse reactions were reported in 65% of patients. The most common serious adverse reactions

My apologies for any confusion this may cause.

Regards,

Deleted: (b) (4)
Deleted:

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Yu, Tai
Sent: Wednesday, November 26, 2014 10:04 AM
To: 'Kolibab, Kristopher'; Chi, Amy H
Subject: Response to BLA 125557/Revised PI/Due Nov 26

Hi Kris and Amy,

Attached please find Amgen's response (clean and tracked Word files) to the Agency's revised PI. We agreed to the Agency's addition of tremor and rash to the Adverse Reaction section in the Highlight page and the addition of the hyphen for "T-cell" in the Mechanism of Action section (12.1).

- Tracked changes version: S-blinatumomab-US-PI-v0.7-Initial USPI-AR 2014-1126
- Clean version: S-blinatumomab-US-PI-v0.7-Initial USPI-C 2014-1126

Amgen would appreciate the Agency's confirmation that this acceptable and consider final for approval. We would like to proceed to generating the PI in the fold-out format for printing.

Amgen will be closed for business on Thursday and Friday; however, our team will be available on Friday to respond to any questions the Agency may have. Please feel free to contact me with any questions you may.

Regards,
Tai H. Yu, MS
Regulatory Affairs
AMGEN
One Amgen Center Drive
17-2-A
Thousand Oaks, CA 91320
work: 805.447.2748
mobile: (b) (6)
email: tyu@amgen.com

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Tuesday, November 25, 2014 12:44 PM
To: Yu, Tai
Cc: Chi, Amy H
Subject: BLA 125557/Revised PI/Due Nov 26
Importance: High

Hello Tai,

Please find attached the FDA revised version of the PI for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)

After you have made the changes, please email a revised Med Guide (in tracked changes word document) to **me and Amy Chi** by **5PM (EDT) Wednesday, November 26, 2014.**

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
12/01/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, December 01, 2014 11:14 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/PMC Clarification/Agency Response

Importance: High

Hello Tai,

The Agency does not agree with the additional language for PMCs 2 and 3.

As was indicated in Amgen's previous response,

(b) (4)

Therefore, we think that the addition should not be a part of the PMC. However, we have no objection to the entire initial response in general.

Regarding PMC 8, the Agency does not agree with the changes. PMC 8 relates to regulatory requirements for release testing (refer to 21 CFR 211.167(a) and 21 CFR 610.10 (b)) and is linked to product safety. If Amgen is not successful in developing a reliable endotoxin detection method within the timelines of the PMC, Amgen should request an extension and contact the Agency to set up a meeting to discuss a path forward.

Regarding PMC 9; the Agency agrees with the changes.

The Agency ask that Amgen provide a commitment officially to the BLA by 5pm (EDT) December 1, 2014.

Please confirm receipt of this message via e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

Hi Amy,

Thanks for the clarification. Prior to sending the PMR/PMCs to the BLA on Monday, Amgen requests clarification on PMCs #2, 3, 8 and 9 as indicated below. Amgen has proposed minor modifications to the PMCs that reflect the approach taken to fulfill the commitments as explained in Sequence Number 0018 (submitted 18 November 2014, attached). Are the modifications acceptable?

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Baird, Amy [<mailto:Amy.Baird@fda.hhs.gov>]
Sent: Friday, November 28, 2014 7:58 AM
To: Yu, Tai
Cc: Kolibab, Kristopher; Chi, Amy H; Carioti, Theresa; Leaman, Diane V
Subject: RE: Request for clarification: BLA 125557/PMR PMC Agreement

Tai,

Please disregard the FDA email dated November 26, 2014, wherein the FDA requested Amgen commit to Post-Marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs) for BLA 125557 Blincyto.

Below are the proposed PMRs and PMCs for BLA 125557 Blincyto. Please note the correction to PMC#5 (product name change and # of lots correction). We ask that Amgen provide a commitment officially NLT December 1, 2014.

Please submit an amendment stating that Amgen agrees with the following PMR and PMCs officially to BLA 125557.

PMR #####-1 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.

Final Protocol Submission: Completed 08/2014
Trial Completion: 08/2016
Final Report Submission: 06/2017

PMC#####-#2 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 report.

You will conduct this study according to the following schedule:

Final Report Submission: 04/2015

PMC #####-3 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 report.

You will conduct this study according to the following schedule:

Final Report Submission: 08/2016

PMC #####-4 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 report.

You will conduct this study according to the following schedule:

Final Report Submission: 01/2021

PMC #####-5 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.

You will conduct this study according to the following schedule:

Final Report Submission: 10/2018

PMC #####-6 To conduct maximum hold time validation of (b) (4) for two additional batches (for a total of three batches).

You will conduct this study according to the following schedule:

Final Report Submission: 12/2016

PMC #####-7 To conduct bioburden qualification of (b) (4) and to conduct endotoxin method qualification of (b) (4)

You will conduct this study according to the following schedule:

Final Report Submission: 4/2015

PMC #####-8 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.

You will conduct this study according to the following schedule:

Final Report Submission: 10/2015

PMC #####-9 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 input materials.

You will conduct this study according to the following schedule:

Final Report Submission: 12/2015

PMC #####-10 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.

You will conduct this study according to the following schedule:

Final Report Submission: 02/2015

PMC #####-11 To conduct (b) (4)
The results from these studies will be used to support the proposed (b) (4)
s supported by currently available microbial data.

You will conduct this study according to the following schedule:

Final Report Submission: 12/2015

Regards,

Amy Baird
Chief, Project Management Staff
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2329
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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
12/01/2014

Baird, Amy

From: Baird, Amy
Sent: Friday, November 28, 2014 10:58 AM
To: 'Yu, Tai'
Cc: Kolibab, Kristopher; Chi, Amy H; Carioti, Theresa; Leaman, Diane V
Subject: RE: Request for clarification: BLA 125557/PMR PMC Agreement

Tai,

Please disregard the FDA email dated November 26, 2014, wherein the FDA requested Amgen commit to Post-Marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs) for BLA 125557 Blincyto.

Below are the proposed PMRs and PMCs for BLA 125557 Blincyto. Please note the correction to PMC#5 (product name change and # of lots correction). We ask that Amgen provide a commitment officially NLT December 1, 2014.

Please submit an amendment stating that Amgen agrees with the following PMR and PMCs officially to BLA 125557.

PMR #####-1 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.

Final Protocol Submission: Completed 08/2014
Trial Completion: 08/2016
Final Report Submission: 06/2017

PMC#####-#2 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 report.

You will conduct this study according to the following schedule:
Final Report Submission: 04/2015

PMC #####-3 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 report.

You will conduct this study according to the following schedule:
Final Report Submission: 08/2016

PMC #####-4 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 report.

You will conduct this study according to the following schedule:

Final Report Submission: 01/2021

PMC #####-5 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.

You will conduct this study according to the following schedule:

Final Report Submission: 10/2018

PMC #####-6 To conduct maximum hold time validation of (b) (4) for two additional batches (for a total of three batches).

You will conduct this study according to the following schedule:

Final Report Submission: 12/2016

PMC #####-7 To conduct bioburden qualification of (b) (4) and to conduct endotoxin method qualification of (b) (4).

You will conduct this study according to the following schedule:

Final Report Submission: 4/2015

PMC #####-8 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.

You will conduct this study according to the following schedule:

Final Report Submission: 10/2015

PMC #####-9 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 input materials.

You will conduct this study according to the following schedule:

Final Report Submission: 12/2015

PMC #####-10 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.

You will conduct this study according to the following schedule:

Final Report Submission: 02/2015

PMC #####-11 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.

You will conduct this study according to the following schedule:

Final Report Submission: 12/2015

Regards,

Amy Baird
Chief, Project Management Staff
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2329
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Yu, Tai [mailto:tyu@amgen.com]
Sent: Friday, November 28, 2014 9:17 AM
To: Baird, Amy
Cc: Kolibab, Kristopher; Chi, Amy H
Subject: Request for clarification: BLA 125557/PMR PMC Agreement

Dear Amy,

Amgen would like clarification regarding the Agency request to amend the BLA to state that Amgen agrees with the PMR and the ten CMC Postmarketing Commitments (PMCs) listed in the email received from the Agency on 26 November 2014 (below). Please refer to the attached BLA amendments previously submitted on November 18 and 19, 2014 (SN 0018 and 0020), which state Amgen's agreements to all of the CMC PMCs. Does the Agency agree that the referenced amendments adequately state Amgen's agreement to the PMCs? If the previously stated commitments are not adequate, Amgen would appreciate feedback regarding any changes that are needed to meet Agency requirements.

Regards,

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Chi, Amy H [<mailto:Amy.Chi@fda.hhs.gov>]
Sent: Wednesday, November 26, 2014 11:06 AM
To: Yu, Tai
Cc: Kolibab, Kristopher
Subject: RE: BLA 125557/PMR PMC Agreement
Importance: High

Dear Tai,

Please submit an amendment stating that Amgen agrees with the following PMR and PMCs officially to BLA 125557.

(b) (4)

Please contact us if you have any questions.

Thanks,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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

/s/

AMY C BAIRD
11/28/2014

Baird, Amy

From: Baird, Amy
Sent: Wednesday, November 26, 2014 9:32 PM
To: 'tyu@amgen.com'
Cc: Kolibab, Kristopher; Chi, Amy H; Carioti, Theresa
Subject: BLA 125557 Blincyto - REMS Documents

The DRISK has the following required revisions on the amendment to the proposed REMS for Blincyto (received on November 25, 2014) that the applicant must accept for the amendment on proposed REMS for Blincyto, all of the appended materials, the Blincyto REMS website (landing page), and the REMS assessment plan to be acceptable to the Agency. The Agency cites that these comments are provided using the substantially complete product labeling (PI) for Blincyto. All REMS communication plan materials must be revised to incorporate any changes to the final PI. Submit the below materials (including all track changes) to the Agency by 2:00 PM, Eastern Standard Time on December 1, 2014.

1. REMS Document

The 3rd bullet point in the Blincyto goals is revised to align informing pharmacists and nurses with the risks of preparation and administration errors, respectively. See the attached REMS Document with revisions (included in track changes) that must be accepted for this REMS Document to be accepted by the Agency. See **Attachment** of the REMS Document.

2. REMS Materials (see the Attachments)

The applicant must submit all the REMS appended materials in PDF format, so that FDA is able to view the actual layout of materials as they would be printed. We cannot comment on the usability of the materials if they are not presented with appropriate formatting. In addition, submit each of the REMS appended materials in WORD.

REMS Letters

If regular mail (print format) is the preferred method of distribution, the outside of the mailed envelopes should state: "**FDA Required REMS Safety Information**". It should be printed in red font, bolded and a minimum size 14 font. It may be on two lines and should be boxed.

FDA Required
REMS Safety Information

REMS Letters for Healthcare Providers (email and print versions)

- The proposed revisions are acceptable. No further comments.

REMS Letters for Hospital and Home Healthcare Pharmacists (email and print versions)

- See track changes that must be accepted in the **Attachment**.

REMS Letters for Professional Societies (print version)

- The proposed revisions are acceptable. No further comments.

REMS Letters for Professional Societies (email version)

- See track changes that must be accepted in the **Attachment**.

REMS Fact Sheet for Healthcare Providers

- See comments that must be accepted in the **Attachments**

REMS Website

- *REMS Letter for Hospital and Home Healthcare Pharmacists* must be included in the materials on the website landing page. See track changes that must be accepted in the attachment.

- The REMS website should be available via a prominent, REMS-specific link in the Blincyto commercial website for the duration of the REMS. This link should direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The separate REMS website should contain background information on the REMS along with the REMS appended materials. The content of the website should be easily viewed in a handheld device. Ensure that the REMS website, www.BLINCYTOREMS.com, is independent of links to the promotional and/or commercial website and non-REMS materials about the product.
- Do not include a link from the REMS website back to the [www.BLINCYTO](http://www.BLINCYTO.com) website. The REMS website should also be accessible directly through a search engine.

3. REMS Assessment Plan

The REMS assessment plan must include, but is not limited to the following:

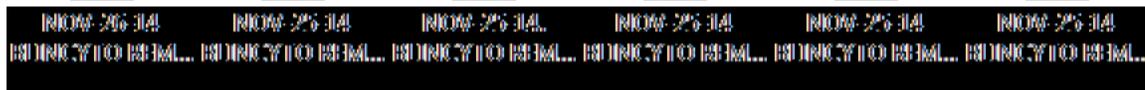
The REMS assessment plan must include, but is not limited to, the following:

1. An evaluation of healthcare providers' awareness and understanding of the following risks associated with Blincyto use. The evaluation should include only prescribers who have prescribed Blincyto, pharmacists who have prepared and dispensed Blincyto, and nurses who have administered Blincyto.
 - Life-threatening or fatal cytokine release syndrome
 - Severe, life-threatening or fatal neurological toxicities
2. An evaluation of pharmacists' and infusion nurses' awareness and understanding of the risks of preparation and administration errors associated with Blincyto. The evaluation should include only pharmacists who have prepared and dispensed Blincyto, and nurses who have administered Blincyto.
3. A description of the implementation of the communication plan, including
 - Number of healthcare providers, pharmacists, and professional societies targeted by the REMS.
 - Number of REMS letters sent to healthcare providers, pharmacists, and professional societies via email and standard mail with the dates the letters were sent. Include the number of letters sent via mail because the emailed letter was undeliverable. Also include the number of returned or undeliverable letters. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - Which professional societies distributed the REMS letters to their membership.
 - Sources of the distribution lists for healthcare providers and pharmacists
 - Number of REMS fact sheets distributed by Amgen representatives during follow-up details/visits with healthcare providers during the 12 months after approval of the REMS.
 - Date and name of the scientific meetings where Amgen had a booth and a list of the materials displayed.
 - Date the REMS website became active, and the number of unique site visits to the Blincyto REMS website during the assessment period.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

4. REMS Supporting Document

You are reminded that the REMS supporting document must be consistent with the revised proposed Blincyto REMS Document and all appended materials (as cited in these above comments with some additional track changes).



Regards,

Amy Baird

Chief, Project Management Staff

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 2329

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

13 Page(s) 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/

AMY C BAIRD
11/26/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, November 25, 2014 3:44 PM
To: Yu, Tai (tyu@amgen.com)
Cc: Chi, Amy H
Subject: BLA 125557/Revised PI/Due Nov 26
Attachments: blinatumomab PI Nov 25.doc

Importance: High

Hello Tai,

Please find attached the FDA revised version of the PI for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**

After you have made the changes, please email a revised Med Guide (in tracked changes word document) to **me and Amy Chi** by **5PM (EDT) Wednesday, November 26, 2014.**

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/25/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, November 25, 2014 3:00 PM
To: Yu, Tai (tyu@amgen.com)
Cc: Chi, Amy H
Subject: BLA 125557/Med Guide/Due Nov 25
Attachments: Blincyto Med Guide Nov 25.doc

Importance: High

Hello Tai,

Please find attached the FDA revised version of the Med Guide for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)

After you have made the changes, please email a revised Med Guide (in tracked changes word document) to **me and Amy Chi** by **5PM (EDT) Wednesday, November 25, 2014.**

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/25/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, November 21, 2014 9:15 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/REMS/Due Nov 24

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

The DRISK has the following necessary revisions on the proposed REMS for Blincyto (received by the Agency on October 29, 2014), the appended materials, and the Blincyto REMS website (landing page) to be acceptable to the Agency. The Agency notes that these comments are provided using the draft substantially complete product labeling (PI) for Blincyto. All REMS communication plan materials must be revised to incorporate any changes to the final PI. Submit the below materials (with the accepted track changes) and the new requested *REMS Letter to Hospital and Home Healthcare Pharmacists* by **5 pm (EDT) Monday** November 24, 2014.

1. REMS Document

See the attached REMS Document with the revisions (included in track changes). Language has been added that clarifies how healthcare providers will receive the *REMS Letter for Healthcare Providers*, the *REMS Letter for Professional Societies* and the *REMS Fact Sheet for Providers*. The *Patient/Caregiver Safety Information Wallet Card* is deleted from the proposed REMS for Blincyto as this material is considered duplication of the safety information provided in the Medication Guide to inform patients on the safety risks associated with Blincyto. See Comment # 4 below for comment on the timetable for submission of assessments to the FDA. See the **Attachments**, the REMS Document.

2. Communication Plan materials (see the **Attachments**)

Some of the formatting in the communication plan materials (e.g., spacing in sentences, text font size) was modified inadvertently as FDA reviewed/edited these documents. Revise any formatting as appropriate in each of the appended REMS materials.

- a. Accept the track changes in the *REMS Letter for Healthcare Providers* to be consistent with the substantially complete proposed blinatumomab labeling.
- b. Accept the track changes in the *REMS Letter to Professional Societies* to be consistent with the substantially complete proposed blinatumomab labeling.
- c. Revise and shorten the *REMS Fact Sheet for Providers* (per track changes) to be consistent with the substantially complete proposed blinatumomab labeling. This material has been condensed to focus on the serious risk of preparation and administration errors with the Blincyto continuous infusion over 4 weeks.
- d. Develop and submit to the Agency an additional material, a *REMS Letter for Hospital and Home Healthcare Pharmacists*, to support informing pharmacists in a hospital setting or in a home healthcare setting on the risk of preparation and administration errors with use of blinatumomab.
- e. Delete the *Patient/Caregiver Safety Information Wallet Card*.

3. BLINCYTO REMS Website

Amgen will ensure that all materials listed or appended to the REMS for BLINCYTO will be available through the Blincyto REMS program website, www.BLINCYTOREMS.com

4. Timetable for Submission of Assessments

The timetable for submission of assessments to the FDA will be at 18 months, 3 years, and 7 years.

5. REMS Assessment Plan

The Blincyto REMS Assessment plan will be forthcoming in under separate comments.



REMS
REMS ECRP Post
REMS Letter
REMS Letter Post
REMS
Blincyto.docx; Blincyto.docx; ECRP.docx; ECRP.docx; WeHealth.docx

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

26 Page(s) 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/

KRISTOPHER KOLIBAB
11/22/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 6, 2014

Application Number: BLA 125557

Product Name: blinatumomab

Sponsor/Applicant Name: Amgen, Inc.

Subject: To discuss the following:

1. DS and DP potency acceptance criterion
2. Reconstitution time in DP release specifications
3. DS protein concentration acceptance criterion in stability
4. Reference standard stability program

FDA Participants

Sarah Kennett, PhD, Review Chief

Rashmi Rawat, PhD, Team Leader

Qing Zhou, PhD, Biologist

Deborah Schmiel, PhD, Biologist

Kris Kolibab, PhD, Regulatory Project Manager

Sponsor/Applicant Participants

Matt Canning, Principal Product Quality Lead

Keith Cockerill, Manager, Regulatory Affairs CMC

Darrin Cowley, Executive Director, Product Quality

Mary Ellen Cosenza, Executive Director, Regulatory Affairs

Michelle Frazier, Director, Regulatory Affairs CMC

Angie Lint, Director, Product Quality

Chandra Ma, Senior Associate, Regulatory Affairs CMC

Mike McCormick, Principle Engineer, Drug Substance Process Development

Alex Mercier, Director, Product Quality

Brad Prater, Senior Scientist, Analytical Sciences

Ananth Sethuraman, Principal Scientist, Drug Product Process Development

Tai Yu, Senior Manager, Regulatory Affairs

1.0 BACKGROUND:

FDA requested a teleconference with Amgen to discuss blinatumomab CMC issues.

2.0 DISCUSSION:

FDA discussed the DS and DP potency acceptance criterion with the applicant and expressed their concern regarding the sponsor's proposed acceptance criterion for the potency assay ((b) (4) %) in response to IR dated Oct. 30, 2014, because the proposed acceptance criterion is not

supported by the potency of the DP lots used in the clinical trials, especially under protocol MT-211. FDA stated that based on an internal discussion with the clinical review team it was agreed that due to the narrow therapeutic window and safety risk to the patients due to cytotoxicity, it is important to have appropriately tight control over the product's potency. FDA suggested that a potency acceptance criterion of (b) (4) % is more appropriate based on the potency of the lots used in the study MT-211, which is the key study for this BLA, and other clinical studies. However, the applicant suggested a (b) (4) %; FDA agreed that the proposed (b) (4) % potency criterion is acceptable. FDA further stated that as more clinical experience is gained with the product, the criterion can be reassessed and modified. In order to do so, FDA told the sponsor that they would not request that the potency acceptance criterion be tightened for the product used under IND.

FDA informed the applicant that the reconstitution time should be included in the DP release specifications since this is an important attribute that can be affected by any change in the lyophilization process. The applicant agreed to include reconstitution time in DP release testing. The sponsor asked if a reconstitution time of (b) (4), based on overall data and knowledge, would be sufficient, or if a statistically derived acceptance criterion was expected. FDA agreed with acceptance criterion of (b) (4).

FDA and the applicant discussed the limit set for protein concentration on stability; no additional changes the proposed control strategy will be made at this time.

FDA stated that the plan for monitoring reference standard stability is not clearly described. A clear link between newly qualified reference standards and prior standards needs to be established. In addition, acceptance criteria (potency) for qualification of new reference standards or reference standard stability should be tighter than the DP release criteria to more easily identify reference standard drift/degradation. The sponsor responded that control samples are run as a system control to ensure acceptable assay performance and for monitoring trends with time. After discussion, the applicant agreed to tighten potency equivalence acceptance criterion to (b) (4) % by increasing the number of replicates run in the assay. Additional information will be submitted to the BLA.

3.0 ACTION ITEMS:

None.

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
11/21/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, November 21, 2014 2:58 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Labeling PI/Due Nov 24
Attachments: BLA 125557 PI Nov 21.doc

Importance: High

Hello Tai,

Please find attached the FDA revised version of the PI for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**

After you have made the changes, please email a revised PI (in tracked changes word document) to me by **3PM (EDT) Monday, November 24, 2014.**

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

20 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/

KRISTOPHER KOLIBAB
11/21/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, November 20, 2014 11:12 AM
To: 'Yu, Tai'
Subject: BLA 125557/Carton and Container Labels Acceptable/Official Submission

Importance: High

Hello Tai,

The carton and container labels and labeling are acceptable. Please officially submit this information to the BLA as soon as possible.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [mailto:tyu@amgen.com]
Sent: Wednesday, November 19, 2014 11:35 AM
To: Kolibab, Kristopher
Subject: RE: Response to BLA 125557/DMEPA CMC IR/Response Due Nov 19

Hi Kris,

Attached please find Amgen response to the CMC team and DMEPA comments for the vials, cartons, and PI (email below). Also attached are the revised vials and carton labeling. The clarification provided below is also included in the response document. These documents will be submitted to the BLA.

Amgen would appreciate the Agency's prompt feedback on the vials and carton labeling to allow progression to printing of these labeling for launch.

Regards,

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [mailto:Kristopher.Kolibab@fda.hhs.gov]
Sent: Monday, November 17, 2014 6:53 AM

To: Yu, Tai
Cc: Cupp, Crys
Subject: Agency Response to Clarification Questions - BLA 125557/DMEPA CMC IR/Response Due Nov 19
Importance: High

Hello Tai,

Please see our response below regarding your clarification questions. Please submit Container Labels and Carton Labeling by 2 PM (EDT) Wednesday November 19, 2014.

Clarification is needed regarding the Agency request to change the labeled amount of blinatumomab from (b) (4) mcg/vial to 35 mcg/vial to reflect the extractable amount.

- Should the excipients also be changed to extractable amounts (example text from Prescribing Information below)?

Yes, FDA will make the edits using tracked changes in the PI.

- Should Section 3.2.P.1 Description and Composition of Drug Product, Table 1, be updated with the extractable amounts?

Table 1 should remain as is. However, revise the first sentence in Dosage Form to state:

(b) (4)

- Should the word (b) (4) be added for clarification in the detailed text (carton and prescribing information)?

Overall, FDA will omit (b) (4) from all labeling.

Carton Labeling: state at the end of the list of ingredients of BLINCYTO vial: “After reconstitution with 3 mL of preservative free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.”

PI: FDA will make the edits using tracked changes in the PI.

- If the word (b) (4) is used in the detailed text, can it be omitted on the orange circular strength statement and other prominent strength statements on the vial and carton, which will show the strength as 35 mcg/vial?

Omit (b) (4)” on Carton Labeling and Container Label. Strength should appear as “35 mcg/vial”.

- (b) (4) ?

(b) (4) will be deleted in the PI. FDA will make the edits using tracked changes in the PI.

- Regards the Agency’s comment IIA1 (NDC code), Amgen would like clarify that the Blincyto vial and IV Solution Stabilizer vial labels currently contains NDC numbers 55513-150-01 and 55513-155-01, respectively. (b) (4)

No. The product codes for the inner components (Blincyto drug vial and IV SS vial) should differ from the outer carton. Currently, the outer carton and the Blincyto drug vial have the NDC. **Therefore, assign the Blincyto drug vial a unique product code.**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

From: Yu, Tai [<mailto:tyu@amgen.com>]
Sent: Tuesday, November 11, 2014 12:22 AM
To: Kolibab, Kristopher
Cc: Cupp, Crys
Subject: RE: Request for Clarification - BLA 125557/DMEPA CMC IR PI

Hi Kris,

Amgen is seeking clarification for the Agency's comment regarding the strength statement (comment IA1) and NDC numbers (comment IIA1).

Clarification is needed regarding the Agency request to change the labeled amount of blinatumomab from (b) (4) mcg/vial to 35 mcg/vial to reflect the extractable amount.

- Should the excipients also be changed to extractable amounts (example text from Prescribing Information below)?
- Should Section 3.2.P.1 Description and Composition of Drug Product, Table 1, be updated with the extractable amounts?
- Should the word (b) (4) be added for clarification in the detailed text (carton and prescribing information)?
- If the word (b) (4) is used in the detailed text, can it be omitted on the orange circular strength statement and other prominent strength statements on the vial and carton, which will show the strength as 35 mcg/vial?
- (b) (4) ?

Example text (Section 11 of PI)

BLINCYTO is supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-use vial of BLINCYTO contains (b) (4) 35 mcg blinatumomab (b) (4) citric acid monohydrate ((b) (4) 3.35 mg), lysine hydrochloride ((b) (4) 23.23 mg), polysorbate 80 ((b) (4) 0.64 mg), trehalose dihydrate ((b) (4) 95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free

Sterile Water for Injection, USP, the resulting (b) (4) 12.5 mcg blinatumomab.

Regards the Agency's comment IIA1 (NDC code), Amgen would like clarify that the Blincyto vial and IV Solution Stabilizer vial labels currently contains NDC numbers 55513-150-01 and 55513-155-01, respectively. (b) (4)

?

Regards,
Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Monday, November 10, 2014 11:51 AM
To: Yu, Tai
Cc: crys.cupp@amgen.com
Subject: BLA 125557/DMEPA CMC IR PI

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

DMEPA and CMC have reviewed your revised container labels and carton labeling submitted via email on November 3, 2014 and your response to our IR regarding withdrawable volume of reconstituted Blincyto submitted on November 6, 2014. The following deficiencies require your attention.

I. Prescribing Information: respond with your planned November 12, 2014 submission.

A. Strength Statement

1. 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 (b) (4) 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. (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidance/s/ucm389069.pdf>)

II. Container Labels and Carton Labeling: respond by 2PM (EDT) November 14, 2014.

A. General Comment

1. Assign the Blincyto vial and IV Solution Stabilizer vial a different NDC by revising the different product codes/second segment of the NDC. See <http://www.fda.gov/drugs/informationondrugs/ucm142438.htm>.

B. Carton Labeling

1. See comment I.A.1 regarding revision of Blincyto strength to 35 mcg/vial.
2. 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. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>
3. For CDER-regulated biological products, the proper name "blinatumomab" should not include the finished dosage form "for Injection". The dosage form should appear on the line below the proper name on the principal display panel (PDP) and all side panels and flaps (see aforementioned Guidance in comment B1).

Blincyto
(blinatumomab)
for Injection

4. Consider revising the strength of the product to increase the prominence of the measurement units "mcg" next to the numerical strength if space permits. Additionally, if space permits place "mcg" next to the numerical strength of the product to ensure comprehension of the strength.
5. If the statement, " (b) (4) " is intended to comply with US Customs Border and Protection country of origin regulation 19 CFR 134.11, revise the statement to read "Product of United Kingdom".

C. Blincyto Vial Container Label

1. See comment I.A.1 regarding revision of Blincyto strength to 35 mcg/vial.
2. See comment II.B.2 regarding capitalizing the first letter of the proprietary name, Blincyto.
3. For CDER-regulated biological products, the proper name "blinatumomab" should not include the finished dosage form "for Injection". The dosage form should appear on the line below the proper name. However if space is limited, you may omit the dosage form from this small container label. Thus, the PDP should appears as:

Blincyto
(blinatumomab)

or

Blincyto
(blinatumomab)
for Injection

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.

D. IV Solution Stabilizer Container Label

1. See comment II.B.2 regarding capitalizing the first letter of the proprietary name, Blincyto.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/20/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, November 18, 2014 11:00 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Labeling Package Insert/Due Nov 19
Attachments: BlincytoThesaurus.xpt; BLA 125557 PI Nov 18.doc

Importance: High

Hello Tai,

Please find attached the FDA revised version of the PI for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)
- The attached SAS transport file refers to a comment in the PI

After you have made the changes, please email a revised PI (in tracked changes word document) to me by **3PM (EDT) Wednesday, November 19, 2014.**

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

21 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/

KRISTOPHER KOLIBAB
11/18/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, November 17, 2014 10:44 AM
To: Yu, Tai (tyu@amgen.com)
Cc: crys.cupp@amgen.com
Subject: BLA 125557/Product Quality IR PMC/Immediate Response Requested

Importance: High

Hello Tai and Crys,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Product Quality Microbiology Review Team, please provide a response to the following information request **as soon as possible (Today)**.

Information Requests:

1. **Update BLA Section 3.2.P.3.5 to include qualification/validation information provided in Amendments 0005 and 0017.**

2. **Adjust the [REDACTED] (b) (4) or the IV stabilizer solution to reflect manufacturing capability.**

PMC:

To conduct an [REDACTED] (b) (4) The results from these studies will be used to support the proposed [REDACTED] (b) (4) [REDACTED] as supported by currently available microbial data.

PMC Schedule Milestones:

Final Report Submission: **MM/YYYY**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration*

*10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
11/17/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, November 17, 2014 9:53 AM
To: 'Yu, Tai'
Cc: Cupp, Crys
Subject: Agency Response to Clarification Questions - BLA 125557/DMEPA CMC IR/Response Due Nov 19

Importance: High

Hello Tai,

Please see our response below regarding your clarification questions. Please submit Container Labels and Carton Labeling by 2 PM (EDT) Wednesday November 19, 2014.

Clarification is needed regarding the Agency request to change the labeled amount of blinatumomab from (b) (4) mcg/vial to 35 mcg/vial to reflect the extractable amount.

- Should the excipients also be changed to extractable amounts (example text from Prescribing Information below)?

Yes, FDA will make the edits using tracked changes in the PI.

- Should Section 3.2.P.1 Description and Composition of Drug Product, Table 1, be updated with the extractable amounts?

Table 1 should remain as is. However, revise the first sentence in Dosage Form to state:

“(b) (4)” (b) (4)

- Should the word “(b) (4)” be added for clarification in the detailed text (carton and prescribing information)?

Overall, FDA will omit “(b) (4)” from all labeling.

Carton Labeling: state at the end of the list of ingredients of BLINCYTO vial: “After reconstitution with 3 mL of preservative free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.”

PI: FDA will make the edits using tracked changes in the PI.

- If the word “(b) (4)” is used in the detailed text, can it be omitted on the orange circular strength statement and other prominent strength statements on the vial and carton, which will show the strength as 35 mcg/vial?

Omit “(b) (4)” on Carton Labeling and Container Label. Strength should appear as “35 mcg/vial”.

- (b) (4)?

(b) (4) will be deleted in the PI. FDA will make the edits using tracked changes in the PI.

- Regards the Agency's comment IIA1 (NDC code), Amgen would like clarify that the Blincyto vial and IV Solution Stabilizer vial labels currently contains NDC numbers 55513-150-01 and 55513-155-01, respectively. (b) (4)

No. The product codes for the inner components (Blincyto drug vial and IV SS vial) should differ from the outer carton. Currently, the outer carton and the Blincyto drug vial have the NDC. **Therefore, assign the Blincyto drug vial a unique product code.**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [mailto:tyu@amgen.com]
Sent: Tuesday, November 11, 2014 12:22 AM
To: Kolibab, Kristopher
Cc: Cupp, Crys
Subject: RE: Request for Clarification - BLA 125557/DMEPA CMC IR PI

Hi Kris,

Amgen is seeking clarification for the Agency's comment regarding the strength statement (comment IA1) and NDC numbers (comment IIA1).

Clarification is needed regarding the Agency request to change the labeled amount of blinatumomab from (b) (4) mcg/vial to 35 mcg/vial to reflect the extractable amount.

- Should the excipients also be changed to extractable amounts (example text from Prescribing Information below)?
- Should Section 3.2.P.1 Description and Composition of Drug Product, Table 1, be updated with the extractable amounts?
- Should the word (b) (4) be added for clarification in the detailed text (carton and prescribing information)?

- If the word (b) (4) is used in the detailed text, can it be omitted on the orange circular strength statement and other prominent strength statements on the vial and carton, which will show the strength as 35 mcg/vial?
- (b) (4) ?

Example text (Section 11 of PI)

BLINCYTO is supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-use vial of BLINCYTO contains (b) (4) 35 mcg blinatumomab (b) (4), citric acid monohydrate (b) (4) 3.35 mg), lysine hydrochloride (b) (4) 23.23 mg), polysorbate 80 (b) (4) 0.64 mg), trehalose dihydrate (b) (4) 95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting (b) (4) 12.5 mcg blinatumomab.

Regards the Agency's comment IIA1 (NDC code), Amgen would like clarify that the Blincyto vial and IV Solution Stabilizer vial labels currently contains NDC numbers 55513-150-01 and 55513-155-01, respectively. (b) (4)

?

Regards,
Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Monday, November 10, 2014 11:51 AM
To: Yu, Tai
Cc: crys.cupp@amgen.com
Subject: BLA 125557/DMEPA CMC IR PI

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

DMEPA and CMC have reviewed your revised container labels and carton labeling submitted via email on November 3, 2014 and your response to our IR regarding withdrawable volume of reconstituted Blincyto submitted on November 6, 2014. The following deficiencies require your attention.

I. Prescribing Information: respond with your planned November 12, 2014 submission.

A. Strength Statement

1. 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) (b) (4) 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.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf>

II. Container Labels and Carton Labeling: respond by 2PM (EDT) November 14, 2014.

A. General Comment

1. Assign the Blincyto vial and IV Solution Stabilizer vial a different NDC by revising the different product codes/second segment of the NDC. See <http://www.fda.gov/drugs/informationondrugs/ucm142438.htm>.

B. Carton Labeling

1. See comment I.A.1 regarding revision of Blincyto strength to 35 mcg/vial.
2. 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. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>
3. For CDER-regulated biological products, the proper name "blinatumomab" should not include the finished dosage form "for Injection". The dosage form should appear on the line below the proper name on the principal display panel (PDP) and all side panels and flaps (see aforementioned Guidance in comment B1).

Blincyto
(blinatumomab)
for Injection

4. Consider revising the strength of the product to increase the prominence of the measurement units "mcg" next to the numerical strength if space permits. Additionally, if space permits place "mcg" next to the numerical strength of the product to ensure comprehension of the strength.
5. If the statement, " (b) (4) is intended to comply with US Customs Border and Protection country of origin regulation 19 CFR 134.11, revise the statement to read "Product of United Kingdom".

C. Blincyto Vial Container Label

1. See comment I.A.1 regarding revision of Blincyto strength to 35 mcg/vial.
2. See comment II.B.2 regarding capitalizing the first letter of the proprietary name, Blincyto.

3. For CDER-regulated biological products, the proper name “blinatumomab” should not include the finished dosage form “for Injection”. The dosage form should appear on the line below the proper name. However if space is limited, you may omit the dosage form from this small container label. Thus, the PDP should appear as:

Blinicyto
(blinatumomab)

or

Blinicyto
(blinatumomab)
for Injection

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.

D. IV Solution Stabilizer Container Label

1. See comment II.B.2 regarding capitalizing the first letter of the proprietary name, Blincyto.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/17/2014



BLA 125557/0

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Amgen, Inc.
One Amgen Center Drive
Mail Stop: 17-2-A
Thousand Oaks, CA 91320-1799

ATTENTION: Tai H Yu, MS
Senior Manager, Regulatory Affairs

Dear Mr. Yu:

Please refer to your Biologics License Application (BLA) dated September 19, 2014, received September 19, 2014, submitted under section 351(a) of the Public Health Service Act for Blinatumomab, (b)(4) mcg per vial.

We also refer to your September 26, 2014, correspondence, received September 26, 2014, requesting review of your proposed proprietary name, Blincyto.

We have completed our review of the proposed proprietary name, Blincyto and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your September 26, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Kris Kolibab, PhD, Regulatory Project Manager in the Office of New Drugs, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
11/14/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, November 13, 2014 1:08 PM
To: Yu, Tai (tyu@amgen.com); crys.cupp@amgen.com
Subject: BLA 125557/Stats IR/Immediate Response Requested

Importance: High

Hello Tai and Crys,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Stats Review Team, please provide a response to the following information request **as soon as possible**.

1. Regarding your clarification requested comment in label section 14, FDA does consider (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Please clarify the location of data supporting the minimum RFS to be (b) (4) in CR responders. Also clarify any discrepancy with the ADTTEEFF dataset.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/13/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, November 11, 2014 8:14 PM
To: Yu, Tai (tyu@amgen.com); crys.cupp@amgen.com
Subject: BLA 125557/CMC IR and PMCs/Due Nov 13

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC Review Team, please provide a response to the following information request by **3PM (EDT) Thursday November 13, 2014**.

1. Submit revised drug substance and drug product lot release and post-approval stability specifications, as were agreed upon in the November 6, 2014 submission to the BLA and November 7, 2014 email communication (response to the November 4, 2014 information request), to the appropriate BLA sections. Update the on-going stability studies, including the studies for the primary and the process validation lots, with the revised specifications and submit these updates to the appropriate sections of the BLA.
2. The acceptable range for the (b) (4) (Table 14, Section 3.2.S.2.2, (b) (4)) has not yet been updated based on the (b) (4). Update Table 14 according to the October 30, 2014 response to the October 20, 2014 CMC information request (Question 1; Table 12 foot note).
3. Regarding blinatumomab reference standard stability testing:
 - a. Clarify the reference standard (RS) lot (s) against which the potency of the primary and working RS were evaluated during the stability monitoring (i.e., the data included in Tables 54 and 55 of section 3.2.P.8.3).
 - b. Clarify the RS against which the current and future primary and working RS will be tested as part of the stability protocols (e.g., whether the potency of primary RS will be evaluated relative to the working RS).
 - c. The control strategy for monitoring the potency of the RS over time includes the use of the assay control that is included in routine potency testing. Multiple requirements for a valid assay result are included in the method SOP (UKSL-9050) section 18.1; these include a criterion of (b) (4) % for "% potency relative to reference of the control" and a "provisional" criterion of (b) (4) % for "% potency relative to reference of the (b) (4)." Clarify these assay acceptance criteria with respect to the assay control discussed in your November 7 email response to the November 4, 2014 information request. In addition, provide a description of the current method for trending the potency assay control, as discussed in the information request response.

4. Provide estimated dates for the completion of the following post-market commitments, which were discussed during the November 7, 2014 Late-Cycle Communication:
 - a. To perform real-time drug substance storage container leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of the dating period. The results of this study and the toxicology risk evaluation for the levels of leachates present in the drug substance will be provided in the final study report.
 - b. To perform real-time drug product storage container leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the (b) (4) end of the dating period. The results of this study and the toxicology risk evaluation for the levels of leachates present in the drug product will be provided in the final study report.
 - c. 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.
 - d. 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.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/11/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, November 10, 2014 2:51 PM
To: Yu, Tai (tyu@amgen.com)
Cc: 'crys.cupp@amgen.com'
Subject: BLA 125557/DMEPA CMC IR PI

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

DMEPA and CMC have reviewed your revised container labels and carton labeling submitted via email on November 3, 2014 and your response to our IR regarding withdrawable volume of reconstituted Blincyto submitted on November 6, 2014. The following deficiencies require your attention.

I. Prescribing Information: respond with your planned November 12, 2014 submission.

A. Strength Statement

1. 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) (b) (4) 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.
(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidance/s/ucm389069.pdf>)

II. Container Labels and Carton Labeling: respond by 2PM (EDT) November 14, 2014.

A. General Comment

1. Assign the Blincyto vial and IV Solution Stabilizer vial a different NDC by revising the different product codes/second segment of the NDC. See <http://www.fda.gov/drugs/informationondrugs/ucm142438.htm>.

B. Carton Labeling

1. See comment I.A.1 regarding revision of Blincyto strength to 35 mcg/vial.

2. 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. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>
3. For CDER-regulated biological products, the proper name "blinatumomab" should not include the finished dosage form "for Injection". The dosage form should appear on the line below the proper name on the principal display panel (PDP) and all side panels and flaps (see aforementioned Guidance in comment B1).

Blincyto
(blinatumomab)
for Injection

4. Consider revising the strength of the product to increase the prominence of the measurement units "mcg" next to the numerical strength if space permits. Additionally, if space permits place "mcg" next to the numerical strength of the product to ensure comprehension of the strength.
5. If the statement, "[REDACTED] (b) (4)" is intended to comply with US Customs Border and Protection country of origin regulation 19 CFR 134.11, revise the statement to read "Product of United Kingdom".

C. Blincyto Vial Container Label

1. See comment I.A.1 regarding revision of Blincyto strength to 35 mcg/vial.
2. See comment II.B.2 regarding capitalizing the first letter of the proprietary name, Blincyto.
3. For CDER-regulated biological products, the proper name "blinatumomab" should not include the finished dosage form "for Injection". The dosage form should appear on the line below the proper name. However if space is limited, you may omit the dosage form from this small container label. Thus, the PDP should appear as:

Blincyto
(blinatumomab)
or
Blincyto
(blinatumomab)
for Injection

4. Improve the color contrast between the [REDACTED] (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.

D. IV Solution Stabilizer Container Label

1. See comment II.B.2 regarding capitalizing the first letter of the proprietary name, Blincyto.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
11/10/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, November 10, 2014 11:50 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Drug Substance IR/Immediate Response Requested

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Drug Substance CMC review team, please provide a response to the following information request as soon as possible (today).

Information Requests:

- 1. Please refer to eCTD sequence number 17 received on 11/6/2014.**
Include endotoxin results prior to polysorbate addition as part of the drug substance CofA until a suitable endotoxin method for drug substance release is in place.
- 2. Please refer to eCTD sequence number 16 received on 11/5/2014.**
Include endotoxin results prior to polysorbate addition as part of the intravenous solution stabilizer (IVSS) CofA until a suitable endotoxin method for IVSS release is in place.

PMCs:

As we continue our review of your BLA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by TCON if needed.

Upon mutual agreement for the content and timing of all PMR/PMCs, submit to us, both by email and officially, the full text and the timeline for each PMR and PMC study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date. Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times. Final PMR designation numbers will be assigned later.

1. To conduct maximum hold time validation of [REDACTED] ^{(b) (4)} for two additional batches (for a total of three batches).

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>

Final Report Submission: MM/YYYY

2. To conduct bioburden qualification of [REDACTED] (b) (4)
and to conduct endotoxin method qualification of [REDACTED] (b) (4).

PMC Schedule Milestones: Final Protocol Submission: MM/YYYY
Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

3. 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: MM/YYYY
Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

4. To conduct a risk assessment to ensure microbial control and mitigate risks of endotoxin ingress during drug substance (DS), drug product (DP), and intravenous solution stabilizer (IVSS) manufacturing processes. Risk assessment mitigating factors should include endotoxin limits of input material.

PMC Schedule Milestones: Final Protocol Submission: MM/YYYY
Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

5. To assess the pyrogenic response in rabbits of drug product (DP) and intravenous stabilizing solution (IVSS) spiked with control standard endotoxin. If the pyrogenic response is positive, the rabbit pyrogen test should be used as an interim test until a reliable endotoxin detection method is developed.

PMC Schedule Milestones: Final Protocol Submission: MM/YYYY
Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs

**Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
11/10/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, November 05, 2014 3:28 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Labeling Package Insert/Due Nov 12
Attachments: Blinatumomab PI Nov 5.doc

Importance: High

Hello Tai,

Please find attached the FDA revised version of the PI for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**

After you have made the changes, please email a revised PI (in tracked changes word document) to me by **3PM (EST) Wednesday, November 12, 2014.**

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

24 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/

KRISTOPHER KOLIBAB
11/05/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, November 04, 2014 5:59 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Due Nov 6

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information request by **4pm (EDT) Thursday November 6, 2014**.

1. Regarding Blinatumomab Reference Standard:
 - a. Section 3.2.P.6 states that the primary reference standard (PRS) and working reference standard (WRS) are monitored on stability and that "future reference standard stability will be assessed according to a defined stability program"; however, the stability program was not described. Provide protocols for the evaluation of stability of the PRS and WRS. Include information on the testing frequency, analytical methods and acceptance criteria. Update the appropriate section(s) in the BLA with this information.
 - b. We note that the acceptance criteria listed in the stability testing result Tables for the current PRS and WRS (Section 3.2.P.8.3) are the same as those used for drug product (DP) stability monitoring. These acceptance criteria, specifically for the potency assay, are not acceptable for the purpose of monitoring stability of RS because they would not sufficiently control for a drift in drug substance and drug product potency. The potency of the PRS and WRS should be anchored to the potency at the time of the original qualification of the PRS. In the stability protocol/description of the stability program in the BLA, clearly define the criteria for monitoring the potency to prevent a drift of the reference standards and the commercial product.
2. Based on the information provided under the drug substance (DS) and DP stability sections 3.2.S.7.2 and 3.2.P.8.2, it is not clear if you expect to report extensions of the shelf life of the DS and DP in BLA annual reports based on the commercial lot data meeting the extended stability protocol criteria at the time points in the post-approval testing schedule. Update the BLA stability sections to reflect your plans for the extension of DS and DP shelf life.
3. The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 and 3.2.P.8.2) do not include information regarding the intention to submit data from the stability studies. Provide commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager

*Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
11/04/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 30, 2014 10:58 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Due Nov 3

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information request by **4pm (EDT) Monday November 3, 2014**.

1. Regarding blinatumomab drug substance (DS) and drug product (DP) lot release and stability specifications:
 - a. The DP protein content acceptance criterion (b)(4) proposed in response to the October 20, 2014 CMC information request (IR-3) question 6 is not acceptable. Due to the narrow therapeutic index of this product, the wide range of protein content raises safety and efficacy concerns. Revise the protein content acceptance criterion to (b)(4) for the DP release and stability specifications.
 - b. We do not agree with the justification that (b)(4) because there are limited DS and DP release and stability data and product and method characterization (or validation) data to support this claim (e.g., (b)(4)). The current control strategy of monitoring aggregates alone in DS and DP release and stability program does not provide sufficient control over the levels of (b)(4) in the DS and DP. Revise the DS and DP release and stability specifications to include monitoring of (b)(4) with appropriate acceptance criteria.
 - c. Different reference standard (RS) lots were generated at the time of major changes in blinatumomab manufacturing process (e.g., Process 3, 4, 5 and commercial process) and used for the lot release and stability testing for related lots. Therefore, your approach of using the (b)(4) tolerance interval calculations of combined lot release and stability data from Process 3, 4, 5 and commercial process DS lots to establish the acceptance criterion for blinatumomab DS potency is not appropriate. Based on the information provided on the lot release data from DP lots used to prepare RS lots AS2137-093A, 2071-073, 900427, RSN53808E, RSN100148 and 10010170301 (primary commercial RS lot) and additional information provided regarding qualification/testing of the RS lots, the potency of each DS and DP lot at the time of lot release was adjusted to estimate the potency of all clinical materials relative to the commercial primary RS. Based on the adjusted DS and DP lot release data from clinical materials manufactured using Process 3, 4, 5 or commercial process and what can be assessed regarding manufacturing capability based on a limited number of Process 5 and commercial process lots, the acceptance criterion for potency

should be tightened to “(b) (4) % relative to reference standard” for blinatumomab DS and DP lot release and stability.

- d. The lot release and stability data from historical DS and DP lots do not support your proposed acceptance criteria for color and clarity for the DS and DP release and stability specifications. The acceptance criteria for the color and clarity of blinatumomab should be tightened to (b) (4) respectively, for DS and DP lot release and stability.
 - e. We note that the (b) (4) DS is performed as an in process test. Include the result of the (b) (4) from the in-process testing (final measurement) on the DS Certificate of Analysis (CoA).
 - f. The current acceptance criterion for protein concentration for DS in stability studies is too wide and is insufficient to provide control over DS protein concentration during storage. Based on the fact that the DS protein concentration can be variable between different DS batches, we recommend that monitoring of the DS protein concentration during stability should be performed based on a percent change relative to the actual DS protein concentration reported in the DS lot release CoA. Update the stability protocol acceptance criterion to ensure that adequate control over DS protein concentration is implemented.
 - g. Your justification for excluding reduced SDS-PAGE for the control of DP is not adequate. This assay provides control over the (b) (4). The proposed DP control strategy includes no other assay that would detect this impurity. Therefore, reduced SDS-PAGE assay should not be removed from the DP lot release and stability specifications. Update the specifications to provide adequate control of (b) (4).
 - h. Include “Reconstitution time”, with appropriate acceptance criterion, in the DP lot release and stability specifications.
2. Update appropriate BLA sections (Sections 1.1.2, 3.2.S.2.1, 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.1, 3.2.P.3.3 and 3.2.P.3.4) according to your responses to CMC information requests including but not limited to IR-1, question 1; IR-2 dated Oct. 7, 2014, question 7; and IR-3 questions 1 and 3a.
 3. In Section 2.3.S, pg. 8, the IPC for (b) (4) step is listed as (b) (4) %,” which is inconsistent with the control for (b) (4) listed in Figure 1 in Section 3.2.S.2.2 and Table 5 in section 3.2.S.2.4. Correct the error in section 2.3.S.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products

*Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
10/30/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 30, 2014 11:25 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Due Nov 5

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information request by **3pm (EDT) Wednesday November 5, 2014**.

- 1. The Blincyto preparation instructions state that after reconstitution with 3 mL of Sterile Water for Injection, USP, the resulting volume is ^{(b) (4)} mL with a concentration of 12.5 mcg/mL. Provide data from extractable volume testing to justify the withdrawable volume of reconstituted Blincyto solution (mL) and amount of Blincyto (mcg).**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/30/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, October 29, 2014 3:32 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Drug Substance IR/Follow up to eCTD #10/Due Oct 3

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014 and the amendment received on October 21, 2014 (eCTD sequence number 10).

Per the request of the Microbial Quality - Drug Substance review team, please provide a response to the following information request by **3pm (EDT) Monday November 3, 2014**.

Control of Critical Steps and Intermediates (S.2.4)

- [REDACTED] (b) (4)
- [REDACTED]

Process Validation and/or Evaluation – Process Validation Batches (S.2.5.2)

- With regard to your response to item 4.a, submit results of the [REDACTED] (b) (4) validation study for microbial control.
- With regard to your response to item 4.b, include endotoxin monitoring in the [REDACTED] (b) (4) study and indicate when the study will be conducted and when (date) the results will be submitted to the Agency

Process Validation and/or Evaluation – Shipping Validation (S.2.5.3)

- With regard to your response to item 5.b, amend the BLA to show the actual container used for Blinatumomab DS shipping.
- With regard to your response to item 5.c, clarify which shipper was used for the vibration and shock studies; if the shipper was not the actual one used for DS transportation justify your response. Clarify if temperature was monitored during and after the shipping simulation studies, provide acceptance criteria and indicate if the results were within the acceptance criteria.

Analytical Procedures (S.4.2)

With regard to your response to item 7.b, there are several methods that comply with USP <85>. Provide a description of the method used, concentrations of the standard curve, how positive and negative controls are prepared, routine dilutions used for each type of sample, and acceptance criteria.

Validation of Analytical Procedures – Bioburden Method Qualification (S.4.3)

With regard to your response to item 8.a, [REDACTED] (b) (4)

in section 3.2.S.4.2 and indicate when (date) the qualification will be submitted to the Agency.

Validation of Analytical Procedures – Endotoxin Method Qualification (S.4.3)

- With regard to your response to item 9.a, (b) (4)

Based on your response to Question 9.c, it appears that your current endotoxin test method may not be reliable in detecting endotoxin in drug substance due to low endotoxin recovery; therefore, a reliable endotoxin detection method for the previous (b) (4) is critical and the qualification of the (b) (4) should be conducted. Conduct endotoxin qualification for the (b) (4) indicate when those studies will be conducted and when (date) the results will be submitted to the Agency.

- With regard to your response to item 9.c, (b) (4)

conduct unmasking studies to develop a reliable alternative endotoxin detection method.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
 Regulatory Health Project Manager
 Division of Hematology Products
 Office of New Drugs
 Center for Drug Evaluation and Research
 Food and Drug Administration
 10903 New Hampshire Avenue, Rm 2311
 Silver Spring, MD 20903

Phone: 240-402-0277

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
10/29/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, October 28, 2014 10:16 AM
To: 'Yu, Tai'
Subject: BLA 125557/PMR for Blinatumomab/Agreed Milestone Dates

Importance: High

Hello Tai,

The Agency agrees with the milestone dates. Please officially submit this information to the BLA.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [<mailto:tyu@amgen.com>]
Sent: Monday, October 27, 2014 8:03 PM
To: Kolibab, Kristopher
Subject: RE: Response to BLA 125557/PMR for Blinatumomab

Hi Kris,

Below please find the PMR study milestones dates. Amgen agrees to the PMR description without changes. Can you confirm if I can go ahead and submit this to the BLA?

PMR Description: CONFIRMATORY TRIAL- Complete the trial and submit the final study 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 study 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:	Final Protocol Submission:	<u>08/2014</u>
	Trial Completion:	<u>08/2016</u>
	Final Report Submission:	<u>06/2017</u>

Regards,

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Friday, October 17, 2014 12:29 PM
To: Yu, Tai
Subject: BLA 125557/PMR for Blinatumomab

Hello Tai,

Please refer to the BLA 125557 blinatumomab received September 19, 2014, which provides for the proposed indication "treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL)."

As we continue our review of your BLA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by TCON if needed.

Upon mutual agreement for the content and timing of all PMR/PMCs, submit to us, both by email and officially, the full text and the timeline for each PMR and PMC study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date. Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times. Final PMR designation numbers will be assigned later.

#1

BLA # 125557
Product Name: blinatumomab

PMR Description: CONFIRMATORY TRIAL- Complete the trial and submit the final study 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 study 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:	Final Protocol Submission:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

Regards,

Kris Kolibab, Ph.D.

**Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/28/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, October 28, 2014 5:16 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Quality Micro IR/Due Nov 3

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Quality Micro review team, please provide a response to the following information request by **3pm (EDT) Monday November 3, 2014**.

Section 3.2.P.3.3 Description of Manufacturing and Process Controls

Indicate if the proposed  (b) (4) of the manufacturing process.

Section 3.2.P.3.5 Process Validation



(b) (4)

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/28/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 24, 2014 9:19 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Follow up from TCON

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information requests.



Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/24/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 23, 2014

Application Number: BLA 125557

Product Name: Blinatumomab

Sponsor/Applicant Name: Amgen, Inc.

Subject: To discuss manufacturing and inspection plans for blinatumomab

FDA Participants

Ann T. Farrell, MD, Director

Albert Deisseroth, MD, PhD, Medical Officer, Clinical Team Leader

Donna Przepiorcka, MD, PhD, Medical Officer

Kris Kolibab, PhD, Regulatory Project Manager

Patricia Hughes, PhD, Team Leader

Reyes Candau-Chacon, PhD, Biologist

Rashmi Rawat, PhD, Team Leader

Deborah Schmiel, PhD, Biologist

Gerald Feldman, PhD, Biologist

Sponsor/Applicant Participants

Amgen Attendees

Keith Cockerill, Manager, CMC Regulatory Affairs

Michelle Frazier, Director, CMC Regulatory Affairs

Brent Kendrick, Director Process Development

David Kolwyck, Principal Scientist

Paul Lewus, Director, Process Development

Angie Lint, Product Quality Director

Chandra Ma, Sr. Associate, Regulatory Affairs

Michael McCormick, Principal Engineer, Process Development

Brad Prater, Sr. Scientist, Attribute Sciences

Dvora Szego, Sr. Manager, Contract Manufacturing Quality

Troy Wright, Director, Contract Manufacturing Quality

Tai Yu, Sr. Manager, Regulatory Affairs

(b) (4)

1.0 BACKGROUND:

FDA requested a teleconference with (b) (4) and Amgen to discuss the manufacturing and inspection plans for blinatumomab.

2.0 DISCUSSION:

FDA requested clarification of the timeline for the manufacturing of blinatumomab. (b) (4) indicated the process is underway and are ready for the pre-approval inspection next week. FDA also asked (b) (4) to provide a table to indicate what equipment is multi-purpose versus strictly blinatumomab only equipment; (b) (4) agreed to provide the information. FDA asked when the product quality results will be available from the pilot study and the GMP run that was started on 10/23/2014. (b) (4) said for the pilot study late December and for the GMP run early January. FDA also asked how much clinical launch material is available and how much is used per month. Amgen indicated they have enough material for launch and a (b) (4) supply however these numbers will be confirmed with an information request sent by FDA.

3.0 ACTION ITEMS:

FDA will be sending information requests for more information regarding the product quality and confirmation of the (b) (4) of blinatumomab.

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
10/24/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 23, 2014 9:35 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical IR 2/Due Oct 27

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Clinical review team, please provide a response to the following information request by **12pm (EDT) Monday October 27, 2014**.

Please provide 30- and 90-day mortality rates for the 1139 subjects in the primary analysis set for the historical controls in Study 20120310. Specifically provide:

- a) Deaths \leq 30 days from start of therapy: #/1139 (% , 95% CI)
- b) Death \leq 90 days from start of therapy: #/1139 (% , 95%CI)

Indicate whether your calculation is binomial or the KM estimate. Describe any limitations or caveats regarding your calculation.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
10/23/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 23, 2014 9:25 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical IR/Due Oct 27

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Clinical review team, please provide a response to the following information request by **4pm (EDT) Monday October 27, 2014**.

1. **What is the amount of clinical launch material you have on hand?**
2. **What is the projected use per month for this product?**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
10/23/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 23, 2014 2:42 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Microbial Quality IR/Due Oct 30

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the Microbial Quality review team, please provide a response to the following information request by **3pm (EDT) Thursday October 30, 2014**.

1. Specifications

(b) (4)

2. Analytical Procedures

For Blinatumomab DP and IVSS, submit the following in section 3.2.P.5.2 of the BLA:

a.

(b) (4)

b.

c.

3. Validation of Analytical Procedures

a.

(b) (4)

b.

c.



(b) (4)

4.



(b) (4)

5. Submit report for the rabbit pyrogen test.

6. Justification to Specification: Submit endotoxin “Justification to Specification” for the IVSS in section 3.2.P.5.6 of the BLA. Justification of endotoxin specification of lyophilized Blinatumomab and IVSS should consider the complete material that is infused into the patient, i.e. lyophilized product, IVSS stabilizer, and saline solution in the infusion bag.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/23/2014



BLA 125557

MID-CYCLE COMMUNICATION

Amgen, Inc.
Attention: Tai H. Yu, MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Blincyto (blinatumomab).

We also refer to the teleconference between representatives of your firm and the FDA on October 17, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions contact, Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 17, 2014, 12:00 PM – 12:30 PM (EDT)

Application Number: BLA 125557
Product Name: Blincyto (blinatumomab)
Indication: Treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL).
Applicant Name: Amgen, Inc.

Meeting Chair: Albert Deisseroth, MD, PhD

Meeting Recorder: Kris Kolibab, PhD, RPM

FDA ATTENDEES

Division of Hematology Products (DHP):

Ann T. Farrell, MD, Director
Albert Deisseroth, MD, PhD, Medical Officer, Clinical Team Leader
Donna Przepiorka, MD, PhD, Medical Officer
Kris Kolibab, PhD, Regulatory Project Manager

Biotech Manufacturing Assessment Branch (BMAB):

Patricia Hughes, PhD, Team Leader
Reyes Candauchacon, PhD, Biologist
Candace Gomez-Boughton, PhD, Microbiologist

Division of Risk Management (DRISK):

Naomi Redd, PharmD, Acting Team Leader
Carolyn Yancey, MD, Medical Officer

Office of Biotechnology Products (OBP):

Sarah Kennett PhD, Review Chief
Deborah Schmiel, PhD, Biologist

Division of Hematology, Oncology, Toxicology (DHOT):

Christopher Sheth, PhD, Supervisory, Pharmacologist
Brenda Gehrke, PhD, Pharmacologist

Office of Biostatistics, Division of Biometrics V (DBV)

Lei Nie, PhD, Mathematical Statistician Team Leader

APPLICANT ATTENDEES

Deborah Arrindell, JD, MD, Executive Director, Global Safety
Keith Cockerill, PhD, Manager, Regulatory Affairs CMC
Mary Ellen Cosenza, PhD, Executive Director, Global Regulatory Affairs
Crystina Cupp, PhD, Director, Global Regulatory Affairs
Michelle Frazier, PhD, Director, Regulatory Affairs CMC
Greg Freiberg, MD, Executive Director, Clinical Development
Christopher Holland, MS, Director, Biostatistics
Catherine Jia, Senior Manager, Biostatistics
Bill Kormany, MD, Director, Global Safety
Rick Lit, Vice President, Regulatory Affairs CMC, Devices, and Biosimilars
Chandra Ma, Senior Associate, Regulatory Affairs CMC
Tap Maniar, MD, Director, Global Development
Dirk Nagorsen, MD, PhD, Director, Global Development Leader
David Reese, MD, Vice President, Translational Sciences
Katie Sprugel, PhD, Scientific Director, Toxicology Sciences
Mark Taisey, Vice President, Global Regulatory Affairs
Rhian Thomas, BSc, Executive Director, Global Regulatory Affairs
Tom Sun, PhD, Director, Pharmacokinetics and Drug Metabolism
Jackie Wright, BScRN, Director, Global Safety
Tai Yu, MS, Senior Manager, Global Regulatory Affairs
Min Zhu, PhD, Scientific Director, Pharmacokinetics and Drug Metabolism

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical

1. The primary endpoint of Protocol MT103-211 is CR+CRh*. We have accepted CR with durability as reasonably likely to predict clinical benefit, but the value of CRh* is not established, and the use of that component of the endpoint in regulatory decision-making is still under review.
2. If your product is approved under Subpart E, you will need to provide confirmatory evidence of clinical benefit as a postmarketing requirement.

Manufacturing

3. A separate teleconference was planned to discuss potential changes to the drug substance (DS) manufacturing schedule.

3.0 INFORMATION REQUESTS

Clinical

1. Among the 475 individuals treated with blinatumomab, we have identified 30 subjects whose deaths were considered related to the treatment with your product. As requested by email 10/15/2014, you will need to provide additional information about these cases, including a root cause of death and your rationale for the determination of the root cause of death in each case.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

1. We list below several major safety issues that may affect labeling. Additional information request regarding these issues will be sent to you with the first review of the Prescribing Information.
 - a) Infusion reactions, cytokine release syndrome and capillary leak syndrome appear to occur in the same timeframe after start of therapy and have overlapping manifestations. We have not been able to clearly distinguish these events. Since they are all presumed to be mediated by cytokines released in response to your product, we view them as a single toxicity. Your labeling should describe the manifestations under a single entity, so that healthcare providers can initiate proper intervention on the basis of the etiology rather than arbitrary designations.
 - b) We have identified cytokine release syndromes and neurotoxicity as serious and potentially fatal complications from treatment with blinatumomab that may require a boxed warning.
 - c) We have identified cytokine release syndrome, neurotoxicity, neutropenia and potential medication errors as serious complications from treatment with blinatumomab that may require warnings in the labeling.
2. A substantial proportion of the treatment period with blinatumomab may occur in the home setting without direct supervision of a healthcare provider. Several of the toxicities that require dose interruption to avoid serious or fatal events may occur during this period. A Medication Guide will be required in order to apprise the patient of these potentially serious risks and what actions should be taken when they occur outside a healthcare facility.

3. In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Blincyto (blinatumomab) to ensure that the benefits of the drug outweigh the risks based on the risk reported in BLA 125-557 (received on September 19, 2014).

Your proposed REMS must include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe for Blincyto (blinatumomab) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the increased risk of cytokine release syndrome, neurologic events and medication errors associated with use of blinatumomab.

The communication plan must include, at a minimum, the following:

- Blincyto REMS Letter to Healthcare Providers
- Blincyto REMS Letter for Professional Societies
- Blincyto REMS Fact Sheet for Providers
- Journal Information Piece
- Blincyto Patient/Caregiver Safety Information Wallet Card
- Make Blincyto REMS materials available at professional meetings or conferences where commercial Blincyto product information is displayed.
- Blincyto REMS website (to include the above cited communication plan materials that will provide education on the serious risks with use of blinatumomab and US Prescribing Information)

Timetable for Submission of Assessments: The proposed Blincyto REMS must include a timetable for submission of assessments that shall be no less frequent than 1 year, 3 years, and 7 years after the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the Communication Plan REMS is meeting the goals of your REMS and whether the goals or elements should be modified.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a proposed REMS as a supplement to your BLA.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” All relevant proposed REMS materials including communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS.

Refer to the following Guidance for Industry for the correct format and content for your proposal and submit the necessary documents.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>.

In order to facilitate an efficient review of a proposed risk mitigation plan, all materials identified within the needed proposal that will be necessary to implement the plan should be submitted as soon as possible.

Proposed REMS submissions must be submitted as separate supplements to the BLA. For administrative purposes, designate the proposed REMS submission to be sent in response to this letter as “**PROPOSED REMS for BLA 125557**” and all subsequent submissions related to the proposed REMS as “**PROPOSED REMS-AMENDMENT for BLA 125557.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

We anticipate we will begin labeling discussions by November 5, 2014.

The Late-Cycle Meeting is tentatively scheduled to take place November 7, 2014.

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for November 7, 2014. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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

/s/

ALBERT B DEISSEROTH
10/21/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, October 20, 2014 2:02 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Due Oct 27

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information request by **3pm (EDT) Monday October 27, 2014**.

1. The process validation data provided in your response to question 7 from the September 30, 2014 CMC information request (IR; CMC IR-1) are incomplete. Question 7 included a request for the data for the operating parameters (OPs) listed in question 1. While these parameters might not have been included in the validation protocol, the data are expected to have been collected during the manufacturing process. Provide data corresponding to the OPs provided in your response to CMC IR-1 (i.e., OPs listed in Tables 1-5 and 7-20) for the three process validation batches.
2. Insufficient process characterization data to support the acceptable ranges (ARs) proposed for the OPs for the (b) (4) DS manufacturing process were provided in your response to CMC IR-1. The following data and additional information should be provided to justify the ARs:
 - a. In the response to CMC IR-1, Amgen indicates that (b) (4)

 - i. Provide the product quality assessment data and process performance data from these small scale studies and all additional characterization studies performed to support the ARs for the OPs for the (b) (4)
 - ii. We note that the ranges studied are not equivalent to the acceptable ranges listed in section 3.2.S.2.2. The small scale studies included only relatively short excursions to the extreme ends of the "acceptable" ranges. Therefore, it appears that the data would only support manufacturing at these extremes for the duration of the excursions and would not support routine manufacturing at these extremes. The description of the manufacturing process and process controls (section 3.2.S.2.2) should be adjusted to include "acceptable" ranges that are supported by characterization and other process development data. Identify the adjustments that will be made.

- b. In your response to CMC IR-1, Amgen indicates that process characterization studies using small scale models were performed to evaluate operating parameters for [REDACTED] (b) (4) operations (page 28-29, Table 26). Provide the product quality assessment data and process performance data from these small scale studies and all additional characterization studies performed to support the ARs for the OPs for [REDACTED] (b) (4).
- c. Provide any additional Process 5 manufacturing data used to set the operating ranges for the OPs listed in Tables 1-5 and 7-20 in your response to IR-1.
- d. It appears that CMC IR-1 question 3/3d was not clear. [REDACTED] (b) (4)

[REDACTED]

3. Regarding analytical procedures and their validation:

- a. The information provided in your response to CMC IR-1 (Table 18) indicates that a total of six testing facilities are involved in the testing for blinatumomab drug substance (DS) and drug product (DP) lot release and stability. However, each facility is qualified for performing only some, but not all, tests for lot release and stability. Therefore, information/tables in the related BLA sections (Sections 1.1.2, 3.2.S.2.1 and 3.2.P.3.1) should be updated to specify the tests each facility can perform, according to the current status of method validation/method transfer provided in your response to IR-1. Remove the facilities at which method transfer is on-going from the list of manufacturer(s) in Sections 3.2.S.2.1 and 3.2.P.3.1. Data from completed method transfer studies should be submitted to the BLA prior to performing these blinatumoamb lot release and stability tests in the additional testing facilities.
- b. It appears that two assays [REDACTED] (b) (4) have been used to determine [REDACTED] (b) (4) levels in blinatumomab samples during development (CSRP-000233, page 53-54), and the results show [REDACTED] (b) (4) [REDACTED] detected in the same samples using these two assays. Clarify which assay will be used for the control of [REDACTED] (b) (4) for the commercial process and identify the assay for which the validation report (RPT-048395) and qualification of [REDACTED] (b) (4) was provided in your response to the October 7, 2014 CMC IR (CMC IR-2).

4. We note that in your response to CMC IR-1 (Table 15), [REDACTED] (b) (4)

[REDACTED]

5.

6.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/20/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 17, 2014

Application Number: BLA 125557

Product Name: Blinatumomab

Sponsor/Applicant Name: Amgen, Inc

Subject : To discuss the raw materials issue with (b) (4) and Amgen

FDA Participants

Ann T. Farrell, MD, Director

Albert Deisseroth, MD, PhD, Medical Officer, Clinical Team Leader

Kris Kolibab, PhD, Regulatory Project Manager

Patricia Hughes, PhD, Team Leader

Reyes Candau-Chacon, PhD, Biologist

Sarah Kennett PhD, Review Chief

Rashmi Rawat, PhD, Team Leader

Deborah Schmiel, PhD, Biologist

Qing Zhou, PhD, Biologist

Sponsor/Applicant Participants

Amgen attendees

Keith Cockerill, Ph.D. Manager, Regulatory Affairs CMC

Michelle Frazier, Ph.D., Director, Regulatory Affairs CMC

Greg Freiberg, M.D., Executive Director, Clinical Development

Rick Lit, Vice President, Regulatory Affairs CMC, Devices, and Biosimilars

Chandra Ma, Senior Associate, Regulatory Affairs CMC

Tap Maniar, M.D., Director, Global Development

Tai Yu, M.S., Senior Manager, Global Regulatory Affairs

(b) (4) attendees

(b) (4)

1.0 BACKGROUND:

FDA requested a teleconference with (b) (4) and Amgen to discuss the raw materials issue.

2.0 DISCUSSION:

FDA requested clarification of the raw materials issue with manufacturing of blinatumomab.

(b) (4)

(b) (4)

(b) (4) was not able to provide a timeline for when they will be able to resume manufacture of blinatumomab. FDA indicated that it would send an information request through Amgen for further clarification on this issue.

3.0 ACTION ITEMS:

FDA will be sending information requests for more information regarding the status of the (b) (4) issue.

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
10/20/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Sunday, October 19, 2014 8:34 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/BMAB IR

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the biotech manufacturing assessment branch (BMAB), please provide the following requested information.

According to the T-con on Oct 17, 2014 between FDA, Amgen, and (b) (4) the manufacturing schedule for blinatumomab at the drug substance (DS) manufacturing facility at (b) (4) has been postponed due to (b) (4)

A prelicense inspection of the (b) (4) facility is currently scheduled for (b) (4) and may have to be postponed due to the inability to manufacture blinatumomab DS. Based on the recent developments we have the following questions:

1. Please summarize the problems encountered with the (b) (4) and the root cause analysis to date. The summary should include:
 - a. How the issue was identified.
 - b. Information and all available data to show the difference(s) between this lot of (b) (4) and the previous lots (e.g., dissolution properties, structural properties, impurities profile).
 - c. Investigation into changes/differences in the (b) (4) manufacturing process that could potentially lead to the (b) (4) quality differences that have been identified.
2. Can an alternative supplier of (b) (4) be identified, if (b) (4) from the current supplier is found to be unsuitable for use in manufacture? If so, describe the plans for qualification of this supplier and qualification of the use of the new (b) (4) in manufacturing of blinatumomab (e.g., cell growth and product quality evaluations).
3. Provide a summary of your current plans to resolve the (b) (4) problems and to reinstate DS manufacturing.
 - a. If the current (or similar) lot of (b) (4) is determined by Amgen to be suitable for use in commercial manufacturing of blinatumomab DS, provide:
 - i. the rationale, including data regarding the (b) (4) properties, for such a determination;
 - ii. manufacturing process and product quality data to support that the root cause differences in (b) (4) lots would not lead to differences in the quality of blinatumomab manufactured using the (b) (4)
 - b. Please let us know when you are able to resume manufacture of blinatumomab DS in order to proceed with the prelicense inspection planning.
4. Provide updated information regarding the root cause analysis and plans as they become available.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/19/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 17, 2014 3:29 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/PMR for Blinatumomab

Hello Tai,

Please refer to the BLA 125557 blinatumomab received September 19, 2014, which provides for the proposed indication "treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL)."

As we continue our review of your BLA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by TCON if needed.

Upon mutual agreement for the content and timing of all PMR/PMCs, submit to us, both by email and officially, the full text and the timeline for each PMR and PMC study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date. Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times. Final PMR designation numbers will be assigned later.

#1

BLA # 125557
Product Name: blinatumomab

PMR Description: CONFIRMATORY TRIAL- Complete the trial and submit the final study 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 study 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:	Final Protocol Submission:	<u>MM/YYYY</u>
	Trial Completion:	<u>MM/YYYY</u>
	Final Report Submission:	<u>MM/YYYY</u>

Regards,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager

*Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
10/17/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 17, 2014 9:05 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/DMEPA IR - Fold out PI vs Unfolded PI

Hello Tai,

Please provide a detailed explanation of what the fold-out version of the PI is versus the unfolded PI.

Amgen: Regarding the comments for vials and carton labeling, Amgen agrees to implement the FDA recommendations for the final approved labeling. Due to the tight timeline to create new labeling, Amgen will not be able implement these changes prior to the supplemental summative study. Upon review, Amgen considers that these changes are minor and will not affect the study endpoints of this supplemental summative study which is to determine if the modifications to specific steps in the IFA effectively mitigate the risk of use errors observed during safety critical steps in the original summative study.

FDA Response to carton and container: This is acceptable.

Thanks,
Kris

From: Yu, Tai [mailto:tyu@amgen.com]
Sent: Wednesday, October 15, 2014 4:07 PM
To: Kolibab, Kristopher
Subject: RE: BLA 125557/DMEPA IR/Due Oct 31

Hi Kris,

We acknowledge the Agency's comments below and would like to propose the following regarding the comments provided by the medication error prevention and analysis team. We would appreciate the team's feedback as soon as possible.

Amgen agrees to incorporate the FDA comments regarding the PI for the upcoming supplemental summative study (planned to start on October 20, Monday); however, Amgen would not be able to generate a fold-out version of the revised PI without delaying the study. We propose to create an unfolded revised PI with the layout that is similar to the fold-out version already in the blinatumomab package. During the study, the participant will open the blinatumomab package, remove and unfold a placeholder PI, upon which the moderator will provide the revised, unfolded PI to the participant to be used for the study. The study will then proceed accordingly per the supplemental summative study.

Does the Agency agree that this is acceptable?

Regarding the comments for vials and carton labeling, Amgen agrees to implement the FDA recommendations for the final approved labeling. Due to the tight timeline to create new labeling, Amgen will not be able

implement these changes prior to the supplemental summative study. Upon review, Amgen considers that these changes are minor and will not affect the study endpoints of this supplemental summative study which is to determine if the modifications to specific steps in the IFA effectively mitigate the risk of use errors observed during safety critical steps in the original summative study.

Regards,
Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Tuesday, October 14, 2014 6:58 AM
To: Yu, Tai
Subject: BLA 125557/DMEPA IR/Due Oct 31
Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014 and the human factors study protocol for the supplemental summative study. It has been determine the human factors study protocol is acceptable.

Per the request of the medication error prevention and analysis team, please provide a response to the following information request by **4pm (EDT) Friday October 31, 2014**.

The proposed labels and labeling, Instructions for Admixing (IFA), and PI can be improved to increase the readability and prominence of important information, to clarify information and promote the safe use of the product. We provide recommendations below. We recommend the following recommendations regarding the IFA and any other labels and labeling that will be used in the HF study are implemented before you conduct an HF study and HF study is conducted with revised labels and labeling;

A. PI, Section 2.5, Dosage and Administration, IFA

1. Consider developing separate Instructions for Admixing (IFA) in color that healthcare practitioners can refer to. This may help mitigate some of the errors seen in the Human Factors Study due to a lengthy procedure with many steps involved. Consider using different colors depending on the dose prepared and amount of time to infuse over. For example,
 - a. One color for 9 mcg over 24 hours,
 - b. Another color for 9 mcg over 48 hours,
 - c. Another color for 28 mcg over 24 hours, and
 - d. Another color for 28 mcg over 48 hours.
2. In Section 2.5 of the PI increase prominence of the following statement by bolding, **“It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose).”** We recommend increasing the prominence of this statement to mitigate possible preparation errors as

seen during the Human Factors study where participants did not use the provided IVSS and/or reconstituted blinatumomab using the IVSS instead of sterile water.

3. In Section 2.5.3-A of the PI, please bold and underline the statements after the first statement, **“Therefore, add IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride, USP. Do not use IV Solution Stabilizer for reconstitution of BLINCYTO.”** We provide this recommendation to increase the prominence of this instruction to reduce the likelihood of users using IVSS to reconstitute blinatumomab as seen during the Human Factors study.
4. In Sections 2.5.4.1, 2.5.4.2, 2.5.4.3, and 2.5.4.4 Step 3, please remove “(b) (4)” so the instructions read “The addition of preservative-free Sterile Water for Injection, USP to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.” We make this recommendation based on two errors from the Human Factors study where two participants added (b) (4) instead of 3 mL sterile water to the Blincyto during reconstitution. The current statement including “(b) (4)” does not provide any additional benefit, but adds confusion among many numbers as is.
5. In Sections 2.5.4.1, 2.5.4.2, 2.5.4.3 and 2.5.4.4 Step 2, please revise the statement to read “Using a 10 mL syringe, aseptically transfer 5.5 mL of **IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride.**” Also, bold the ending of the statement as stated above. We provide this recommendation to increase the prominence of how the IVSS should be used during preparation of blinatumomab, and reduce the likelihood of using the IVSS incorrectly due to errors seen in the HF study.
6. In Sections 2.5.4.1, 2.5.4.2, 2.5.4.3 and 2.5.4.4 Step 7, please bold and underline the statement **“prime the IV line only with prepared solution for infusion”** to increase its prominence. We provide this recommendation since two participants in the Human Factors study primed the IV tubing using Sodium Chloride instead of the prepared drug.

B. Blinatumomab Product Vial:

1. 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.
2. Revise the prominent strength presentation in the orange colored circle to “(b) (4) mcg/vial”. Consider deleting the duplicate strength presentations on this small label.
3. 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.
4. Please remove the abbreviation “(b) (4).” and revise the current statement “For I.V. Infusion Only” to “For Intravenous Infusion Only” to avoid any ambiguity with the route of administration.
5. Decrease the prominence of “Rx Only” to allow the user to read the most important information clearly.

6. 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)
(b) (4) mcg/vial
For Intravenous Infusion Only
Amgen Inc. US Lic No 1080 Rx Only

or

Trade Name
(blinatumomab)
for Injection
(b) (4) mcg/vial
For Intravenous Infusion Only
Amgen Inc. US Lic No 1080 Rx Only

C. IV Solution Stabilizer (IVSS) Vial:

1. Currently, the IV Solution Stabilizer vial label and blinatumomab vial label look identical in terms of colors, which may cause confusion and misinterpretation that both vials contain the active ingredient. Ensure that the IVSS vial label appears different from the blinatumomab vial in terms of use of coloring, so that there is no confusion between them.
2. Reduce the size of the trade name of the product and bold “IV Solution Stabilizer”, so that it is not confused with the blinatumomab vial and thus avoiding the likelihood of the IVSS being administered alone.
3. Revise the current statement of “(b) (4)” to “NOT FOR DIRECT RECONSTITUTION OF TRADE NAME” to make the instructions clear and direct.
4. 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 TRADE NAME
NOT FOR DIRECT RECONSTITUTION OF TRADE NAME

5. Decrease the prominence of “Rx Only” to allow the user to read the most important information clearly.
6. Place a volume statement on the label.

D. Carton Labeling:

1. Revise the prominent strength presentation in the orange colored circle to “ (b) (4) mcg/vial”.
2. Revise the dosage form (b) (4) to “for Injection” per USPC 8/1/2014 – 11/30/2014 USP 37/NF 32, General Chapter, Injection <1>, Nomenclature and Definitions.
3. For biologic products, the preferred CDER format is to include the dosage form “For Injection” on the line below the proper name “(blinatumomab)”.

Trade Name
(blinatumomab)
for Injection

(b) (4) mcg/vial

For Intravenous Infusion Only

4. Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t). Thus the manufacturer information must appear as “Manufactured by:” or “Manufacturer:”
5. Relocate the manufacturer information to appear with the US License Number on a side panel to provide space on the PDP for the critical information for this product. For example:

Manufactured by: Amgen, Inc. Thousand Oaks, CA 91320 USA
US Lic No 1080
Product of Germany

6. 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.
7. Add a Medication Guide statement such as “Dispense the enclosed Medication Guide to each patient”.
8. Change the font color of the statement “See Package Insert for complete instructions on preparation and administration” from (b) (4) to red.
9. Revise the statement of ingredients to comply with USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients such that the names of the inactive ingredients are in alphabetical order in the following format: inactive ingredient (amount). Thus, the statement of ingredients should appear as:

Each vial of Trade Name contains blinatumomab ((b) (4) mcg), citric acid monohydrate ((b) (4) mg), lysine hydrochloride ((b) (4) mg), polysorbate 80 ((b) (4) mg), and trehalose dihydrate ((b) (4) mg) with a pH of 7.0.

Each vial of IV Stabilizer Solution for Trade Name 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.

Note the deletion of “μg” and the trailing zero from “ (b) (4) mg”. Both “μ” and trailing zeroes appear on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations¹. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.

Vial Ferrules and Caps:

1. Confirm there is no text on the ferrule and cap overseal of both drug product and Solution Stabilizer vials to comply with a revised United States Pharmacopeia (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
2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/17/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 17, 2014 8:45 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/DRISK REMS IR/Due Oct 27

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of Division of Risk Management (DRISK), please be prepared to discuss the following at the Mid Cycle Communication TCON on October 17th, 2014. **Please provide the proposed REMS Document and proposed appended REMS materials by 5pm (EDT) October 27, 2014.**

In accordance with section 505-1(g)(4) of the Food, Drug and Cosmetic act, we have determined that your biologic application license (BLA) 125-557 for BLINCYTO (blinatumomab) will require a risk evaluation and mitigation strategy (REMS) to ensure that the benefits of this therapeutic biologic product outweigh its risks for the proposed for the treatment of Philadelphia chromosome negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. We have determined that the BLINCYTO REMS must include a communication plan to mitigate the risks of cytokine release syndrome, neurologic events and medication errors associated with use of blinatumomab.

Communication Plan: We have determined that a communication plan is sufficient to mitigate the serious risks associated with use of BLINCYTO (blinatumomab) for Philadelphia chromosome negative relapsed or refractory acute lymphoblastic leukemia. Your REMS must include at least the following additional tools to manage these risks:

- *REMS Letter to Healthcare Providers* will be distributed within 30 days after the REMS approval date. The letter will be distributed electronically, twice-a-year for 24 months, to oncologists and hematologists who are likely to prescribe BLINCYTO. If a targeted healthcare provider's email address is not available, or if an email is undeliverable, the provider will receive the letter through the mail. The *REMS Letter to Healthcare Providers* will inform healthcare providers of the risks of neurologic events and medication errors. The letter will be accompanied by the Prescribing Information and the *BLINCYTO REMS Fact Sheet for Providers*. The *REMS Letter to Healthcare Providers* will be available from the BLINCYTO REMS website at the time of distribution and will remain on the website for the duration of the REMS.
- *REMS Letter for Professional Societies:* A REMS Letter for Professional Societies will be distributed electronically within 30 days after the REMS approval date. If a targeted professional society's email address is not available, or if an email is undeliverable, the letter will be sent through the mail. The REMS Letter for Professional Societies will inform the leadership of the professional society described below of the risk of neurologic events and medication errors associated with BLINCYTO treatment. Amgen will request the leadership of each professional society to distribute this risk information to their membership.

The *REMS Letter for Professional Societies* will be distributed to the following organizations:

- American Society of Clinical Oncology (ASCO)

- American Society of Hematology (ASH)
 - Oncology Nursing Society (ONS)
 - National comprehensive Cancer Network (NCCN)
 - Hematology Oncology Pharmacy Association (HOPA)
 - American Pharmacists Association (APhA)
 - American Society of Health System Pharmacists (ASHP)
- *REMS Fact Sheet for Providers:* A BLINCYTO Fact Sheet will be distributed to healthcare providers. The BLINCYTO REMS Fact Sheet for Providers will be included in mailings of *the REMS Letter to Healthcare Providers* and the *REMS Letter for Professional Societies* and will be available on the BLINCYTO REMS website. Hard copies of the *BLINCYTO REMS Fact Sheet for Providers* will also be distributed by Amgen’s sales representatives and medical field-based personnel to healthcare providers during the follow-up details/visits with healthcare providers for the first 24 months after the approval of the BLINCYTO REMS.
 - *Journal Information Pieces:* Amgen will publish in the following professional journals an information piece that includes the risks of neurologic events and medication errors associated with use of BLINCYTO treatment.
 - Journal of Clinical Oncology
 - Blood
 - Hematology Today
 - Biology of Blood and Marrow Transplantation

The information piece will be published bi-annually in each publication for 24 months.

- *Scientific Meetings:* The BLINCYTO REMS Fact Sheet for Providers and the US Prescribing Information will be prominently displayed at scientific meetings where Amgen has a presence (e.g., exhibit booth) through 24 months following the REMS approval.
- *BLINCYTO Patient/Caretaker Safety Information Wallet Card:* A patient/caretaker safety information wallet card will highlight the risks with use of BLINCYTO and include information on management of these risks, among other serious risks reported with BLINCYTO treatment. Amgen sales representatives or medical field-based personnel will distribute the patient/caretaker safety information card to prescribers for prescribers to review with their patients considering BLINCYTO treatment. The BLINCYTO Patient/Caretaker Safety Information Wallet Card will also be available on the BLINCYTO REMS website.
- *BLINCYTO REMS website:* The REMS specific website will contain information on the BLINCYTO REMS and will provide access to all the REMS materials, the Prescribing Information and the Medication Guide. The website will be available for the duration for the REMS.
- Amgen will submit *REMS Assessments* to the FDA at 1 year, 3 years, and 7 years and annually from the date of approval of the initial REMS.

Please officially submit the materials to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/17/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, October 15, 2014 4:42 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical IR/Due October 21

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical review team, please provide the following requested information by **3pm (EDT) Tuesday October 21, 2014**.

We have identified 30 subjects for whom we have concluded that the root cause of death was related to blinatumomab therapy. The data file addth.xpt indicates that in some of these cases you either concluded that the cause of death was not related or you did not provide an assignment of relatedness at all. Also, for some cases, there was no narrative in the BLA, and in nearly all of the narratives that were provided, there was no discussion of your rationale for assignment of relatedness.

For each of the following cases, provide a **brief** narrative that identifies the proximate cause of death and your conclusion as to the root cause of death (relapse, blinatumomab or a cause not related to either relapse or blinatumomab). Provide a rationale for your determination of the root cause of death. If you conclude that the root cause was relapse, please indicate the date on which the marrow or peripheral blood test in adlb.xpt shows disease that is persisting or worsening (i.e., blasts). Please also note that we conclude that blinatumomab is the root cause when death resulted either from a direct organ toxicity (such as with cytokine release syndrome and multi-organ failure) or indirectly from a toxicity caused by blinatumomab (such as infection without evidence of relapse).

USUBJID	Cause of Death
104-105005	E. coli sepsis
104-109027	No narrative
104-153004	PCP pneumonia
203-1201001	No narrative
203-1502001	No narrative
205-1001004	GPC sepsis, intracranial hemorrhage
205-1001006	Cytokine release syndrome
205-1301005	Cytokine release syndrome
205-2201001	No narrative
205-2302001	Neurological toxicity
206-155007	Candida sepsis
206-157005	Aspergillus infection
206-159002	Intracranial hemorrhage
208-1011002	No narrative
208-1013001	No narrative

208-1016001	No narrative
208-1017001	No narrative
211-1003003	Pulmonary hemorrhage
211-1010006	Sepsis
211-1010013	Sepsis
211-1010027	Sepsis
211-1010028	Sepsis
211-1206004	No narrative
211-1302002	Respiratory failure
211-1302003	No narrative
211-1305001	Pneumonia
211-1305003	No narrative
211-1406005	No narrative
211-1406006	Aspergillus infection
211-2312003	Pneumonia
211-2321005	No narrative

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/15/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, October 14, 2014 10:52 AM
To: 'Yu, Tai'
Subject: BLA 125557/Drug Substance IR/Due Oct 17 request for clarification/Agency Response
Importance: High

Hello Tai,

With regards for the clarification of Question 3a, the request to eliminate rejection limits refers to the (b) (4) limits for endotoxin and bioburden. The request for implementation of tighter limits refers to the bioburden limits for the (b) (4) (currently, (b) (4)).

Thanks,
Kris

From: Yu, Tai [mailto:tyu@amgen.com]
Sent: Friday, October 10, 2014 7:13 PM
To: Kolibab, Kristopher
Subject: RE: BLA 125557/Drug Substance IR/Due Oct 17 - request for clarification

Hi Kris,

With regard to the Information Request received from the microbial quality drug substance review team below, Amgen requests clarification of Question 3a which asks that we "Implement tighter action limits and eliminate the reject limits." The scope of this request is not clear as a number of (b) (4) controls are associated with safety tests for adventitious agents, which require reject limits. As parts b, c, and d of that question discuss only bioburden, please clarify if this request is to implement a tighter bioburden action limit for the (b) (4) in place of the current reject limit of (b) (4).

Regards,
Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [mailto:Kristopher.Kolibab@fda.hhs.gov]
Sent: Friday, October 10, 2014 11:07 AM
To: Yu, Tai
Subject: BLA 125557/Drug Substance IR/Due Oct 17

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the microbial quality drug substance review team, please provide a response to the following information request by **1pm (EDT) Friday October 17, 2014**.

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/14/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, October 14, 2014 9:58 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/DMEPA IR/Due Oct 31

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014 and the human factors study protocol for the supplemental summative study. It has been determine the human factors study protocol is acceptable.

Per the request of the medication error prevention and analysis team, please provide a response to the following information request by **4pm (EDT) Friday October 31, 2014**.

The proposed labels and labeling, Instructions for Admixing (IFA), and PI can be improved to increase the readability and prominence of important information, to clarify information and promote the safe use of the product. We provide recommendations below. We recommend the following recommendations regarding the IFA and any other labels and labeling that will be used in the HF study are implemented before you conduct an HF study and HF study is conducted with revised labels and labeling;

A. PI, Section 2.5, Dosage and Administration, IFA

1. Consider developing separate Instructions for Admixing (IFA) in color that healthcare practitioners can refer to. This may help mitigate some of the errors seen in the Human Factors Study due to a lengthy procedure with many steps involved. Consider using different colors depending on the dose prepared and amount of time to infuse over. For example,
 - a. One color for 9 mcg over 24 hours,
 - b. Another color for 9 mcg over 48 hours,
 - c. Another color for 28 mcg over 24 hours, and
 - d. Another color for 28 mcg over 48 hours.
2. In Section 2.5 of the PI increase prominence of the following statement by bolding, **“It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose).”** We recommend increasing the prominence of this statement to mitigate possible preparation errors as seen during the Human Factors study where participants did not use the provided IVSS and/or reconstituted blinatumomab using the IVSS instead of sterile water.
3. In Section 2.5.3-A of the PI, please bold and underline the statements after the first statement, **“Therefore, add IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride, USP. Do not use**

IV Solution Stabilizer for reconstitution of BLINCYTO.” We provide this recommendation to increase the prominence of this instruction to reduce the likelihood of users using IVSS to reconstitute blinatumomab as seen during the Human Factors study.

4. In Sections 2.5.4.1, 2.5.4.2, 2.5.4.3, and 2.5.4.4 Step 3, please remove “(b) (4)” so the instructions read “The addition of preservative-free Sterile Water for Injection, USP to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.” We make this recommendation based on two errors from the Human Factors study where two participants added (b) (4) instead of 3 mL sterile water to the Blincyto during reconstitution. The current statement including “(b) (4) does not provide any additional benefit, but adds confusion among many numbers as is.
5. In Sections 2.5.4.1, 2.5.4.2, 2.5.4.3 and 2.5.4.4 Step 2, please revise the statement to read “Using a 10 mL syringe, aseptically transfer 5.5 mL of **IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride.**” Also, bold the ending of the statement as stated above. We provide this recommendation to increase the prominence of how the IVSS should be used during preparation of blinatumomab, and reduce the likelihood of using the IVSS incorrectly due to errors seen in the HF study.
6. In Sections 2.5.4.1, 2.5.4.2, 2.5.4.3 and 2.5.4.4 Step 7, please bold and underline the statement “**prime the IV line only with prepared solution for infusion**” to increase its prominence. We provide this recommendation since two participants in the Human Factors study primed the IV tubing using Sodium Chloride instead of the prepared drug.

B. Blinatumomab Product Vial:

1. 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.
2. Revise the prominent strength presentation in the orange colored circle to “(b) (4) mcg/vial”. Consider deleting the duplicate strength presentations on this small label.
3. 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.
4. Please remove the abbreviation (b) (4) and revise the current statement “For I.V. Infusion Only” to “For Intravenous Infusion Only” to avoid any ambiguity with the route of administration.
5. Decrease the prominence of “Rx Only” to allow the user to read the most important information clearly.
6. 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)

(b) (4) mcg/vial

For Intravenous Infusion Only

Amgen Inc. US Lic No 1080 Rx Only

or

Trade Name

(blinatumomab)

for Injection

(b) (4) mcg/vial

For Intravenous Infusion Only

Amgen Inc. US Lic No 1080 Rx Only

C. IV Solution Stabilizer (IVSS) Vial:

1. Currently, the IV Solution Stabilizer vial label and blinatumomab vial label look identical in terms of colors, which may cause confusion and misinterpretation that both vials contain the active ingredient. Ensure that the IVSS vial label appears different from the blinatumomab vial in terms of use of coloring, so that there is no confusion between them.
2. Reduce the size of the trade name of the product and bold “IV Solution Stabilizer”, so that it is not confused with the blinatumomab vial and thus avoiding the likelihood of the IVSS being administered alone.
3. Revise the current statement of (b) (4) ” to “NOT FOR DIRECT RECONSTITUTION OF TRADE NAME” to make the instructions clear and direct.
4. 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 TRADE NAME

NOT FOR DIRECT RECONSTITUTION OF TRADE NAME

5. Decrease the prominence of “Rx Only” to allow the user to read the most important information clearly.
6. Place a volume statement on the label.

D. Carton Labeling:

1. Revise the prominent strength presentation in the orange colored circle to “ (b) (4) mcg/vial”.
2. Revise the dosage form (b) (4) to “for Injection” per USPC 8/1/2014 – 11/30/2014 USP 37/NF 32, General Chapter, Injection <1>, Nomenclature and Definitions.

3. For biologic products, the preferred CDER format is to include the dosage form “For Injection” on the line below the proper name “(blinatumomab)”.

Trade Name
(blinatumomab)
for Injection

(b) (4) mcg/vial

For Intravenous Infusion Only

4. Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t). Thus the manufacturer information must appear as “Manufactured by:” or “Manufacturer:”
5. Relocate the manufacturer information to appear with the US License Number on a side panel to provide space on the PDP for the critical information for this product. For example:

Manufactured by: Amgen, Inc. Thousand Oaks, CA 91320 USA
US Lic No 1080
Product of Germany

6. 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.
7. Add a Medication Guide statement such as “Dispense the enclosed Medication Guide to each patient”.
8. Change the font color of the statement “See Package Insert for complete instructions on preparation and administration” from (b) (4) to red.
9. Revise the statement of ingredients to comply with USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients such that the names of the inactive ingredients are in alphabetical order in the following format: inactive ingredient (amount). Thus, the statement of ingredients should appear as:

Each vial of Trade Name contains blinatumomab ((b) (4) mcg), citric acid monohydrate ((b) (4) mg), lysine hydrochloride ((b) (4) mg), polysorbate 80 ((b) (4) mg), and trehalose dihydrate ((b) (4) mg) with a pH of 7.0.

Each vial of IV Stabilizer Solution for Trade Name 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.

Note the deletion of “μg” and the trailing zero from (b) (4) mg”. Both “μ” and trailing zeroes appear on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations¹. As part of a national campaign to avoid the use of dangerous abbreviations and dose

designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.

Vial Ferrules and Caps:

1. Confirm there is no text on the ferrule and cap overseal of both drug product and Solution Stabilizer vials to comply with a revised United States Pharmacopeia (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
2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/14/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 10, 2014 7:14 AM
To: 'Yu, Tai'
Subject: BLA 125557/Response Regarding Inspection

Importance: High

Hi Tai,

The Agency is planning to waive the pre-approval inspection of the [REDACTED] for BLA 125557 finished drug product manufacturing operations. (b) (4)

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [<mailto:tyu@amgen.com>]
Sent: Wednesday, October 08, 2014 12:44 AM
To: Kolibab, Kristopher
Subject: RE: BLA 125557/ Follow up on inspection of [REDACTED] (b) (4)

Hi Kris,

As a follow up to the email below dated September 29, Amgen would appreciate the Agency's confirmation on the requirement for a [REDACTED] (b) (4) pre-approval inspection (PAI). The development of Amgen's launch strategy to supply patients will greatly benefit from learning about your feedback by the end of this week.

If the FDA was to conduct a PAI of [REDACTED] (b) (4) facility located in [REDACTED] (b) (4) would it be acceptable for the FDA to witness fill or lyophilize operations of a commercial drug product that would not be blinatumomab (or some other surrogate)? Our request is driven by the need to fill the balance of available blinatumomab drug substance at [REDACTED] (b) (4) as early as mid-October to ensure supply to patients immediately after the pending approval of the blinatumomab BLA.

Best Regards,

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Yu, Tai
Sent: Monday, September 29, 2014 10:57 AM
To: Kolibab, Kristopher (Kristopher.Kolibab@fda.hhs.gov)
Subject: BLA 125557/Inspection of (b) (4)

Hi Kris,

Amgen's contract manufacturer for blinatumomab drug substance, (b) (4) informed Amgen that FDA will inspect their facility from (b) (4). Amgen's drug product manufacturer, (b) (4) (b) (4) has inquired whether FDA will conduct a prior-approval inspection of their facility in (b) (4), in relation to the blinatumomab BLA.

Does FDA have a time frame for making this determination? Can the decision be communicated directly to Amgen or to (b) (4)

Regards,

Tai H. Yu, MS
Regulatory Affairs
AMGEN
One Amgen Center Drive
17-2-A
Thousand Oaks, CA 91320
work: 805.447.2748
mobile: (b) (6)
email: tyu@amgen.com

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
10/10/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 10, 2014 2:07 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Drug Substance IR/Due Oct 17

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the microbial quality drug substance review team, please provide a response to the following information request by **1pm (EDT) Friday October 17, 2014**.

(b) (4)



Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/10/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, October 10, 2014 11:09 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Revised PI/Due October 14

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical review team, please provide the following requested information by **5pm (EDT) Tuesday October 14, 2014**.

Please submit a revised Prescribing Information addressing the following issues in Section 14 Clinical Studies.

1. Delete (b) (4) from Section 14. The PI will include efficacy information only from the pivotal trial.
2. We have identified four subjects in the PAS population whose characteristics are not consistent with the relapsed/refractory ALL having a high unmet medical need as follows:
Subject 1005-001 - (see variable DISTAGE in adbase.xpt)
Subject 1006-001 - (see variable DISTAGE in adbase.xpt)
Subject 2309-016 - (see variable DISTAGE in adbase.xpt)
Subject 1201-002 - No evidence of relapse at screening by marrow exam, peripheral blood blasts or extramedullary disease

Please repeat the analysis of the primary efficacy outcomes with these four subjects deleted from the analysis population. The final number of subjects for labeling will be n=185. Revise Section 14 to reflect this analysis.

3. Subject 2309-009 was coded a (b) (4). The marrow report dated 4.4.2012 was read as insufficient, and the prior and subsequent marrows showed relapse. Please recode this subject as no response for labeling.
4. Delete (b) (4) from Table 3. (b) (4) cannot be interpreted in a single-arm trial and will not be included in the PI.
5. Revised Table 3 to show only the components of the primary endpoint, duration of response, and MRD response. Include in the footnotes how you define duration of response (i.e., ending at relapse only, or ending at relapse or death, etc). Abbreviations may also be defined in the footnotes to allow for simplification of the table. As an example:

	CR	CRh*	CR+CRh*
n (%) [95% CI]			
MRD negative, n (%) [95% CI]			
Median duration (range)			
Footnotes			

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/10/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 09, 2014 2:54 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Advice

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

The immunogenicity review team has the following recommendation.

- 1. Submit all the validation reports and corresponding SOPs used to evaluate the immunogenicity of blinatumomab in human serum samples under section to be included under Section 5.3.1. Reports of Biopharmaceutic Studies, Subsection 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies.***

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/09/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, October 08, 2014 2:52 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Immunogenicity IR/Due Oct 10

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the immunogenicity review team, please provide a response to the following information request by **1pm (EDT) Friday October 10, 2014**.

Current guidances recommend the use of 50-100 human serum samples in the calculation of immunogenicity assays cut points to account for biological variability among human samples. Furthermore, the estimated cut point should be confirmed in the patient population where anti-drug antibodies will be determined.

The validation reports you provided on September 23rd, 2014, describe the use of 6 serum samples in the calculation of the screening assays cut point. Provide any additional information you may have to justify the selection of this sample size or any additional data you may have from additional healthy volunteer samples or ALL. Alternatively, indicate where in your submission can that information be found.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/08/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, October 07, 2014 7:51 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Due October 14

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the product quality review team, please provide a response to the following information request by **12pm (EDT) Tuesday October 14, 2014.**

(b) (4)





Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
10/07/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, October 07, 2014 6:52 AM
To: 'Yu, Tai'
Subject: BLA 125557/Clinical Pharmacology IR/Extension Response

Importance: High

Hello Tai,

It is fine to submit your written response regarding renal impairment by 4pm (EDT) Wednesday October 8, 2014. Please also submit related datasets and programs for the additional analyses.

Please submit a dataset including baseline creatinine clearance for each subject in trials MT103-211 and MT103-206 by 4pm (EDT) Tuesday October 7, 2014.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [<mailto:tyu@amgen.com>]
Sent: Monday, October 06, 2014 3:00 PM
To: Kolibab, Kristopher
Subject: RE: BLA 125557/Clinical Pharmacology IR/Due October 7

Hi Kris,

Amgen has to perform some additional analyses/assessment for this request. Can Amgen provide a response to this request on Wednesday, October 8?

Also, I confirm receipt of the Filing Letter.

Regards,

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Monday, October 06, 2014 6:49 AM

To: Yu, Tai
Subject: BLA 125557/Clinical Pharmacology IR/Due October 7
Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical pharmacology review team, please provide a response to the following information request by **4pm (EDT) Tuesday October 7, 2014**.

- 1. Please evaluate whether the patients with mild or moderate renal impairment have worse safety profiles (including AE incidence, as well as incidence of drug discontinuation and interruption) than the patients with normal renal function. Please provide your assessment regarding whether dose should be adjusted in patients with mild or moderate renal impairment in the context of efficacy and safety data in addition to the PK data.**

Also please clarify whether/how you plan to determine the appropriate dose for the patients with severe renal impairment and the patients on dialysis.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/07/2014



BLA 125557

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Amgen, Inc.
Attention: Tai H. Yu, MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Biologics License Application (BLA) dated September 19, 2014, received September 19, 2014, submitted under section 351(a) of the Public Health Service Act for Blincyto (blinatumomab).

We also refer to your amendments dated September 25, 26 (2), and 30, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is May 19, 2015.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 21, 2015. In addition, the planned date for our internal mid-cycle review meeting is December 19, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
10/06/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, October 06, 2014 9:49 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical Pharmacology IR/Due October 7

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical pharmacology review team, please provide a response to the following information request by **4pm (EDT) Tuesday October 7, 2014**.

1. Please evaluate whether the patients with mild or moderate renal impairment have worse safety profiles (including AE incidence, as well as incidence of drug discontinuation and interruption) than the patients with normal renal function. Please provide your assessment regarding whether dose should be adjusted in patients with mild or moderate renal impairment in the context of efficacy and safety data in addition to the PK data.

Also please clarify whether/how you plan to determine the appropriate dose for the patients with severe renal impairment and the patients on dialysis.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
10/06/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 02, 2014 10:38 AM
To: 'Yu, Tai'
Subject: BLA 125557/CMC IR/Response to Extension Request

Importance: High

Hi Tai,

Please see below for our response to your questions.

Amgen: Would the Agency agree to receiving responses to questions 1, 3 and 7 on 16 October 2014 (4pm EDT)?

FDA Response: Due to our internal time lines for the review process, we can only extend the response timeline to Oct 10, 2014. However, the official updates to the BLA sections 3.2.S2.2 and S.2.4 requested in Question 1 can be made at a later time, if the sponsor provides the requested information in a format similar to that which will be used to update these sections.

Amgen: Question 3 received from the Agency's CMC review team on 30 September 2014 requests additional process design and characterization data to support various aspects of drug substance and drug product manufacture. Several examples are provided in bullets, which detail specific information requested for drug substance. Amgen considers the drug product characterization data to be better represented in the BLA, and is unclear whether the Agency has identified gaps related to drug product.

Are there specific items of concern regarding drug product characterization data, or is there general guidance the Agency can provide on the appropriate granularity of information, relative to the information provided in the drug product sections?

FDA Response: For question 3, at this time, Amgen needs to provide information only regarding the DS characterization. We will send a separate information request for the DP characterization data.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

From: Yu, Tai [mailto:tyu@amgen.com]
Sent: Wednesday, October 01, 2014 9:07 PM
To: Kolibab, Kristopher
Subject: RE: BLA 125557/CMC IR/Due October 9

Hi Kris,

Amgen appreciates the Agency's immediate attention to the CMC sections of the BLA and is preparing responses to the Agency's questions. With regard to questions received on 29 September 2014 from the Agency's quality micro review team, Amgen intends to provide responses by 06 October 2014 as requested.

The 18 questions received from the Agency's CMC review team on 30 September 2014 (below) are more substantial, but Amgen believes it is feasible to answer most of the questions by the requested date of 09 October 2014. However, questions 1, 3 and 7 are considerably broader in scope and will require substantial efforts to consolidate information, both from historical sources and from Amgen's contract manufacturers. Amgen would very much appreciate an additional 5 working days to develop effective responses to those questions.

Would the Agency agree to receiving responses to questions 1, 3 and 7 on 16 October 2014 (4pm EDT)?

Question 3 received from the Agency's CMC review team on 30 September 2014 requests additional process design and characterization data to support various aspects of drug substance and drug product manufacture. Several examples are provided in bullets, which detail specific information requested for drug substance. Amgen considers the drug product characterization data to be better represented in the BLA, and is unclear whether the Agency has identified gaps related to drug product.

Are there specific items of concern regarding drug product characterization data, or is there general guidance the Agency can provide on the appropriate granularity of information, relative to the information provided in the drug product sections?

Tai Yu
Regulatory Affairs
805-447-2748
17-2-A

From: Kolibab, Kristopher [<mailto:Kristopher.Kolibab@fda.hhs.gov>]
Sent: Tuesday, September 30, 2014 11:27 AM
To: Yu, Tai
Subject: BLA 125557/CMC IR/Due October 9
Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information requests by **4pm (EDT) Thursday October 9, 2014**.

- 1. The level of detail and amount and types of data provided in the Manufacturing Process Development and Process Validation sections (3.2.S.2.6 and 3.2.S.2.5) are not sufficient to support the limited process parameters and controls presented in the Description of Manufacturing Process and Process Controls and Controls of Critical Steps and Intermediates sections (3.2.S.2.2 and 3.2.S.2.4). The following information should be provided and the appropriate BLA sections (Sections 3.2.S.2.2 and 3.2.S.2.4) should be updated to include the requested information. Ranges or limits for the parameters should be supported by historical data from appropriate manufacturing processes if they were not determined during the process development studies. Data that will support the proposed ranges should be submitted to provide the information needed to reach agreement on the proposed ranges or limits.**

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

18. Regarding the Reference Standard:

- a. **Identify the reference standard used for DS and DP lot release and stability testing of each lot.**
- b. **Identify the reference standard against which each other reference standard was qualified.**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
10/02/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, October 02, 2014 9:48 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Stats IR/Due Friday October 10

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the statistical review team, please provide a response to the following information request by **4pm (EDT) Friday October 10, 2014**.

1. For Study 20120310, please provide an additional estimate for overall complete remission rate based on: age at treatment, prior lines of treatment, relapsed versus refractory for 1st salvage patients, and duration of complete remission for 1st salvage in relapsed patients.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
10/02/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, September 22, 2014 10:50 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical Pharmacology IR

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical pharmacology review team, please provide a response to the following information request.

1. We could not locate the analysis ready datasets for the Exposure-Response Analysis Report: 117729. Please submit the analysis datasets with define files for all the exposure-response analysis conducted as part of this study report. If you have already submitted the datasets, please point us to the correct location in the EDR. Please provide this information by **COB September 23**.
2. We acknowledge your rationale on conducting the time to event analysis for CR/CRh* instead of CR/CRh* occurrences. While time to event analysis provides useful information, we would also recommend you to conduct exposure-response analysis using occurrence of CR/CRh* since the primary endpoint of study MT103-211 was CR/CRh* rate within 2 cycles of treatment with blinatumomab. Adequate rationale for the exposure metric you intend to use for this analysis should be provided. Both univariate and multivariate analysis should be conducted. Please submit the results, datasets and define files by **COB September 25**.
3. We also noticed that you have conducted exposure-time to neurological event analysis and acknowledge your rationale behind this approach. However, we would also recommend you to conduct the exposure-response analysis for occurrence of neurological events. Adequate rationale for the exposure metric you intend to use for this analysis should be provided. Both univariate and multivariate analysis should be conducted. Please submit the results, datasets and define files by **COB September 25**.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
09/22/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, September 22, 2014 9:18 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Immunogenicity IR

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the immunogenicity review team, please provide a response to the following information request **as soon as possible**.

Table 1.- Summary of Assays for Immunogenicity Measurements, 2.7.2 – Summary of Clinical Pharmacology Studies describes three validation reports for testing of anti-drug antibodies in human serum samples: VP/VR538IM (ELISA), VP/VR-BIA-103-004 (ECL), and VP/VR BIA-103-006 (neutralizing assay). **Please indicate where** in the submission can those reports be found, or provide the validations reports and corresponding SOPs for review.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
09/22/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, September 30, 2014 11:27 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/CMC IR/Due October 9

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the CMC review team, please provide a response to the following information requests by **4pm (EDT) Thursday October 9, 2014**.

- 1. The level of detail and amount and types of data provided in the Manufacturing Process Development and Process Validation sections (3.2.S.2.6 and 3.2.S.2.5) are not sufficient to support the limited process parameters and controls presented in the Description of Manufacturing Process and Process Controls and Controls of Critical Steps and Intermediates sections (3.2.S.2.2 and 3.2.S.2.4). The following information should be provided and the appropriate BLA sections (Sections 3.2.S.2.2 and 3.2.S.2.4) should be updated to include the requested information. Ranges or limits for the parameters should be supported by historical data from appropriate manufacturing processes if they were not determined during the process development studies. Data that will support the proposed ranges should be submitted to provide the information needed to reach agreement on the proposed ranges or limits.**

(b) (4)

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

18. Regarding the Reference Standard:

- a. Identify the reference standard used for DS and DP lot release and stability testing of each lot.
- b. Identify the reference standard against which each other reference standard was qualified.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
09/30/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, September 30, 2014 6:39 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical IR/Due Wednesday October 1

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical review team, please provide a response to the following information request by **12pm (EDT) Wednesday October 1, 2014**.

1. Please clarify what is meant by "Premature stop of infusion cycle" in adex.xpt. Is this an interruption for adverse event, relapse or error?
2. Please clarify if eligibility was determined by marrow examination in the central lab or at the local lab. If the latter, please clarify where the marrow reports from the local lab are located in the BLA.
3. We have identified the following discrepancies in blast percentage between the central lab reports and the data file adlb.xpt. Please clarify the discrepancies:
Subject 1603009 12/4/2012 6% blasts on report vs 10% in data file
Subject 2306009 10/3/2012 4% blasts on report vs 10% in data file
Subject 2311003 9/11/2012 4% blasts on report vs 20% in data file
4. Two reports for patients who achieved a CRh* are dated nearly a year after the sample was taken. Please clarify why the report was so late. If there is an earlier report, please submit it and indicate why revisions were made, if any. The following subjects were noted to have late reports for documentation of response:
Subject 1604003 for marrow done 6/28/2013 (report 8/10/2014)
Subject 1302005 for marrow done 7/17/2013 (report 7/28/2014)
5. It appears that three subjects achieved CRh* based on a marrow that was considered insufficient by the central lab. Please clarify if there are other reports to verify the response for the following:
Subject 2309005 (marrow for response 2/24/2012)
Subject 2309009 (marrow for response 4/4/2012)
Subject 2309013 (marrow for response 6/19/2012)

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs*

**Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
09/30/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, September 29, 2014 9:15 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Quality Micro IR/Due October 6

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the quality micro review team, please provide a response to the following information requests by **4pm (EDT) Monday October 6, 2014**.

1. Please indicate which site will be used for sterility testing for drug product (DP) release.
2. Compare [REDACTED] (b) (4) during validation and media fill studies to those proposed for commercial manufacturing.
3. Provide [REDACTED] (b) (4) validation reports listed in Table 27 in Section 3.2.P.3.5 Process Validation and/or Evaluation.
4. Provide [REDACTED] (b) (4) validation reports completed using IV solution stabilizer.
5. Describe action taken in the event of a media fill failure.
6. Provide summary of microbiological monitoring completed during each media fill run [REDACTED] (b) (4)
7. Provide the type of media used for the media fill along a description of the growth promotion test completed.
8. Provide a description of the routine environmental monitoring program.
9. Specify which drug product batches were used to complete the rabbit pyrogen test.
10. Provide summary validation data and information for, [REDACTED] (b) (4) [REDACTED] for both drug product and IV solution stabilizer (IVSS).
11. Provide the protocol and report for qualification of the sterility test method used for both drug product and IVSS.
12. Please provide microbial data from media simulations that demonstrate that [REDACTED] (b) (4) [REDACTED] under the proposed conditions:
 - a. [REDACTED] (b) (4)
 - b. [REDACTED] (b) (4)

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

**Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903**

Phone: 240-402-0277

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
09/29/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, September 29, 2014 9:15 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical Pharmacology Information Request/Due Sept 30

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical pharmacology review team, please provide a response to the following information request by **4pm (EDT) Tuesday September 30, 2014**.

1. **Bioanalytical method validation report for blinatumomab**
2. **Bioanalytical report for blinatumomab concentration measurements using patients samples in trials of MT103-211, MT103-206, MT103-104, MT103-202 and MT103-205. The bioanalytical reports should include the details on the acceptance of each batch run, the storage time of the samples from blood collection to analysis, and incurred sample reanalysis, etc.**
3. **Submit datasets containing blinatumomab concentrations and PK parameters in pediatric patients that your reported in the Interim Study Report for Trial MT103-205. The PK datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
09/29/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, September 26, 2014 8:41 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical Pharmacology IR

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical pharmacology review team, please provide a response to the following information request.

1. Please submit [REDACTED]

(b) (4)

by 3pm (EDT) September 29, 2014.

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
*Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903*

Phone: 240-402-0277

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
09/26/2014

Wright, Kevin

From: Yu, Tai <tyu@amgen.com>
Sent: Tuesday, September 23, 2014 12:14 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: BLA 125557 blinatumomab: proprietary name request

Categories: DMEPA

Hi Kevin,

Thank you for this information. Amgen is planning to submit the request for proprietary name review by this Friday, 9/27.

Regards,

*Tai H. Yu, MS
Regulatory Affairs
AMGEN
One Amgen Center Drive
17-2-A
Thousand Oaks, CA 91320
work: 805.447.2748
mobile: (b) (6)
email: tyu@amgen.com*

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, September 23, 2014 9:12 AM
To: Yu, Tai
Cc: Kang, Sue
Subject: BLA 125557 blinatumomab: proprietary name request
Importance: High

Hi Tai,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to blinatumomab under BLA 125557 within 7 days.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME REVIEW", on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

Please refer to the "Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names" for the information that should be included in your submission.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

 Thinking green when printing

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.

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

/s/

KEVIN WRIGHT
09/23/2014



BLA 125557

BLA ACKNOWLEDGEMENT

Amgen, Inc.
Attention: Tai H. Yu., MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Blincyto (blinatumomab)
Date of Application: September 19, 2014
Date of Receipt: September 19, 2014
Proposed Use: Treatment of adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Kris Kolibab, PhD
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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
09/23/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, September 23, 2014 10:40 AM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Information Request/Med Guide

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the review team, please provide the following information **by COB Wednesday October 15, 2014.**

- 1. Please submit a draft Medication Guide for blinatumomab as described in 21 CFR Part 208.**

Please officially submit the information to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
09/23/2014

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, September 22, 2014 4:59 PM
To: Yu, Tai (tyu@amgen.com)
Subject: BLA 125557/Clinical Information Request

Importance: High

Hello Tai,

Please refer to BLA 125557 received on September 19, 2014.

Per the request of the clinical review team, please provide a response to the following information request **by 12pm (EDT) Wednesday September 24, 2014.**

1. **On pages 30 and 213 of the Summary of Clinical Safety and on page 498 of the Integrated Summary of Safety, you state that “A complete report for the pooled ECG analyses from studies MT103-206 and MT103-203 is provided in Module 5.3.5.3.” Please identify which document in Module 5.3.5.3 has this complete pooled report.**

Please officially submit the responses to BLA 125557 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2311
Silver Spring, MD 20903

Phone: 240-402-0277

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
09/22/2014



IND 100135

MEETING MINUTES

Amgen, Inc.
Attention: Tai H. Yu., M.S.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMG 103 (blinatumomab).

We also refer to the meeting between representatives of your firm and the FDA on June 23, 2014. The purpose of the meeting was to discuss the clinical development plan to support the treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions contact, Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, M.D., Ph.D.
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: June 23, 2014, 2:00 PM – 3:00 PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, MD 20903

Application Number: IND 100135
Product Name: AMG 103 (blinatumomab)
Indication: Relapsed/Refractory B-precursor adult ALL
Sponsor/Applicant Name: Amgen

Meeting Chair: Albert Deisseroth, M.D., Ph.D.
Meeting Recorder: Kris Kolibab, Ph.D.

FDA ATTENDEES

Division of Hematology Products (DHP):

Ann T. Farrell, M.D., Division Director
Edvardas Kaminskas, M.D., Deputy Director
Albert Deisseroth, M.D., Ph.D., Medical Officer, Clinical Team Leader
Donna Przepiorka, M.D., Ph.D., Medical Officer
Kris Kolibab, Ph.D., Regulatory Project Manager

Office of Clinical Pharmacology, DCP5:

Julie Bullock, Pharm.D., Team Leader

Office of Biotechnology Products (OBP):

Sarah Kennett Ph.D., Review Chief
Deborah Schmiel, Ph.D., Biologist
Subramanian Muthukkumar, Ph.D., Biologist

Office of Biostatistics, Division of Biometrics V (DBV)

Lei Nie, Ph.D., Mathematical Statistician Team Leader
Chia-Wen Ko, Ph.D., Mathematical Statistician Reviewer

Division of Medical Error Prevention and Analysis (DMEPA):

Lubna Merchant, Ph.D., Associate Director

Biotech Manufacturing Assessment Branch (BMAB):

Candace Gomez-Boughton, Ph.D, Microbiologist
Kalavati Suvarna, Ph.D., Quality Microbiologist

Office of Combination Products (OCP):

Patricia Love, M.D., Deputy Director
Bindi Nikhar, Ph.D., Associate Clinical Director

SPONSOR ATTENDEES

Shilpa Alekar, M.D., Director, Global Safety
Deborah Arrindell, J.D., M.D., Executive Director, Global Safety
Janet Chow, Ph.D., Senior Associate, Global Regulatory Affairs
Mary Ellen Cosenza, Ph.D., Executive Director, Global Regulatory Affairs
Crystina Cupp, Ph.D., Director, Global Regulatory Affairs
Sameer Doshi, B.S., Senior Scientist, Pharmacokinetics and Drug Metabolism
Katherine Harris, Ph.D., Executive Director, Biostatistics
Christopher Holland, M.S., Director, Biostatistics
Michael Kelsh, Ph.D., M.P.H., Director, Center for Observational Research
Tap Maniar, M.D., Director, Global Development
Dirk Nagorsen, M.D., Ph.D., Director, Global Development Leader
David Reese, M.D., VP Clinical Development
Katie Sprugel, Ph.D., Scientific Director, Toxicology Sciences
Rhian Thomas, B.Sc., Executive Director, Global Regulatory Affairs
Tai Yu, M.S., Senior Manager, Global Regulatory Affairs
Alicia Zhang, Ph.D., Senior Manager, Biostatistics
Min Zhu, Ph.D., Scientific Director, Pharmacokinetics and Drug Metabolism

1.0 BACKGROUND

The Sponsor requested a Type B meeting to discuss the clinical development plan to support the treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL). The meeting was granted on May 12, 2014, and it was scheduled for June 23, 2014.

2.0 DISCUSSION

A. NONCLINICAL

Question 1

The key conclusions of the nonclinical program, including brief summaries of pharmacology, pharmacokinetic, and toxicology and safety pharmacology studies conducted with blinatumomab are presented in Section 8.

Does the Agency require any clarifications regarding the proposed nonclinical content in support of the BLA submission?

FDA Response: Overall, your nonclinical package is acceptable. To assist our understanding of the strengths and limitations of using the murine surrogate muS103new to support the nonclinical safety assessment for blinatumomab, please provide a table that lists side-by-side comparisons of relevant nonclinical test results using blinatumomab or muS103new (e.g. binding affinities, EC50s for mechanistic studies, etc.).

Discussion:

No discussion occurred.

B. CLINICAL

Question 2

A summary of the clinical studies to be included in the BLA, including the status and type of report to be provided for each study, is presented in Section 9.1.

Does the Agency require any clarifications regarding Amgen's approach for inclusion of information from completed and ongoing studies in the BLA submission?

FDA Response: No. We would ask, however, that you please plan to include the data lock date used in the CSR or ISR for each study submitted in the BLA. The data lock date may be incorporated in the Main Table of Clinical Studies (module 5.2) or as an additional stand-alone table with just the data lock date information.

Discussion:

No discussion occurred.

Question 3

The phase 2 study MT103-211 demonstrates that blinatumomab provides a meaningful advantage over available therapies in relapsed or refractory ALL using endpoints of complete remission (CR)/complete remission with partial hematologic recovery (CRh) and duration of response, as measured by relapse-free survival (RFS), that are reasonably likely to predict clinical benefit (Section 9.4.2.1). A phase 3 randomized study 00103311 (with OS as the primary endpoint) is ongoing to directly measure the clinical benefit of blinatumomab and verify the results in Study MT103-211. Additional clinical trial data from a previous phase 2 study in adult relapsed/refractory ALL (Study MT103-206), two phase 2 studies in adult minimal residual disease (MRD)-positive ALL (Studies MT103-202 and MT103-203), a phase 2 study in pediatric relapsed/refractory ALL (Study MT103-205), one phase 2 study in adult relapsed/refractory diffuse large B-cell lymphoma (DLBCL) (Study MT103-208), and a phase 1 study in adult relapsed Non-Hodgkin's lymphoma (NHL) (Study MT103-104) will be included in the BLA (Section 9.1).*

Does the Agency agree that data from Study MT103-211 and the supporting studies provide an adequate basis for filing of a BLA under the Accelerated Approval provisions?

FDA Response: We agree that the data from Study MT103-211 and the supporting studies provide an adequate basis for submission of a BLA. Adequacy of the content for filing will be a review issue.

Discussion:

No discussion occurred.

Question 4

At the Type B (end of phase 2) and Type A meetings held on 25 March 2013 and 25 April 2014, respectively, the Agency has communicated that the value of CRh as a relevant measure of clinical benefit in the treatment of adult relapsed/refractory ALL will be dependent on the assessment of the totality of the dataset from the primary analysis of Study MT103-211 (including outcomes, CR/CRh*, and MRD response). Based on our evaluation of the primary dataset, Amgen considers that CRh* is a relevant measure of clinical benefit. The evidence for the predictive value of CRh* is described in Section 9.4.2.1.3.*

Does the Agency agree that CRh is a relevant endpoint to measure the benefits observed with blinatumomab?*

FDA Response: No. According to your MRD data, the CRh* subgroup was heterogeneous, and a substantial proportion of these patients had residual disease. We recommend that you evaluate outcomes in this subgroup by MRD status at the time CRh* is achieved.

Discussion:

Sponsor provided additional analyses of CRh* patients by MRD. FDA requested that these be included in the BLA.

Question 5

Amgen considers that an indication for blinatumomab in adults with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL may be appropriate. Based on previous FDA feedback to account for duration of previous treatment responses, Amgen modified the eligibility criteria for the population enrolled in Study MT103-211 to ensure a more homogeneous population.

Given the novel mechanism of action of blinatumomab, the consistency of treatment effect observed across all subpopulations studied in Study MT103-211 (Section 9.4.2.1.3), and the high rate of CR/CRh observed in supporting study MT103-206 (Section 9.4.2.1.3), Amgen considers that blinatumomab can provide clinically meaningful benefit as a non-chemotherapy option beyond the currently available treatment options for patients with Philadelphia-negative relapsed or refractory B-precursor ALL.*

Does the Agency agree that patients with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL will benefit from blinatumomab based on the data from Study MT103-211 and supporting study MT103-206?

FDA Response: Whether blinatumomab is active in the treatment of Philadelphia-negative relapsed or refractory B-precursor ALL will be a review issue when the BLA is submitted.

Discussion:

No discussion occurred.

Question 6

As a follow up to the 16 December 2013 Type C teleconference held between the Agency and Amgen to discuss the data structure and format of the BLA, Amgen proposes to submit the final clinical study report (CSR) for Study MT103-203 (a phase 2 study in adult subjects with MRD-positive ALL) within 30 days after the initial BLA submission.

Does the Agency agree that the MT103-203 CSR may be submitted within 30 days after the initial BLA?

FDA Response: Yes, the CSR may be submitted within 30 days after the initial BLA submission. However, we still expect that the data file for Study MT103-203 will be included in the integrated safety data set at the time of submission of the original BLA.

Discussion:

The sponsor indicated they planned to submit in the integrated safety data sets of the original BLA the data available for subjects from MT103-203 at the time of data lock for the safety analysis, and an update with the final data on all accrued subjects will be provided with the CSR and safety update. FDA agreed to this plan.

C. SAFETY

Question 7

An overview of the safety evaluation to be included in the BLA, including exposure, a summary of adverse events, including adverse events of interest, and key conclusions, is presented in Section 9.5.

Does the Agency require any clarifications regarding Amgen's approach for overall safety evaluation?

FDA Response: Yes. We have the following comments:

- a) We understand that you will be submitting both an iSAP for the ISS and a Program Safety Analysis Plan (PSAP). Please clarify whether the PSAP will be included in Module 5 under the ISS or in Module 1 in the Risk Management Plan.**
- b) Please ensure that narratives for neurological serious adverse events include the results of MRIs or any other imaging studies that were performed.**

c) The Program Wide ISS dataset submitted in the original BLA should include integrated files for at least adverse events, demographics, baseline disease information, medical history, concomitant medications, exposure, clinical laboratory tests, and vital signs. For the integrated adverse event data file, please include the cycle number and actual dose at the start of cycle for each adverse event. If the clinical laboratory test data file is too large to submit through the Gateway, you may split the data set, but please describe in the reviewer's guide how the split was made. For additional information, please see Section 2.2 of "Study Data Specifications" available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM312964.pdf>

Discussion:

No discussion occurred.

Question 8

Amgen plans to submit a safety update from all studies included in the BLA in the 120-day safety update. Amgen's proposal for the 120-day safety update is presented in Section 9.5.6. Does the Agency agree with the proposed content and analysis for the 120-day safety update?

FDA Response: Yes, but please be certain to include in the 120-day safety update a dataset specifically for the Adult Relapsed/ Refractory ALL studies (MT103-211 and MT103-206) that includes integrated cumulative files for at least adverse events, demographics, baseline disease information, medical history, concomitant medications, exposure, clinical laboratory tests, and vital signs. For the integrated adverse event data file, please include the cycle number for each adverse event.

Discussion:

No discussion occurred.

D. CLINICAL PHARMACOLOGY

Question 9

An overview of the clinical pharmacology information will be included in the BLA, including descriptions of blinatumomab pharmacokinetics (PK), immune-pharmacodynamic effect, dose selection rationale, effect of baseline factors on PK and pharmacodynamics (PD), and PK/PD/modeling independent reports (eg, population PK modeling, exposure-response analysis, physiological-based PK modeling for cytokine mediated effect on CYP450 enzymes, and model-based meta-analysis of historical therapies for relapsed/refractory ALL). Key conclusions and supportive information are summarized in Section 9.3.

Does the Agency require any clarifications or additional information regarding Amgen's clinical pharmacology package?

FDA Response: Overall, your clinical pharmacology package appears acceptable. However, a final decision cannot be made until review of data submitted with your BLA. We

recommend that you conduct an additional exposure-response analysis for efficacy and safety based on the two manufacturing processes (CTM4 and CTM5) considering the differences in C_{ss}.

Discussion:

Sponsor will present subgroup analyses of safety efficacy by formulation in the BLA. The Agency found this acceptable.

Question 10

The effect of mild or moderate renal impairment on blinatumomab PK was evaluated by summary statistics of clearance value for renal groups based on the classification of renal function definition (Draft Guidance for Industry on Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, March 2010), graphical exploration, and population PK modeling. A preliminary assessment of the effect of renal impairment is described in Section 9.3.2.6.

Does the Agency agree that the information is sufficient to assess the effect of renal impairment and could support the recommended blinatumomab dose for patients with normal renal function and mild and moderate renal impairment (intended population)?

FDA Response: We agree that the information is sufficient to assess the effect of renal impairment. The recommended blinatumomab dose for patients with normal renal function and mild and moderate renal impairment will be a review issue.

Discussion:

No discussion occurred.

Question 11

The physiologically-based pharmacokinetic (PBPK) report was recently submitted to the IND on 04 April 2014 (Serial No. 0548) for the Agency's review. Amgen considers that the potential for a clinically meaningful drug interaction due to the effect of blinatumomab-mediated transient cytokine elevation on CYP450 enzymes in the clinical setting is low. In addition, the sporadic nature and the large variability of cytokine elevation would lead to highly variable drug-drug interaction study results, which limit its application on dose adjustment and product label instruction. A summary of the assessment is provided in Section 9.3.2.9.

Does the Agency agree with Amgen's assessment that a formal PK drug interaction study will not be necessary?

FDA Response: Your PBPK study report is under review. The decision on whether a DDI trial evaluating the effect of blinatumomab on CYP substrates will be a review issue.

Discussion:

No discussion occurred.

E. REGULATORY

Question 12

Amgen's assessment is that blinatumomab meets the qualifying criteria for Priority Review. A summary of the basis for consideration for blinatumomab to treat a serious condition and the assertion that blinatumomab would be a significant improvement in the safety and effectiveness over existing treatments is provided in Section 6.2. A formal request for Priority Review Designation will be included in the BLA.

Does the Agency have any comments on this proposal?

FDA Response: No.

Discussion:

No discussion occurred.

Additional Comments:

Clinical:

1. We remind you that your submission should also comply with all requests made at the Type C meeting held 12/16/2013.
2. Footnote a of Table 3 indicates that "ex-US sites are not conducted under the IND." We note that you received an IRB waiver for foreign clinical sites 12/12/2013, and you have been submitting clinical site information to the IND. For each study conducted under IND, please include in the BLA a list of sites not under the IND. Please also plan to submit the information required under 21 CFR 312.120 for foreign clinical trials and foreign clinical sites.
3. Please include in the BLA a letter of permission to use safety information from IND 100135 and IND (b) (4)
4. Submit in the BLA a data file listing all available MRD assay results. The pcr assay target, quantitative result and units should be identified for each measurement. Please also submit in Module 5 a description of each MRD assay used in the study, including where the assay was performed.

Discussion #4:

FDA clarified that the MRD assay data was specifically for protocol 211, and that scanned copies of results were needed only for marrow biopsies not for MRDs.

CMC:

We note that a chemistry pre-submission meeting was held on April 9, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

Discussion:

Additional comments will be forthcoming for the human factor protocol.

Statistical:

Please be reminded that patient-level historical data used in Study 20120310 should also be submitted for review.

Discussion:

Sponsor will submit whole data set. The Agency found this acceptable.

CDRH Human Factors:

We have reviewed your Human Factors Validation (Summative) Study Concept. We have the following comments:

- Please confirm that pharmacists and pharmacy technicians are the intended users and that the nurses are not expected to use this product.
- Please describe the tasks to be evaluated as part of scenario 2 and success criteria.
- Please clarify how these tasks have been prioritized based on the use-related risk analysis.
- Please clarify if the user is expected to program the infusion pump to set the delivery rate
- Please submit a use-related risk analysis along with your finalized study protocol for review.

3.0 IMPORTANT MEETING LANGUAGE

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 12, 2014, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. **SUMMARIZE DISCUSSION AND AGREEMENTS**

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that **TEXT**.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 - The MT103-203 Clinical Study Report

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA NUMBER: LATE COMPONENT - BIOMETRICS
NDA/BLA NUMBER: LATE COMPONENT - CLINICAL
NDA/BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
NDA/BLA NUMBER: LATE COMPONENT - NONCLINICAL
NDA/BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor provided slides regarding question 4.

10 Page(s) 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/

ALBERT B DEISSEROTH
06/25/2014



IND 100135

MEETING MINUTES

Amgen, Inc.
Attention: Keith Cockerill, Ph.D.
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Cockerill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for blinatumomab.

We also refer to the meeting between representatives of your firm and the FDA on April 9, 2014. The purpose of the meeting was to discuss key aspects of the CMC strategy to ensure submission of a biologics license application that contains appropriate and complete information for Agency review and potential approval.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lyndsay Hennessey, Regulatory Project Manager at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Sarah Kennett, Ph.D.
Review Chief
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC pre-BLA

Meeting Date and Time: April 9, 2014 from 3:00 - 4:30 P.M. Eastern Standard Time (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1537
Silver Spring, Maryland 20903

Application Number: 100135
Product Name: blinatumomab
Indication: Treatment of B-cell lymphoma/leukemia
Sponsor/Applicant Name: Amgen, Inc.

Meeting Chair: Sarah Kennett, Ph.D.
Meeting Recorder: Lyndsay Hennessey

FDA ATTENDEES

Sarah Kennett, Ph.D.	Review Chief, DMA
Rashmi Rawat, Ph.D.	Product Quality Team Lead, DMA
Deborah Schmiel, Ph.D.	Product Quality Reviewer, DMA
Subramanian Muthukkumar, Ph.D.	Product Quality Reviewer, DMA
Patricia Hughes, Ph.D.	Microbiology Team Lead, BMAB
Candace Gomez-Broughton, Ph.D.	Microbiology Reviewer, BMAB
Patricia Love, M.D.	Deputy Director, OCP
Bindi Nikhar, M.D.	Associate Clinical Director, OCP
Quynh Nhu Nguyen, M.S.	Human Factors Specialist, CDRH
Albert Deisseroth, M.D., Ph.D.	Medical Officer, Clinical Team Leader, DHP
Donna Przepiorka, M.D., Ph.D.	Clinical Reviewer, DHP
Lyndsay Hennessey	Regulatory Health Project Manager, OBP

SPONSOR ATTENDEES

Keith Cockerill, Ph.D.	Manager, Regulatory Affairs CMC
Michelle Frazier, Ph.D.	Director, Regulatory Affairs CMC
Michael McCormick	Principle Engineer, Drug Substance Process Development
Ananth Sethuraman, Ph.D.	Principal Scientist, Drug Product Process Development
Angie Lint	Director, Product Quality
Brad Prater	Senior Scientist, Analytical Sciences
Dirk Nagorsen, M.D., Ph.D.	Director, Global Development Leader
Cristina Cupp, Ph.D.	Director, Global Regulatory Affairs

Tai Yu, M.S.
Julia Yeh, M.S.E

Senior Manager, Global Regulatory Affairs
Senior Manager, Device Regulatory Affairs

1.0 BACKGROUND

- (i) **Purpose of meeting:** To reach agreement on key aspects of the CMC strategy to ensure submission of a BLA that contains appropriate and complete information for FDA review and potential approval.
- (ii) **Names of drug:** blinatumomab, a novel single-chain antibody derivative of the bispecific T-cell engager (BiTE®) class.
- (iii) **Product development:** BLA is currently planned for Q3 2014
- (iv) **Expected outcome for the meeting:**
- Provide the Agency with an overview of the manufacturing history for the blinatumomab drug substance, drug product and IV solution stabilizer.
 - Gain agreement on analytical comparability between process 4 and process 5 clinical trial material previously raised at the Type B end of phase 2 meeting.
 - Reach agreement with the Agency on the presented CMC strategies, and on the proposed BLA structure and format.

2.0 DISCUSSION

2.1. Master Cell Bank

Question 1a: Amgen will provide in the BLA a complete data package as outlined in this briefing document and required by guidance to support the commercial use of the blinatumomab cell banks (MCB2 and WCB2). Does the Agency agree that the proposed data package provides the necessary information to support a review of the suitability of the cell banks for commercialization?

FDA Response to Question 1a:

The information outlined in the data package appears reasonable to support a review of the suitability of the cell banks with respect to many attributes. See the response to Question 2b for additional comments.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

Question 1b:

(b) (4)

FDA Response to Question 1b:

(b) (4)

Discussion: *The sponsor accepted FDA's response and confirmed that a control strategy will be provided in the application; no further discussion occurred.*

2.2. Comparability of Process 4 and Process 5

Question 2a: Does the Agency agree that the data from the expanded cytotoxicity assays and the qualified binding methods presented in this briefing document demonstrate that the biological activities of process 4 and process 5 materials are not statistically different?

Question 2b: Does the Agency agree that process 4 and process 5 blinatumomab can be considered highly similar and therefore comparable as no differences have been identified that would be expected to impact the safety or efficacy of the product?

FDA Response to Question 2a and 2b:

Based on the data from the potency assay used for lot release, the expanded cytotoxicity assays, and the qualified binding method; the information provided in the meeting package; and the previously submitted data, process 4 and 5 materials appear to be sufficiently

comparable to support the use of clinical data obtained from studies in which process 4 material was administered. However, we have the following comments related to the comparability data:

- i. The BLA should include sufficient information on the experimental design and methods to critically evaluate validity of the assays used to evaluate the biological activities of AMG 103 and all raw data (not only mean results) from these assays.

ii.

(b) (4)

Discussion: *The sponsor accepted FDA's response and confirmed that expanded information on the AMG103 biological activities study design and methodology and the control strategy for (b) (4) will be provided in the application; no further discussion occurred.*

2.3. Drug Product Process Validation

Question 3: Does the Agency agree that the process characterization and process performance qualification data and approach outlined are supportive of a validated target fill weight range of (b) (4)?

FDA Response to Question 3:

The approach to process characterization and qualification to support a validated target fill range appears reasonable. The BLA should include data that demonstrate that the pilot scale filling and lyophilization models used in the process characterization studies are fully representative of the commercial scale processes. The characterization data provided in the BLA should support, for example, (b) (4)

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

2.4. Stability

Question 4a: Does the Agency agree that the proposed stability strategy for drug substance, drug product and IVSS is appropriate to enable a complete review to support commercial registration?

FDA Response to Question 4a:

The stability strategy appears to be appropriate to initiate review; however, final acceptability is a BLA review issue. Please note that sufficient data to demonstrate that the primary stability lots are fully representative of material generated using the commercial manufacturing process should be provided in the BLA. We have the following additional comments related to the drug product stability protocol.

- i. The stability protocol should include reconstitution time.
- ii. Container closure integrity testing should be part of the stability program for the commercial drug product and IVS solution lots. The testing should be performed at annual time points and at expiry and should be performed using validated testing methods.

Discussion: *The sponsor stated they did not include reconstitution time in the stability testing because they planned to provide a complete stability package with reconstitution data in the application. These data will include six drug product lots, three of which have reconstitution data out to 24 months, and data from accelerated stability studies. The sponsor stated that these stability data do not show any trends for reconstitution time. The Agency responded that the plan to submit data seems reasonable but the acceptability of this will be a review issue. The sponsor also stated they would provide container closure integrity testing as part of the stability package.*

Question 4b: For the drug substance, where the primary stability lots were manufactured at the commercial site using the commercial scale and were shown to be analytically comparable to the commercial process, and where stability data will be collected in accordance with an approved protocol, does the Agency agree that shelf-life extensions based on real time data may be notified through an annual report?

Question 4c: For the drug product, where the primary stability lots were manufactured at the commercial site using the commercial scale and were shown to be analytically comparable to the commercial process, and where stability data will be collected in accordance with an approved protocol, does the Agency agree that shelf-life extensions based on real time data may be notified through an annual report?

FDA Response to Question 4b and 4c:

The acceptability of protocol-based shelf-life extension notification in annual reports and the acceptability of the stability protocol are BLA review issues.

Discussion: *The sponsor requested clarification of the reporting category of protocol-based shelf-life extension notifications. The Agency stated that assuming the stability protocol was acceptable, which will be a review issue, a reduced reporting category for extensions of DS and DP shelf-life would be allowed. The acceptance of shelf-life extension protocols is part of BLA approval letter language.*

The sponsor also asked if it would be acceptable to submit a simple stability update in the first 30 days of the initial application submission. The Agency stated this would be acceptable. The sponsor asked if the Agency would request additional stability data updates during the review process. The Agency responded they may request simple stability updates if deemed useful, but this would be determined during the review. The sponsor said that they would provide information in the application regarding when subsequent stability updates will be available during the PDUFA clock.

2.5. Assessment of Microbiological Risk

Question 5a: Does the Agency agree that Amgen has adequately addressed the risks associated with continuous intravenous infusion of blinatumomab, and that the proposed preparation and handling procedures are adequate to support its use in the treatment of adult patients with relapsed/refractory ALL?

FDA Response to Question 5a:

No, the Agency does not agree that the risks have been adequately addressed. The data presented in Table 35 and Table 36 of the meeting package do not support continuous intravenous infusion of blinatumomab at (b) (4)

(b) (4) Under the proposed conditions of use there is a serious risk of infection to patients. Based on these results, the blinatumomab infusion solution bags should be replaced at a frequency that is supported by microbial challenge data and should include a safety margin. In addition, the microbial study does not assess the number of entries into the infusion bag (Table 37). A path forward should be developed to ensure patient safety.

In addition, based on Section 6 of the briefing document, several devices are used at different facilities. How is the risk of the different devices and related procedures incorporated in the risk analysis? Also, will the home use procedures differ? What are the parameters for connect and disconnect procedures?

Because of the above and complexity of the procedure in hospital and for home use, we strongly recommend that you submit your draft human factors validation study protocol, and use-related risk analysis for review and comment prior to your study implementation as discussed in the December 16, 2013 type C meeting minutes, dated December 23, 2013, (page 15).

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. There is a more recent draft guidance document that includes the current thinking on human factors at CDRH and recommended approaches to human factors

evaluation and testing: Applying Human Factors and Usability Engineering to Optimize Medical Device Design:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Question 5b: Does the Agency agree with the proposed continuation of the clinical strategy into the commercial setting, to support storage of prepared blinatumomab infusion bags up to 8 days at 2°C to 8°C, and administration at ambient temperature for periods of up to 48 hours per IV bag?

FDA Response to Question 5b:

See response to Question 5a.

Discussion of Questions 5a and 5b: *The sponsor confirmed that the drug is administered in a continuous 28 day infusion and acknowledged the Agency's two primary concerns of microbial safety and the complexity of administration. In regard to the microbial safety, the sponsor stated* (b) (4)

They also have imposed controls on preparation and administration of the drug and have not seen a problem with accidental contamination.

The Agency responded that the product is (b) (4) *and that it is a concern that should have been addressed during the development of the product. The Agency recommended* (b) (4)

The Agency also inquired about the possibility of (b) (4) *, The feasibility of conducting a sterility test (using a rapid microbial test method) on the bag after administration was also explored. Also, the sponsor should determine if the bags being used are approved/cleared for the 48-hour use time.*

Additionally, (b) (4) *The sponsor would need to include information regarding how this would be performed, monitored, and tracked.*

The Agency also stated that much more granular details on how things are handled, what procedures are done, and what specific devices are used should be provided. This would include, for example, the SOPs that the pharmacists actually followed in each facility during the clinical trials (both in Germany and US) and the procedures taken to mitigate risks. What happens after the bags are filled; what storage and shipping conditions are used? The sponsor stated they would provide a summary of information representative of what is being used.

The Agency recommended that the sponsor develop an SOP for the pharmacists to use instead of relying on the pharmacists to be compliant with USP<797>. The Agency also recommended that an operating manual (instructions for use) that would include, but not necessarily be limited to, directions for appropriate bags used for filling, the access lines, proper cleaning, and preparation procedures be developed. Overall, what is needed is the reassurance that that the drug is being handled in a particular manner when it goes into a

commercial setting. A full risk analysis should be completed for all steps used by all the health care providers, caregivers, and patients involved and the instructions. This full risk analysis should identify critical elements during the administration portion, to ensure that the use across facilities is sufficiently consistent. In addition, the risk analysis needs to encompass the time when patients are at home. It would need to include precise details including but not limited to who is going to do a procedure, what they are going to do, how it is going to occur, what happens in between, the kind of care of the access site that will occur while the patient is at home, and how the patient/caregiver should be trained. The full risk analysis should list when there is a risk for contamination and what steps need to be taken to minimize the risk.

The sponsor acknowledged the two aspects of product preparation and administration care that need to be addressed in a risk assessment and agreed to further discuss and develop an assessment. The sponsor inquired how this information should be presented. Also, the sponsor indicated that they wish to separate the product preparation steps from the patient/home care setting. The Agency replied that all aspects of care including home setting must be addressed. How the information is conveyed can vary based on what makes the most sense. The sponsor was also told to keep in mind that the instructions would be considered labeling instructions for use and should be appropriately validated prior to submission.

The Agency emphasized that the goal is to reduce the risk of contamination and that this should be considered high priority. They encouraged the sponsor to submit the risk analyses for comment.

Life-Cycle Management

The sponsor inquired about life-cycle management and whether it would be acceptable if the risk was substantially reduced but not eliminated. They explained that their intention was

(b) (4)
. The Agency responded that it is premature to comment and that data would be needed to provide an informed comment. Overall, the agency would look at the totality of product and risk, and look at a control strategy based on risk assessment and how the risks are mitigated.

Human Factors Testing

The sponsor confirmed they were conducting a use-related risk analysis to evaluate all steps of the drug product manufacturing process and will submit this to the Agency as soon as complete. They also stated that they would like to limit the human factor study to the reconstitution and dilution steps and submit a study concept document in advance of the completed human-factor study. The human factor study limited to these steps would start in parallel with the use-related risk protocol. As a first step, the Agency said this appeared to be acceptable; however, if the protocol is complete, it would be preferable if that were submitted now for comment. Additionally, it was communicated that the Agency will need at least four weeks to review the information submitted. The sponsor confirmed they would have the human factors protocol completed prior to their initial BLA submission and this would also include the shipping validation.

In addition to the above, the Agency reiterated the need for home-use information, e.g., risk analysis; instructions for use; and validation of steps for the health care providers in the home, the care-givers and the patients. This need reflects the 28-days of home use. For example, what instructions are given for activities to accommodate daily living (e.g., disconnection of the line, washing, bathing, etc.)? FDA recommended submission of the risk analysis and HF protocol. This is a safety issue and should be completed before BLA submission.

Regarding overdoses, the sponsor asked if it were acceptable to not limit the use of pumps to a single type but keep the range of pumps allowed if the pumps meet certain specifications listed in the protocol. The sponsor stated that a failure-mode-effect analysis would be performed and noted that overdoses were caused by either administration issues in the pharmacy, potential pump malfunctions, or human error. The Agency responded that an analysis and assessment of which pumps were used and what actually happened should be provided. The Agency will review the data and discuss internally before a comment can be made. The sponsor asked if they were allowed to decouple the pump analysis from the compounding. The Agency stated that they would need to see the entire risk hazards analysis to provide comment on what is acceptable; a risk assessment for the home environment and the procedures to maintain the pumps at home will need to be included.

Use of Placebo

The sponsor inquired about the Agency's position and rationale behind using the actual drug product instead of a placebo in the validation tests. The Agency stated that requirement for the material used depends on what is being validated. The sponsor will need to identify the intended use and the safety criteria path as well as provide a characterization study if using a placebo.

Shipping Validation

The sponsor asked the Agency what is necessary for shipping validation. The Agency stated that the sponsor should have a protocol in place because the product is a protein and temperature needs to be appropriately monitored. Any excursions that may occur should be supported by stability data. Furthermore, a description of containers that are used to ship the product should be included. The sponsor stated that this information should already be in the IND and will indicate where it can be found.

2.6. Manufacturing Site Transfer Comparability for Drug Substance

Question 6a: Does the Agency agree that an appropriately designed comparability protocol, submitted with the BLA, may upon favorable review be considered the basis for acceptability of the new drug substance manufacturing site?

Question 6b: Does the Agency agree that inclusion of an acceptable comparability protocol and a successful GMP inspection, either directly for blinatumomab or for a comparable

commercial product, are sufficient to result in a reduced reporting category from a PAS to a CBE-30 for the addition of the new drug product manufacturing site?

FDA Response to Question 6a and 6b: Although an appropriately designed protocol may provide a foundation for the acceptability of the new drug substance manufacturing site, the described protocol is not likely to be sufficient to form the basis for downgrading the reporting category of the anticipated new drug substance manufacturing site. The depth of the detail to be provided in the proposed comparability protocol is not clear. A protocol to support a reduced reporting category for a drug substance site change would require, for example, a significant level of detail regarding the changes to the manufacturing process, the risk evaluation performed to assess the potential for effects of these changes on product quality, and the planned validation strategy, in addition to the details of the analytical comparability approach. An inspection “directly for blinatumomab” would be performed in the context of the review of a PAS. It is unlikely that a successful GMP inspection for a comparable commercial product would be sufficient to result in a reduced reporting category for a drug substance site transfer. Issues related to the anticipated drug substance site transfer and inspections are compounded due to the intended use of a contract manufacturing site.

Discussion: *The sponsor accepted FDA’s response; no discussion occurred.*

2.7. Manufacturing Site Transfer Comparability for Drug Product

Question 7a: Does the Agency agree that an appropriately designed drug product comparability protocol, submitted with the BLA, may upon favorable review be considered the basis for acceptability of the new drug product manufacturing site?

FDA Response to Question 7a:

Yes, we agree that if the DP comparability protocol for manufacturing site transfer is approved by the Agency, it can be considered the basis for the acceptability of the new DP manufacturing site, provided aseptic processing validation data and information are included in the CP and the new drug product site has an acceptable GMP compliance history. Please refer to the December 12, 2011 meeting with the Agency (STN 103951/5290), Amgen’s previous (b) (4) submissions of DP comparability protocols for manufacturing site transfers (STN 125320/70 and STN 103951/5303), and the information requests associated with these supplements.

Discussion: *The sponsor inquired whether data had to be provided with the comparability protocol in the initial application. The Agency stated that data do not have to be provided in the protocol itself, but a plan to provide the data should be included. The data will be a subsequent PAS submission.*

Question 7b: Does the Agency agree that inclusion of an acceptable drug product comparability protocol and a successful GMP inspection, either directly for blinatumomab or for a comparable commercial product, are sufficient to result in a reduced reporting category from a PAS to a CBE-30 for the addition of the new drug product manufacturing site?

FDA Response to Question 7b:

Yes, inclusion of an acceptable drug product comparability protocol and a successful FDA GMP inspection for a comparable commercial product could be sufficient to allow for a reduced reporting category.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

2.8. Inspectional Planning

Question 8a: Assuming a target BLA submission date of September 2014 and a filed application, Amgen proposes inspections for blinatumomab drug substance ((b) (4)) and drug product (b) (4) to occur during (b) (4) in order to meet scheduling needs for both FDA and the contract manufacturing facilities. Does the Agency agree that this time frame will be acceptable?

FDA Response to Question 8a:

Drug substance manufacturing should be planned for an inspection to occur within 3-4 months of the initiation of the PDUFA time clock. In addition, consideration should be made for any year end facility shutdowns.

Discussion:

The sponsor asked if the 3-4 months for the inspection to occur was from Day 0. The Agency confirmed that this was the case but that the potential inspection timeframe could be longer (3-6 months) if the application has a standard review clock. The Agency explained that it is preferable to perform inspections early in the review period to allow for additional inspection follow-up. However, the Agency does take the production schedule into consideration.

The sponsor also asked if a dry run could be considered. The Agency responded that the product under review needs to be in operation for the DS facility inspection. However, this is not the case for the DP, which requires the same facility and fill line to be in operation during the inspection.

Question 8b: Both the drug substance and drug product contract manufacturing facilities are licensed by FDA for manufacture of biologic products. Should either facility have a recent satisfactory FDA biennial inspection, would the Agency consider waiving the need for the pre-approval inspection? If not, what additional information would the Agency require?

FDA Response to Question 8b:

The determination to waive inspections will be made at the time of BLA submission by the review team.

Discussion: *The sponsor inquired whether there was anything that might allow for waiver of the inspection for the DP. The Agency stated that during the review, the past inspection history of the facility along with its GMP status and the area and filling line are used in the determination to waive an inspection or not. This determination is made during the review.*

The Agency stated that a production schedule should be included in the initial application submission and should highlight when the facility is in shutdown. The Agency advised that the inspection timing is important during the review process and early communication of the production schedule would be beneficial.

Question 8c: IV solution stabilizer (manufactured at (b) (4)) is a (b) (4) operation and adequate supply currently exists. Amgen proposes not to manufacture IVSS during the proposed PAI. Does FDA agree with this proposal?

FDA Response to Question 8c:

Yes, provided the area and line in which stabilizer is manufactured has undergone previous FDA inspections. Please identify the area and line in which the stabilizer is manufactured.

Discussion: *This question was addressed in previous discussions. The Agency reiterated that the sponsor should provide a production schedule and identify the area and line in which the stabilizer is manufactured.*

2.9. Structure and Format of the Quality Section of the BLA

Question 9a: Does the Agency agree the proposed Module 3 structure and format of data will facilitate review by CDER?

FDA Response to Question 9a:

Insufficient information is provided to comment on the proposal, with the following exceptions. Information relating to aseptic process validation should be included in section 3.2.P.3.5 of the BLA. The location of relevant information on facilities should be provided within the letters of authorization. Refer to the response provided for Question 9c for additional comments.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

Question 9b: Does the Agency agree that the executed batch records planned for inclusion in the BLA submission are sufficient to enable BLA review?

FDA Response to Question 9b:

Yes.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

Question 9c: Does the Agency agree the proposed content of the CMC information is considered a complete application as intended by PDUFA V?

FDA Response to Question 9c:

While the specific points included in the minimal details provided in the meeting package appear to be acceptable, there is very little information regarding what will be included in sections 3.2.S, 3.2.P, 3.2.A, and 3.2.R. Therefore, we cannot agree that the proposed content would be considered a complete application.

Please ensure that the following information is included in the BLA at the time of submission:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product (b)(4) validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- (b)(4) validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be (b)(4) allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed for (b)(4) (3.4.S.4).

- The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance of the drug product and the IVS solution. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED]. The equipment requalification program should be described.
- In-process microbial controls and hold times. Hold times should be validated at manufacturing scale.
- [REDACTED] (b) (4), if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Lyophilization validation and sterilization
- Shipping validation studies.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed for [REDACTED] (b) (4) (where applicable), the drug product and the IVS solution, as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610.13(b).
- The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and the IVS solution and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product and IVS solution during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

Discussion: *The sponsor asked for clarification of the necessity of the rabbit pyrogen study. The Agency responded that this is a CFR requirement and needs to be conducted at least once on three lots.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. A complete reviewable quality section is expected to be submitted with the original application.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application component may be submitted within 30 calendar days after the submission of the original application: simple stability update.

Prominently identify the submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a multidiscipline pre-submission meeting is not planned at this time. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4.0 POST-MEETING COMMENTS – Use of Generally Available Devices

Within the Type B Meeting Briefing Document provided by your firm, you cite that preparation and administration of the biologic will be accomplished through general use FDA-cleared infusion devices (infusion pumps, IV sets, and single-use containers) and the selection of these devices is largely at the discretion of the user facility. Allowing for use of the biologic with general infusion devices introduces additional risk into the preparation and administration processes. In addition to responding to the Agency responses above, we strongly recommend that you carefully consider each of the potential harms that general use infusion devices may introduce into the preparation and administration processes and perform a hazard analysis for each harm identified.

Examples of harms associated with preparation and administration include but are not limited to patient systemic toxicity, allergic reaction, delay in therapy, over-infusion or under-infusion of medication, and infection as well as altered activity and adsorption of the biologic.

For each hazard you identify, you should determine if the hazard is adequately addressed or if additional controls are required to fully address each hazard.

During your analysis, if you determine that some administration hazards cannot be controlled with general use infusion products at the discretion of the user facility, it may be necessary to label your biologic to identify specific infusion devices which must be used to deliver the biologic product. These products may be specified by particular attribute(s) or through inclusion of specific brand name(s) within labeling. Any infusion devices to be used for administration of the biologic which are specified by particular attribute(s) or through inclusion of specific brand name(s) of devices within labeling should be evaluated for their ability to control the identified hazard. Conversely, if your firm determines that a particular administration hazard can be controlled with general use infusion products, the BLA should state rationale and justification for the determination.

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

/s/

SARAH B KENNETT
04/30/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125557/0

LATE-CYCLE MEETING MINUTES

Amgen, Inc.
Attention: Tai H. Yu, MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Blincyto (blinatumomab).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 7, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kris Kolibab, Regulatory Project Manager at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 7, 2014, 12:00 PM – 1:00 PM (EDT)
Meeting Location: Teleconference

Application Number: BLA 125557
Product Name: Blincyto (blinatumomab)
Applicant Name: Amgen, Inc.

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Kris Kolibab, PhD, RPM

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP):
Richard Pazdur, MD, Director

Division of Hematology Products (DHP):
Ann T. Farrell, MD, Director
Albert Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Reviewer
Robert Kane, M.D., Deputy Division Director for Safety
Qin Ryan, MD, Safety Reviewer
Amy Baird, Chief, Project Management Staff
Kris Kolibab, PhD, Regulatory Project Manager

Biotech Manufacturing Assessment Branch (BMAB):
Patricia Hughes, PhD, Team Leader
Reyes Candauchacon, PhD, Biologist

Division of Risk Management (DRISK):
Carolyn Yancey, MD, Medical Officer

Office of Biotechnology Products (OBP):
Rashmi Rawat, PhD, Acting Team Leader
Deborah Schmiel, PhD, Quality Reviewer
Qing Zhou, PhD, Quality Reviewer
Jibril Abdus-Samad, PharmD, Labeling Reviewer

Division of Medical Error Prevention and Analysis (DMEPA):
Neil Vora, PharmD, MBA, Reviewer
Kevin Wright, PharmD, Safety Regulatory Project Manager

Division of Hematology, Oncology, Toxicology (DHOT):

Christopher Sheth, PhD, Supervisory, Pharmacologist
Brenda Gehrke, PhD, Pharmacologist

Office of Biostatistics, Division of Biometrics V (DBV):

Lei Nie, PhD, Statistician Team Leader
Chia-Wen Ko, PhD, Statistician

Office of Clinical Pharmacology (OCP):

Nam Rahman, PhD, Supervisory, Pharmacologist
Nitin Mehrotra, PhD, Pharmacologist, Team Leader
Qi Liu, PhD, Pharmacologist, Team Leader
Pengfei Song, PhD, Pharmacologist

EASTERN RESEARCH GROUP ATTENDEES

(b) (6) Independent Assessor
(b) (6), Independent Assessor

APPLICANT ATTENDEES

Deborah Arrindell, JD, MD, Executive Director, Global Safety
Tara Barbanell, Director, Regulatory Affairs
Keith Cockerill, PhD, Manager, Regulatory Affairs CMC
Crystina Cupp, PhD, Director, Global Regulatory Affairs
Michelle Frazier, PhD, Director, Regulatory Affairs CMC
Greg Freiberg, MD, Executive Director, Clinical Development
Christopher Holland, MS, Director, Biostatistics
Bill Kormany, MD, Director, Global Safety
Rick Lit, Vice President, Regulatory Affairs CMC, Devices, and Biosimilars
Chandra Ma, Senior Associate, Regulatory Affairs CMC
Tap Maniar, MD, Director, Global Development
Dirk Nagorsen, MD, PhD, Director, Global Development Leader
Katie Sprugel, PhD, Scientific Director, Toxicology Sciences
Mark Taisey, Vice President, Global Regulatory Affairs
Rhian Thomas, BSc, Executive Director, Global Regulatory Affairs
Tai Yu, MS, Senior Manager, Global Regulatory Affairs
Min Zhu, PhD, Scientific Director, Pharmacokinetics and Drug Metabolism

1.0 BACKGROUND

BLA 125557/0 was submitted on September 19, 2014, for Blincyto (blinatumomab) and is currently under review by the FDA. The application has been granted priority review designation.

Proposed indication: Treatment of adult patients with Philadelphia-negative relapsed/refractory B cell-precursor acute lymphoblastic leukemia (ALL).

PDUFA goal date: May 19, 2014

FDA issued a Background Package in preparation for this meeting on November 6, 2014.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion:

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (not planned for this application), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

2. Discussion of Substantive Review Issues

There are no substantive review issues at this time.

Discussion:

No discussion occurred.

3. Information Requests

Chemistry, Manufacturing, and Controls

1. Different reference standard (RS) lots were generated at the time of major changes in blinatumomab manufacturing process (e.g., Process 3, 4, 5 and commercial process) and used for the lot release and stability testing for related lots. Therefore, your approach of using the (b) (4) tolerance interval calculations of combined lot release and stability data from Process 3, 4, 5 and commercial process DS lots to establish the acceptance criterion for blinatumomab DS potency is not appropriate. Based on the information provided on the lot release data from DP lots used to prepare RS lots AS2137-093A, 2071-073, 900427, RSN53808E, RSN100148 and 10010170301 (primary commercial RS lot) and additional information provided regarding qualification/testing of the RS lots, the potency of each DS and DP lot at the time of lot release was adjusted to estimate the potency of

all clinical materials relative to the commercial primary RS. Based on the adjusted DS and DP lot release data from clinical materials manufactured using Process 3, 4, 5 or commercial process and what can be assessed regarding manufacturing capability based on a limited number of Process 5 and commercial process lots, the acceptance criterion for potency should be tightened to (b) (4) % relative to reference standard” for blinatumomab DS and DP lot release and stability.

2. Include “Reconstitution time”, with appropriate acceptance criterion, in the DP lot release and stability specifications.
3. Section 3.2.P.6 states that the primary reference standard (PRS) and working reference standard (WRS) are monitored on stability and that "future reference standard stability will be assessed according to a defined stability program"; however, the stability program was not described. Provide protocols for the evaluation of stability of the PRS and WRS. Include information on the testing frequency, analytical methods and acceptance criteria. Update the appropriate section(s) in the BLA with this information.
4. We note that the acceptance criteria listed in the stability testing result Tables for the current PRS and WRS (Section 3.2.P.8.3) are the same as those used for drug product (DP) stability monitoring. These acceptance criteria, specifically for the potency assay, are not acceptable for the purpose of monitoring stability of RS because they would not sufficiently control for a drift in drug substance and drug product potency. The potency of the PRS and WRS should be anchored to the potency at the time of the original qualification of the PRS. In the stability protocol/description of the stability program in the BLA, clearly define the criteria for monitoring the potency to prevent a drift of the reference standards and the commercial product.
5. Based on the information provided under the drug substance (DS) and DP stability sections 3.2.S.7.2 and 3.2.P.8.2, it is not clear if you expect to report extensions of the shelf life of the DS and DP in BLA annual reports based on the commercial lot data meeting the extended stability protocol criteria at the time points in the post-approval testing schedule. Update the BLA stability sections to reflect your plans for the extension of DS and DP shelf life.
6. The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 and 3.2.P.8.2) do not include information regarding the intention to submit data from the stability studies. Provide commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.
7. The BLINCYTO preparation instructions state that after reconstitution with 3 mL of Sterile Water for Injection, USP, the resulting volume is (b) (4) with a concentration of 12.5 mcg/mL. Provide data from extractable volume testing to justify the withdrawable volume of reconstituted BLINCYTO solution (mL) and amount of BLINCYTO (mcg).

Discussion:

No discussion occurred.

4. REMS or Other Risk Management Actions

Comments on the BLINCYTO REMS Document, appended REMS materials, and BLINCYTO REMS website will be forthcoming from the Division of Risk Management.

Discussion:

No discussion occurred.

5. Postmarketing Requirements/Postmarketing Commitments

Clinical

If your product is approved under 21 CFR 601, Subpart E for accelerated approval, you will need to provide confirmatory evidence of clinical benefit as a postmarketing requirement. We have agreed to accept data from Protocol 00103311 to verify the clinical benefit of blinatumomab, including efficacy and safety.

Chemistry, Manufacturing, and Controls

1. 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 by Month/Year (Amgen to provide date).
2. 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 the 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 by Month/Year (Amgen to provide date).
3. To re-evaluate blinatumomab drug substance lot release and stability specifications after 12 lots have been manufactured using the commercial manufacturing process. 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 by Month/Year (Amgen to provide date).
4. To re-evaluate blinatumomab drug product lot release and stability specifications after 12 lots have been manufactured using the commercial manufacturing process. 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 by Month/Year (Amgen to provide date).

Discussion:

CMC informed the applicant that there will be PMCs regarding the low endotoxin recovery.

6. Major Labeling Issues

Clinical

We list below several major safety issues that may affect labeling. An additional information request regarding these issues will be sent to you with the first review of the Prescribing Information.

1. Infusion reactions, cytokine release syndrome and capillary leak syndrome appear to occur in the same timeframe after start of therapy and have overlapping manifestations. We have not been able to clearly distinguish these events. Since they are all presumed to be mediated by cytokines released in response to your product, we view them as a single toxicity. Your labeling should describe the manifestations under a single entity, so that healthcare providers can initiate proper intervention on the basis of the etiology rather than arbitrary designations.
2. We have identified cytokine release syndromes and neurotoxicity as serious and potentially fatal complications from treatment with blinatumomab that may require a boxed warning.
3. We have identified cytokine release syndrome, neurologic events, infections, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and medication errors as potential serious complications from treatment with blinatumomab that may require warnings in the labeling.

Discussion:

No discussion occurred.

7. Review Plans

Proposed labeling negotiations are ongoing. The facility inspection is still pending.

Discussion:

No discussion occurred.

8. Wrap-up and Action Items

Timeline for submission of revised labeling to the FDA.

Discussion:

No discussion occurred.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

ALBERT B DEISSEROTH
11/07/2014



BLA 125557

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Amgen, Inc.
Attention: Tai H. Yu, MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for BLINCYTO (blinatumomab) lyophilized powder for intravenous infusion ((b) (4) mcg).

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 7, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 7, 2014, 12:00 PM – 1:00 PM (EDT)
Meeting Location: Teleconference

Application Number: BLA 125557
Product Name: BLINCYTO (blinatumomab)
Indication: Treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL)

Sponsor/Applicant Name: Amgen, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests – 5 - 10 minutes

Chemistry, Manufacturing, and Controls

1. Different reference standard (RS) lots were generated at the time of major changes in blinatumomab manufacturing process (e.g., Process 3, 4, 5 and commercial process) and used for the lot release and stability testing for related lots. Therefore, your approach of using the (b)(4) tolerance interval calculations of combined lot release and stability data from Process 3, 4, 5 and commercial process DS lots to establish the acceptance criterion for blinatumomab DS potency is not appropriate. Based on the information provided on the lot release data from DP lots used to prepare RS lots AS2137-093A, 2071-073, 900427, RSN53808E, RSN100148 and 10010170301 (primary commercial RS lot) and additional information provided regarding qualification/testing of the RS lots, the potency of each DS and DP lot at the time of lot release was adjusted to estimate the potency of all clinical materials relative to the commercial primary RS. Based on the adjusted DS and DP lot release data from clinical materials manufactured using Process 3, 4, 5 or commercial process and what can be assessed regarding manufacturing capability based on a limited number of Process 5 and commercial process lots, the acceptance criterion for potency should be tightened to (b)(4)% relative to reference standard” for blinatumomab DS and DP lot release and stability.
2. Include “Reconstitution time”, with appropriate acceptance criterion, in the DP lot release and stability specifications.
3. Section 3.2.P.6 states that the primary reference standard (PRS) and working reference standard (WRS) are monitored on stability and that "future reference standard stability will be assessed according to a defined stability program"; however, the stability program was not described. Provide protocols for the evaluation of stability of the PRS and WRS. Include information on the testing frequency, analytical methods and acceptance criteria. Update the appropriate section(s) in the BLA with this information.
4. We note that the acceptance criteria listed in the stability testing result Tables for the current PRS and WRS (Section 3.2.P.8.3) are the same as those used for drug product (DP) stability monitoring. These acceptance criteria, specifically for the potency assay,

are not acceptable for the purpose of monitoring stability of RS because they would not sufficiently control for a drift in drug substance and drug product potency. The potency of the PRS and WRS should be anchored to the potency at the time of the original qualification of the PRS. In the stability protocol/description of the stability program in the BLA, clearly define the criteria for monitoring the potency to prevent a drift of the reference standards and the commercial product.

5. Based on the information provided under the drug substance (DS) and DP stability sections 3.2.S.7.2 and 3.2.P.8.2, it is not clear if you expect to report extensions of the shelf life of the DS and DP in BLA annual reports based on the commercial lot data meeting the extended stability protocol criteria at the time points in the post-approval testing schedule. Update the BLA stability sections to reflect your plans for the extension of DS and DP shelf life.
6. The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 and 3.2.P.8.2) do not include information regarding the intention to submit data from the stability studies. Provide commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.
7. The BLINCYTO preparation instructions state that after reconstitution with 3 mL of Sterile Water for Injection, USP, the resulting volume is (b) (4) with a concentration of 12.5 mcg/mL. Provide data from extractable volume testing to justify the withdrawable volume of reconstituted BLINCYTO solution (mL) and amount of BLINCYTO (mcg).

3. REMS or Other Risk Management Actions – 5 minutes

Comments on the BLINCYTO REMS Document, appended REMS materials, and BLINCYTO REMS website will be forthcoming from the Division of Risk Management.

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

Clinical

If your product is approved under 21 CFR 601, Subpart E for accelerated approval, you will need to provide confirmatory evidence of clinical benefit as a postmarketing requirement. We have agreed to accept data from Protocol 00103311 to verify the clinical benefit of blinatumomab, including efficacy and safety.

Chemistry, Manufacturing, and Controls

1. 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 by Month/Year (Amgen to provide date).

2. 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 the 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 by Month/Year (Amgen to provide date).
 3. To re-evaluate blinatumomab drug substance lot release and stability specifications after 12 lots have been manufactured using the commercial manufacturing process. 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 by Month/Year (Amgen to provide date).
 4. To re-evaluate blinatumomab drug product lot release and stability specifications after 12 lots have been manufactured using the commercial manufacturing process. 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 by Month/Year (Amgen to provide date).
5. Major labeling issues – 10 minutes

Clinical

We list below several major safety issues that may affect labeling. An additional information request regarding these issues will be sent to you with the first review of the Prescribing Information.

1. Infusion reactions, cytokine release syndrome and capillary leak syndrome appear to occur in the same timeframe after start of therapy and have overlapping manifestations. We have not been able to clearly distinguish these events. Since they are all presumed to be mediated by cytokines released in response to your product, we view them as a single toxicity. Your labeling should describe the manifestations under a single entity, so that healthcare providers can initiate proper intervention on the basis of the etiology rather than arbitrary designations.
 2. We have identified cytokine release syndromes and neurotoxicity as serious and potentially fatal complications from treatment with blinatumomab that may require a boxed warning.
 3. We have identified cytokine release syndrome, neurologic events, infections, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and medication errors as potential serious complications from treatment with blinatumomab that may require warnings in the labeling.
6. Review Plans – 5 minutes

Proposed labeling negotiations are ongoing. The facility inspection is still pending.

7. Wrap-up and Action Items – 5 minutes

Timeline for submission of revised labeling to the FDA.

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

/s/

ALBERT B DEISSEROTH
11/06/2014