

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125409Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: Greeley, George
Sent: Friday, February 24, 2012 12:05 PM
To: Tilley, Amy
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Justice, Robert
Subject: BLA 125409 (b) (4)

Importance: High

Attachments: 1_Peds_Page.doc
Hi Amy,

This email serves as confirmation of the review for (b) (4) (Pertuzumab) conducted by the PeRC PREA Subcommittee on February 22, 2012.

The Division presented a full waiver in pediatric patients because the disease/condition does not exist in the pediatric population which is indicated for the treatment of patients with 1st Line HER2-positive metastatic breast cancer.

The PeRC agreed with the Division to grant a full waiver for this indication.

The pediatric page is attached for (b) (4)



1_Peds_Page.doc (244 KB)

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
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Please consider the environment before printing this e-mail.

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

NDA/BLA#: 125409 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP1 PDUFA Goal Date: 6-8-12 Stamp Date: 12-8-11

Proprietary Name: (b) (4)

Established/Generic Name: pertuzumab

Dosage Form: Liquid single use vial

Applicant/Sponsor: Genentech, 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: For the treatment of patients with 1st Line HER2-positive metastatic breast cancer

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 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.

* 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

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

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 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:

Amy Tilley
Regulatory Project Manager

(Revised: 6/2008)

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

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

/s/

AMY R TILLEY
02/24/2012

1.3.3 Debarment Certification

Genentech, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act for the investigation of product, pertuzumab, in connection with this Biologic License Application at Genentech, Inc.

Signed by: 

Michelle H. Rohrer, Ph.D.
Vice President, U.S. Regulatory Affairs

6 December 2011

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125409/0	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Perjeta Established/Proper Name: Pertuzumab Dosage Form: Injection		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Amy Tilley		Division: DOP1
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>6-8-12</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

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (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).

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Included
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>)	Action(s) and date(s)
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. If it is division-proposed labeling, it should be in track-changes format. 	6-1-12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12-8-11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ 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 type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ 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 	5-18-12; 5-29-12; 6-4-12 kaiseraugst label w/grey background removed
<ul style="list-style-type: none"> ❖ 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>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	PN:Denied 4-5-12; Granted 5-7-12 Revs; 4-5-12; 5-7-12
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 5-9-12; 6-4-12 <input type="checkbox"/> DMPP/PLT (DRISK) <input type="checkbox"/> ODPD (DDMAC) 5-17-12; 6-1-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DMA 5-16-12; 5-31-12; PMHS 5-24-12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	2-6-12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
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
<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
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>2-22-12</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg CMC 8-12-11 Clin 9-30-11
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 4-17-07; 11-5-07; 9-17-09; 11-16-10
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	NA
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6-8-12
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6-8-12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6-8-12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None PMR = 1 PMC = 15
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	5-16-12
• Clinical review(s) (<i>indicate date for each review</i>)	5-16-12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<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>)	See MO Review 5-16-12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None CDRH 5-14-12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<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>)	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested	5-16-12
Clinical Microbiology <input checked="" type="checkbox"/> None		
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None	
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None	
Biostatistics <input type="checkbox"/> None		
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-10-12
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-10-12
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-10-12
Clinical Pharmacology <input type="checkbox"/> None		
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-10-12
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-10-12
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None	5-10-12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None	
Nonclinical <input type="checkbox"/> None		
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-16-12
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None	5-16-12
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None	5-15-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None	PMHS 5-24-12
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc	
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page	
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested	
Product Quality <input type="checkbox"/> None		
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None	6-8-12
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None	6-5-12
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None	6-6-12
❖ Microbiology Reviews	<input type="checkbox"/> Not needed	
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		5-22-12; 5-24-12; 6-6-12; 6-8-12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None	OBP 6-6-12

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See DMA Review 6-6-12
<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) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: 6-7-12 <input 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)

⁷ 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

AMY R TILLEY
06/11/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Center for Drugs Evaluation & Research - Food & Drug Administration

Office of Biotechnology Products, OPS, CDER
White Oak Building 21 Room 1510
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: 301-796-2390
Fax: 301-796-9743

Date: 6/8/2012

To: File

From: Steven Kozlowski, Director, Office of Biotechnology Products, OPS, CDER, FDA

Through: Helen Winkle, Director, Office of Pharmaceutical Science, CDER, FDA

Subject: BLA STN 125409

Therapeutic Agent(s): Pertuzumab (Perjeta)

Sponsor(s): Genentech, Inc.

Clinical Indications(s): HER2-positive locally recurrent, unresectable or metastatic breast cancer

Subject: The licensing of a BLA with deficiencies in the current manufacturing process

Conclusions:

- 1) FDA has determined that in light of the lack of a current manufacturing process that reliably produces safe, pure and potent product, that agency is approving Genentech to market only pertuzumab drug product formulated from drug substance manufactured at Genentech's facility in Vacaville, California during the 2010 campaign, for which we do not share the current manufacturing concerns. FDA has decided to permit marketing of product formulated with drug substance from the 2010 campaign prior to resolution of the current process concerns based on an assessment of a compelling exigent public health need for this product by the Office of Oncology Products at CDER with concurrence by CDER management, and the factors discussed in detail below. Marketing of pertuzumab from the 2012 campaign will require agency approval of a Prior Approval Supplement (PAS). The marketing of any other pertuzumab drug product will require Agency approval of a Prior

Approval Supplement (PAS) that includes a process validation study to support manufacture of pertuzumab, with third party oversight to mitigate the concerns that we have identified with the Quality System's reporting of the manufacturing problems. In particular, there is also a PMC regarding sponsor actions if a drug shortage appears likely. A number of factors played a role in this decision. These include but are not limited to:

- a. The clinical assessment of a compelling exigent public health need.
- b. The sponsor was able to manufacture five registration batches in 2010 without incident, thus there was a reproducible process at one point in time for this product.
- c. CDER compliance did not observe the problems observed during the 2012 campaign during the inspection with respect to the 2010 campaign, compliance did not observe any other significant issues with the 2010 campaign, and that the facility was inspected in 2010 and received a "no action indicted" status.
- d. The sponsor estimates a (b) (4) supply of safe pure and potent product formulated from drug substance from the 2010 campaign without additional manufacturing of drug substance.

- 2) The clinical assessment of a compelling exigent public health need is a critical factor in this decision to license marketing of product from the 2010 campaign prior to Genentech's resolution of its process issues, and was determined by the Office of Oncology Products and supported by CDER. Although this is a clinical assessment, we recommend that future determinations of a compelling exigent public health need should have clear criteria as this determination may enable atypical strategies to mitigate manufacturing process deficiencies. If there are no clear criteria for such determinations, there is a potential slippery slope with a gradual erosion of quality expectations. Such an erosion of quality expectations may lead to future quality failures and drug shortages. There should be a balance between the important short term needs of a specific set of patients and the long term needs of all patients expecting available high quality drugs. The recent drug shortages reflect the consequences of an erosion of quality assurance by some manufacturers. Agency expectations should increase industry quality assurance and limit any exceptions to clearly defined situations. The general impact on quality expectations should be considered in addition to the risk benefit for the target population. In addition, alternative strategies should be considered to make

product available, such as treatment INDs, before any decision to approve a BLA with manufacturing process deficiencies.

Background from DMA CMC TL Executive summary:

DMA Recommendations and Conclusions on Approvability

The Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products, OPS, CDER, does not currently recommend approval of STN 125409 for Pertuzumab manufactured by Genentech. The data submitted in this application are inadequate to support the conclusion that the manufacture of Pertuzumab is well controlled and consistently leads to a product that is pure and potent.

DMA recommends that FDA extend the review clock for 3 months via a major amendment mechanism based on any one of a series of submissions received during May, 2012. The CMC team believes this is potentially the fastest pathway to an adequately supported approval of the BLA. This would be expected to enable the applicant to complete their assessment (root cause analysis) of manufacturing problems and determine whether the problems are due to cell bank and/or other process issues, and to determine/define a modified manufacturing process that is appropriately supported with data.

If the review clock will not be extended, DMA's recommendation is a Complete Response (CR) letter, since data have not been provided consistent with a valid commercial manufacturing process.

Based on the understanding that the applicant has refused to make this product more widely available to patients prior to licensure while the manufacturing issues are being addressed, the clinical review office has indicated their intent to approve this product within a time frame consistent with the PDUFA deadline and to resolve outstanding manufacturing issues post-licensure. To the knowledge of the CMC review team, the initial licensure of a biological product under a BLA without concurrent approval of the manufacturing facility and the manufacturing process is unprecedented. This approach was agreed upon by the CDER Director. Therefore, DMA participated in the drafting of PMRs as the only mechanism available to mitigate risks to product quality from a process which lacks adequate validation.

Cell culture failures identified upon inspection revealed [REDACTED] since the manufacture of the validation lots:

(b) (4)

Five registration batches from the 2010 campaign were manufactured without incident in 2010. However, at the pre-approval inspection of the Vacaville facility in March, 2012, while reviewing discrepancy reports, the DMA reviewers on site became aware that [REDACTED] (b) (4)

[REDACTED] The remaining 2 thaws were still in process, but at the time of the inspection had demonstrated a drop in viability and specific growth rate followed by recovery. The reviewers learned that the Sponsor intended to continue manufacture from these cultures without additional product quality assessment, though such growth patterns could be associated with selection of [REDACTED] (b) (4)

[REDACTED] It was determined that these observations would be further evaluated as a review issue, as an investigation to identify the root cause of these failures was ongoing. Additionally, because WCB [REDACTED] (b) (4) is maintained by the [REDACTED] (b) (4) facility, a root cause attributed to the WCB [REDACTED] (b) (4) would be out of scope of the Vacaville inspection.

In a series of communications between the Agency and Genentech following the inspection, it became clear that [REDACTED] (b) (4)

[REDACTED] Following a series of teleconferences, Genentech agreed to the following actions to allow data necessary to potentially resolve the lack of control over the cell growth process within the PDUFA timeline: characterize product manufactured from thaws exhibiting [REDACTED] (b) (4) to ensure no changes in product quality; assess the stability of the MCB [REDACTED] (b) (4) through their ability to thaw [REDACTED] (b) (4) at the Vacaville facility; and generate a new working cell bank. These approaches were predicated on the understanding that the [REDACTED] (b) (4) were limited [REDACTED] (b) (4)

[REDACTED] The CMC review team believed that these data, along with the associated process validation data, could potentially provide sufficient additional information to support licensure of this BLA. As this appeared to be the fastest mechanism available for BLA approval, the CMC team recommended to the clinical group that FDA extend the review clock for 3 months via a major amendment mechanism based on a major amendment received in May to allow this exercise to be completed and the data to be reviewed by the Agency. In ensuing discussions with the clinical team, the CMC review team was informed that these concerns would be overruled in a BLA approval action in order to allow distribution of the available and suitable drug product lots.

Therefore, the division provided the requested language for the needed information to be provided through a post-approval regulatory requirement.

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/s/

STEVEN KOZLOWSKI
06/08/2012
OBP pertuzumab memo



BLA 125409/0

GENERAL ADVICE

Genentech, Inc.
Attention: Josephine Ing
Sr. Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

Please refer to your Biologics License Application (BLA) dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Perjeta (pertuzumab), all amendments to the BLA, and the BLA Approval Letter dated June 8, 2012.

As we notified you during the conference call among Dr. Woodcock, other representatives of the Agency, and representatives of Genentech on June 7, 2012, in light of the issues that you currently are having in the production of the pertuzumab drug substance, today we are licensing only drug product that was produced from drug substance manufactured at the Vacaville facility during the 2010 campaign that was not produced from any engineering or failed runs.¹ We understand that you estimate this to be a [REDACTED] (b) (4) supply of drug product. We are not, at this time, granting marketing approval of pertuzumab that was produced in the 2012 campaign or any subsequently manufactured product.

We anticipate that marketing approval for product formulated with drug substance from the 2012 campaign and future campaigns will be on a campaign-by-campaign basis based on data that the company will submit through supplements to the approved BLA until the process issues are fully resolved, at which time you may file a supplement to market your product without having to continue to submit campaign-by-campaign supplements. Please note that we are not instituting a lot release program for this product. Rather, we will review each BLA supplement and take action based on the data submitted by the company for each campaign.

In connection with this approval and with Genentech's planned supplements for licensure of subsequently manufactured drug substance, Genentech has agreed to complete certain additional studies. Those studies are identified in summary form in the BLA approval letter and are set forth in more detail below. In addition, we would like reiterate that for any supplement seeking approval to market drug product formulated with drug substance manufactured during the 2012 campaign, the Agency will expect such supplement to include a report on the root cause analysis of the cell growth problems, along with the interim results of the stability studies of the drug substance manufactured from thaws #4 and #6 from Working Cell Bank [REDACTED] (b) (4) and any other information you think supports approval. As Dr. Woodcock mentioned on the June 7 call, we

[REDACTED]

would like to receive this supplement within 60 days of approval (i.e., by August 8, 2012) to minimize the potential for a shortage of the drug, but we understand that sufficient data may not be available until September. We strongly suggest that you request a post-action meeting to discuss the content and timing of the supplement for marketing approval of drug product manufactured from drug substance produced in the 2012 campaign.

With respect to any supplement seeking to market pertuzumab without having to continue to submit campaign-by-campaign supplements, Genentech has agreed that such supplements will include process validation studies to support manufacture of pertuzumab as described Post-Marketing Commitments 4, 5 and/or 6. The company further has agreed that these studies will be overseen by a third-party consultant with appropriate manufacturing and current Good Manufacturing Practices (CGMP) expertise. We suggest that you request a meeting with review division to discuss this supplement.

Post-Marketing Requirement Under Section 505(o) of the FD&C Act

1. Establish a Pregnancy Registry to collect and analyze information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

The timetable you submitted on May 16, 2012, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2012
Final Protocol Submission:	08/2012
Interim Report #1:	08/2013
Interim Report #2:	08/2014
Interim Report #3:	08/2015
Interim Report #4:	08/2016
Interim Report #5:	08/2017
Interim Report #6:	08/2018
Interim Report #7:	08/2019
Interim Report #8:	08/2020
Interim Report #9:	08/2021
Interim Report #10:	08/2022
Study Completion:	08/2022
Final Report Submission:	08/2023

Post-Marketing Commitments

2. Provide a plan for responding to potential pertuzumab shortages. The plan should address your proposed response to a potential or actual shortage situation if inventory falls below a (b) (4) supply, if attempts to re-establish the pertuzumab manufacturing process are unsuccessful, and/or if demand is greater than anticipated. Include in your plan proposed communications to the press, health care professionals, and patients and a description of how these communications will be disseminated. In addition, propose a mechanism for ensuring that patients who are already receiving pertuzumab can continue to be treated according to the agreed-upon package insert.

The timetable you submitted by e-mail on June 8, 2012, states that you will complete this plan according to the following schedule:

Draft Plan Submission:	07/2012
Final Plan Submission:	09/2012

3. Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. Engage a third-party consultant with appropriate manufacturing and CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first Prior Approval Supplement (PAS). Conduct the stressed stability testing to support a demonstration of comparability of these batches of drug substance to those from the 2010 manufacturing campaign. In addition, place one lot of drug substance and drug product arising from both thaws #4 and #6 on real time stability monitoring. Provide a root cause analysis relating to the cell growth issues. Submit the Final Report as a PAS.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Interim Report:	09/2012
Study Completion:	10/2014
Final Report:	12/2014

4. Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank (MCB (b) (4)) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Include in your drug substance testing that is part of this qualification standard drug substance lot release testing, and analysis of the pertuzumab glycosylation profile, (b) (4), antibody-dependent cellular cytotoxicity (ADCC) activity, and purity by non-reduced CE-SDS. Place at least one lot from the 2012 campaign using Master Cell Bank (b) (4) into the annual drug substance and drug product stability programs. Engage a third-party consultant with appropriate manufacturing and CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this

study and submit monthly independent reports between now and approval of the first PAS. Submit the Final Report as a PAS.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Study Completion: 12/2012
Final Report Submission: 02/2013

5. Conduct a process validation study to support manufacture of pertuzumab from a new Working Cell Bank (WCB) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Engage a third-party consultant with appropriate manufacturing and CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study, and submit monthly independent reports between now and approval of the first PAS. In addition to standard drug substance lot release testing, you have agreed that the extended characterization of the first three lots produced from the new WCB will include analysis of the percent ^{(b) (4)} ADCC activity, and purity by non-reduced CE-SDS. Place at least one lot from the new WCB campaign into the annual drug substance and drug product stability programs. Submit the Final Report as a PAS.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2013
Study Completion: 09/2014
Final Report Submission: 10/2014

6. Conduct process validation studies to support manufacture of pertuzumab from working cell banks by a modified process ^{(b) (4)} in order to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Engage a third-party consultant with appropriate manufacturing and CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study, and submit monthly independent reports between now and approval of the first PAS. In addition to standard drug substance lot release testing, conduct extended characterization of the first three lots produced by the ^{(b) (4)} process that includes analysis of the pertuzumab glycosylation profile, ^{(b) (4)} ADCC activity, and purity by non-reduced CE-SDS. Submit the Final Report as a PAS.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2014
Study Completion: 10/2015
Final Report Submission: 11/2015

7. Conduct stability studies of the MCB at more frequent intervals than the currently proposed 10 years. Submit Interim Reports every four years and the Final Report after 20 years.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Interim Report 1:	06/2016
Interim Report 2:	06/2020
Interim Report 3:	06/2024
Interim Report 4:	06/2028
Final Report Submission:	06/2032

8. Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014. Submit the Final Report as a Changes Being Effected-30 Supplement (CBE-30).

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/2014
Final Report Submission:	03/2015

9. Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. If the CE-SDS assay is determined to be non-redundant to the approved SE-HPLC assay, incorporate the CE-SDS assay into the control strategy for pertuzumab and/or the pertuzumab reference standard. Submit the Final Report as CBE-30.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	07/2013
Final Report Submission:	09/2013

10. Conduct a study to establish a drug substance release specification to control for ADCC activity of pertuzumab (e.g. an assay for percent ^{(b)(4)} and to assess process parameter controls to assure that the process is controlled to maintain ADCC activity within clinical experience. Update the control strategy to include ADCC activity and the drug substance release specifications to include an assay capable of controlling ADCC activity, with acceptance criteria based on clinical experience. In addition, update the ^{(b)(4)} manufacturing process to include a list of process parameters, and their ranges, sufficient to assure that ADCC activity will remain within clinical experience. Submit the Final Report as a PAS.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Study Completion: 02/2013
Final Report Submission: 03/2013

11. Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the Final Report as a PAS.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2012
Study Completion: 12/2012
Final Report Submission: 02/2013

12. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4). Submit the Final Report as a Changes Being Effected-0 Supplement (CBE-0).

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2012
Study Completion: 07/2012
Final Report Submission: 12/2012

13. To evaluate the risk of contamination, revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. Test three different lots of raw materials in the re-validation runs. Submit the Final Report as CBE-30.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2013
Study Completion: 08/2013
Final Report Submission: 12/2013

14. To evaluate the risk of resistant microorganisms and contamination, conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the

feasibility of discontinuing (b) (4) the
screening of raw materials for (b) (4) bioburden and endotoxin, (b) (4) the non-sterile
media hold time and temperature (b) (4) and the expanded use of (b) (4)
Submit the Final Report as CBE-30.

The timetable you submitted by e-mail on June 8, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2012
Final Report Submission: 03/2013

15. Conduct a clinical trial to test whether the addition of hormonal therapy increases the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-positive metastatic breast cancer population. Study MO27775 (PERTAIN) as designed will be completed to fulfill this post-marketing commitment.

The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 08/2012
Trial Completion: 09/2016
Final Report Submission: 03/2017

16. Submit the Final Overall Survival Analysis (OS) of trial WO20698/TOC4129g as defined in your protocol and Statistical Analysis Plan (SAP).

The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/2013
Final Report Submission: 05/2014

Please submit all deliverables for your post-marketing obligations to the Agency as provided in the BLA approval letter or otherwise directed by the review division.

If you have any questions about any of these obligations, please call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
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/

RICHARD PAZDUR
06/08/2012

From: Tilley, Amy
Sent: Friday, June 08, 2012 6:46 PM
To: 'Vassia Tegoulia'
Cc: Josephine Ing; Kacuba, Alice
Subject: RE: BLA 125409 Perjeta - Minor revisions to PMCs

Importance: High
Vassia & Josephine,

Please see our responses in red below. We respectfully request your concurrence to the PMCs within 10 minutes of this email.

Reviewing the document that you just sent us, we have two questions.

PMC#3: The Interim Report will not be submitted as a PAS anymore. We would like to understand what will be the Regulatory mechanism to allow the release of the Q1/Q2 2012 (b) (4) Campaign material which is needed to ensure drug supply. Will this be gated to the August 8th submission that Dr. Woodcock referred to yesterday?

If you would like to submit the Interim Report as a PAS, we will review it expeditiously. The course of action for approval of those lots will be explained in the secondary letter that you will receive tonight. Please set up a meeting with the Division to discuss the contents of the letter.

PMC#4: The concurrent release mechanism has been removed. If the material from the MCB campaign is needed prior to the PAS approval, what mechanism is available to release it. Since the concurrent release is governed by the guidance document, can we assume that concurrent release is still applicable if needed for the MCB Campaign.

The course of action for approval of those lots will be explained in the secondary letter that you will receive tonight. Please set up a meeting with the Division to discuss the contents of the letter.

We also noted that the dates are variable. We acknowledge that all the dates on the PMC will be June 8th.

The dates on the PMC will be June 8.

Will we need to submit this officially through the gateway today or a .pdf unofficial document will work?

Please send it through email and follow up with an official submission to the BLA.

We will be taking action shortly and will be contacting you soon.

Amy

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]
Sent: Friday, June 08, 2012 6:19 PM
To: Tilley, Amy
Cc: Vassia Tegoulia; Josephine Ing; Kacuba, Alice
Subject: Re: BLA 125409 Perjeta - Minor revisions to PMCs

Dear Amy,

reviewing the document that you just sent us, we have two questions

PMC#3: The Interim Report will not be submitted as a PAS anymore. We would like to understand what will be the Regulatory mechanism to allow the release of the Q1/Q2 2012 (b) (4) Campaign material which is needed to ensure drug supply. Will this be gated to the August 8th submission that Dr. Woodcock referred to yesterday?

PMC#4: The concurrent release mechanism has been removed. If the material from the MCB campaign is needed prior to the PAS approval, what mechanism is available to release it. Since the concurrent release is governed by the guidance document, can we assume that concurrent release is still applicable if needed for the MCB Campaign.

We also noted that the dates are variable. We acknowledge that all the dates on the PMC will be June 8th.

Will we need to submit this officially through the gateway today or a .pdf unofficial document will work?

We appreciate your help.

Vassia

On Fri, Jun 8, 2012 at 2:42 PM, Tilley, Amy <AMY.TILLEY@fda.hhs.gov> wrote:
Vassia and Josephine,

I reference the telephone conversation between Josephine and us regarding the Agency's minor revisions to the PMCs for your concurrence.

We respectfully request your concurrence to the PMCs within 15 minutes of this email. Send your concurrence to the PMC's via email in the same format in the document below and follow up with an official submission to the BLA.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ [301.796.3994](tel:301.796.3994) (phone) • [301.796.9845](tel:301.796.9845) (fax) | ✉ amy.tilley@fda.hhs.gov



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--

Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : 650 225 7527

Fax: 650 225 4171

Mobile: (b) (6)

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/s/

AMY R TILLEY

06/11/2012

2nd IR sent to GNE on 6-8-12

From: Tilley, Amy
Sent: Thursday, June 07, 2012 7:05 PM
To: 'Josephine Ing'
Cc: Vassia Tegoulia
Subject: BLA 125409 Perjeta - Postmarketing Obligations

Importance: High

Follow Up Flag: Follow up
Due By: Friday, June 08, 2012 2:00 PM
Flag Status: Flagged

Attachments: Perjeta Postmarketing Obligations 6-7-12 .doc
Josephine,

As promised during the teleconference today below is a document containing the Postmarketing Obligations for Pertuzumab.



Perjeta
Postmarketing Obligations

Please note we must have your proposed Milestone officially submitted for PMC 2 as soon as possible tomorrow.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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Postmarketing Obligations

Post-Marketing Requirement Under Section 505(o) of the FD&C Act

1. Establish a Pregnancy Registry to collect and analyze information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

The timetable you submitted on May 16, 2012, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2012
Final Protocol Submission:	08/2012
Interim Report #1:	08/2013
Interim Report #2:	08/2014
Interim Report #3:	08/2015
Interim Report #4:	08/2016
Interim Report #5:	08/2017
Interim Report #6:	08/2018
Interim Report #7:	08/2019
Interim Report #8:	08/2020
Interim Report #9:	08/2021
Interim Report #10:	08/2022
Study Completion:	08/2022
Final Report Submission:	08/2023

Post-Marketing Commitments

2. Provide a plan for responding to potential pertuzumab shortages. The plan should address your proposed response to a potential or actual shortage situation if inventory falls below a (b) (4) supply, if attempts to re-establish the pertuzumab manufacturing process are unsuccessful, and/or if demand is greater than anticipated. The plan should include proposed communications to the press, health care professionals, and patients and a description of how these communications will be disseminated. In addition, you must propose a mechanism for ensuring that patients who are already receiving pertuzumab can continue to be treated according to the agreed-upon package insert.

The timetable you submitted on June X, 2012, states that you will complete this plan according to the following schedule:

Draft Plan Submission:	07/2012
Final Plan Submission:	09/2012

3. Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. The stressed stability testing must be performed prior to release of drug substance arising from thaws #4 and #6 to support comparability of these batches of drug substance to those from the 2010 manufacturing campaign. In addition, one lot of drug substance and drug product arising from both thaws #4 and #6 must be placed on real time stability monitoring. Provide a root cause analysis relating to poor cell growth and viability of the Q1/Q2 2012 pertuzumab campaign. Submit the results of the stressed stability study and a root cause analysis in the Interim Report. Submit the Interim and Final Reports as Prior Approval Supplements (PAS).

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2012
Interim Report:	09/2012
Study Completion:	10/2014
Final Report:	12/2014

4. Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank (MCB (b) (4)) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Drug substance testing that is part of this qualification must include standard drug substance lot release testing, and analysis of the pertuzumab glycosylation profile, (b) (4) ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the 2012 MCB campaign must be placed into the annual drug substance and drug product stability programs. Perform concurrent release of process performance qualification (PPQ) batches as per FDA guidance for industry Process Validation: General Principles and Practices. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/2012
Final Report Submission:	02/2013

5. Conduct a process validation study to support manufacture of pertuzumab from a new Working Cell Bank (WCB) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. You must engage a third party consultant with

appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced from the new WCB must include analysis of the percent (b)(4) ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the new WCB campaign must be placed into the annual drug substance and drug product stability programs. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	09/2014
Final Report Submission:	10/2014

6. Conduct process validation studies to support manufacture of pertuzumab from Working Cell Banks by a modified process (b)(4) in order to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. You must engage a third party consultant with appropriate CGMP expertise to oversee your firm's facility, procedures, processes, and systems relating to this study and submit monthly independent reports between now and approval of the first PAS. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced by the (b)(4) process must include analysis of the pertuzumab glycosylation profile, (b)(4), ADCC activity, and purity by non-reduced CE-SDS. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2014
Study Completion:	10/2015
Final Report Submission:	11/2015

7. Conduct stability studies of the MCB at more frequent intervals than the currently proposed 10 years. Submit Interim Reports every four years and the Final Report after 20 years.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Interim Report 1:	06/2016
Interim Report 2:	06/2020
Interim Report 3:	06/2024
Interim Report 4:	06/2028
Final Report Submission:	06/2032

8. Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2014. Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/ 2014
Final Report Submission:	03/2015

9. Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. If the CE-SDS assay is determined to be non-redundant to the approved SE-HPLC assay, incorporate the CE-SDS assay into the control strategy for pertuzumab and/or the pertuzumab reference standard. Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	07/2013
Final Report Submission:	09/2013

10. Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab [REDACTED] (b) (4) and to assess process parameter controls to assure that the process is controlled to maintain ADCC activity within clinical experience. The control strategy must be updated to include ADCC activity and the drug substance release specifications must be updated to include an assay capable of controlling ADCC activity, with acceptance criteria based on clinical experience. In addition, the [REDACTED] (b) (4) manufacturing process will need to be updated to include a list of process parameters, and their ranges, sufficient to assure that ADCC activity will remain within clinical experience. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	02/2013
Final Report Submission:	03/2013

11. Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2012
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Study Completion: 12/2012
Final Report Submission: 02/2013

12. Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4). Submit the Final Report as a Changes Being Effected-0 (CBE-0).

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2012
Study Completion: 07/2012
Final Report Submission: 12/2012

13. To evaluate the risk of contamination, revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. Test three different lots of raw materials in the re-validation runs. Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2013
Study Completion: 08/2013
Final Report Submission: 12/2013

14. To evaluate the risk of resistant microorganisms and contamination, conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the feasibility of discontinuing (b) (4) the screening of raw materials for (b) (4) bioburden and endotoxin, (b) (4) the (b) (4) media hold time and temperature (b) (4) and the expanded use of (b) (4). Submit the Final Report as CBE-30.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2012
Final Report Submission: 03/2013

15. Conduct a clinical trial to test whether the addition of hormonal therapy increases the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-positive metastatic breast cancer population. Study MO27775 (PERTAIN) as designed will be completed to fulfill this post-marketing commitment.

The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2012
Trial Completion:	09/2016
Final Report Submission:	03/2017

16. Submit the final overall survival (OS) analysis of trial WO20698/TOC4129g as defined in your protocol and Statistical Analysis Plan (SAP).

The timetable you submitted on May 16, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2012
Trial Completion:	12/2013
Final Report Submission:	05/2014

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/s/

AMY R TILLEY
06/07/2012

MEMORANDUM OF TELECONFERENCE

DATE: June 7, 2012

APPLICATION NUMBER: BLA 125409/0

BETWEEN:

Josephine Ing, Sr. Scientist, Regulatory Affairs

Mark "Kip" Benyunes, Senior Group Medical Director, Product Development Oncology
Clinical Science

Dietmar Berger, Vice President, Clinical Development, Hematology/Oncology

Ian Clark, Chief Executive Officer, Genentech and Head of North American Commercial
Operations

Michael Doherty, Senior Vice President, Global Head Product Development Regulatory

Liz Homans, Vice President, HER2 Franchise, Global Product Strategy

Sandra Horning, Senior Vice President, Global Head Clinical Development
Hematology/Oncology

Josephine Ing, Regulatory Program Director, Product Development Regulatory

Karen Jones, Global Head Oncology, Product Development Regulatory

Lynne Krummen, Senior Director, Pharma Technical Regulatory

Theresa Martinez, Lifecycle Leader, Global Product Strategy

Teresa Perney, Director, Product Development Regulatory

Michelle Rohrer, Vice President, US Regulatory Affairs, Product Development
Regulatory

Mary Sliwowski, Vice President, Regulatory Chemistry Manufacturing and Controls
and Information Systems

Pascal Soriot, Chief Operating Officer, Roche Pharmaceuticals Division

Patrick Yang, Executive Vice President, Head Global Technical Operations

Phone: (b) (4)

Representing: Genentech, Inc.

AND

Name:

Janet Woodcock, Director, CDER

Richard Pazdur, Director, OHOP

Robert Justice, Director, DOP1

Amna Ibrahim, Deputy Director, DOP1

Patricia Cortazar, Clinical Team Leader

Gideon Blumenthal, Clinical Reviewer

Nancy Scher, Clinical Reviewer (Safety)

Kathryn Fedenko, Deputy Director Safety

Denise Esposito, Deputy Director, ORP

Maryll Toufanian, Associate Chief Counsel for Drugs, OCC

David Joy, Regulatory Counsel, ORP/DRPI

Elizabeth Giaquinto, Project Manager, OEP

Mary Beth Clarke, Acting Director, OEP
Helen Winkle, Director, OPS
Steven Kozlowski, Director, OPB
Patrick Swann, Deputy Division Director, DMA
Kathryn King, Biologist, DMA
Patricia Hughes, Team Leader, Microbiology Product Quality, OC/OMPQ/BMAB
Bo Chi, Ph.D., CMC Microbiology Reviewer, OC/OMPQ/DGMPA/BMAB
Steven Lynn, Director (Acting), OMPQ
Ilisa Bernstein, Deputy Director, OC
Tara Gooen, LCDR, Acting Chief, OC/OMPQ/DGMPA
Mahesh Ramanadham, LT., Acting Team Leader, OC/OMPQ/DGMPA
Tamy Kim, Associate Director of Regulatory Affairs (Acting), IO/OHOP
Alice Kacuba, Chief Project Management Staff, DOP1
Amy Tilley, Regulatory Project Manager, DOP1

BACKGROUND: Genentech submitted BLA125409/0 for the proposed indication: in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The PDUFA action date is Friday, June 8, 2012. There have been numerous teleconferences between FDA and Genentech discussing the product manufacturing inconsistencies. The FDA notified Genentech that there would be forthcoming PMRs and PMCs from the Agency regarding this topic. On May 7, 2012, FDA sent the sponsor FDA PMRs for the action letter requesting the sponsor to fill in the milestone due dates. On May 16, 2012, the sponsor submitted 1) milestone due dates for the PMRs and 2) agreement to conduct the PMC trials/studies was submitted by e-mail June 8, 2012.

SUBJECT: The purpose of today's teleconference is for Dr. Woodcock to discuss the June 8, 2012 action plan with Genentech

TODAY'S PHONE CALL:

Following introductions, Dr. Woodcock outlined the June 8, 2012 BLA action for Pertuzumab. The Agency will approve Pertuzumab because of the clinical benefit to the patient population for an unmet medical need.

-The Approval of the BLA on June 8, 2012 is contingent upon Genentech completing certain post-marketing activities. The Agency would approve the use of Pertuzumab manufactured from the "2010 campaign". The Agency understands that Genentech estimates that this campaign is sufficient to supply drug product for (b) (4) depending on patient demand.

-Dr. Woodcock stated that we could not approve drug product from the 2012 campaign at this time, contingent on post-marketing activities. Genentech would have to submit additional supplements, such as a supplement or the root cause analysis of the cell bank to be submitted by 8-3-2012, would need to be submitted and reviewed prior to approving full production. This is not a lot release but an action on full production.

-As further campaigns are developed, we have additional questions and perhaps, each campaign may need to be approved separately until fill production can be approved.

-The Agency will issue the action letter on June 8, 2012. That action letter will contain a brief description of each post-marketing obligation, along with milestones. The Agency will then issue a second letter to Genentech that lists the full details of each post-marketing obligations.

-The Agency will review the subsequent supplements for the post-marketing obligations as a priority.

-In light of the patient population that will be receiving this drug, Dr. Woodcock explained to Genentech that are adding a post-marketing obligation for Genentech to develop a plan in the case that appears that there would be a drug shortage. We would want the patients that are already receiving the drug to be able to continue receiving it.

-Dr. Woodcock requested that Genentech submit their copy of their Press Release to the Agency today.

-Dr. Woodcock explained to Genentech that if the highest levels of Genentech were uncomfortable with this overall action plan, the other option would be to extend the PDUFA clock. Genentech stated that they were comfortable with the plan and they committed to owning the problem with inconsistent production issues.

Alice Kacuba
Chief, Project Management Staff

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/s/

AMY R TILLEY
06/12/2012



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

Date: 6/5/2012
To: Administrative File, STN 125409/0
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to review memo for New Biologic License Applications (BLA)
STN125409/0 dated 5/22/2012
Applicant: Genentech, Inc.
US License: 1048
Facility: Genentech
1000 New Horizons Way
Vacaville, CA 95688-9431
FEI: 3002902534
Product: Perjeta™ (pertuzumab)
Dosage: 420 mg/20 mL, liquid single use vial, intravenous injection
Indication: For the treatment of patients with 1st Line HER2-positive metastatic breast cancer
PDUFA date: June 8, 2012

Recommendation: The drug substance part of this application is recommended for approval from product quality microbiology perspective with two post-market requirements (PMRs, see below) and one post-market commitment (PMC, see below).

The BLA is not recommended for approval to manufacture pertuzumab drug substance in the Genentech Vacaville, CA facility under the U.S. License 1048. This is the recommendation from the DGMPA/OMPQ documented in the final TB-EER for BLA 125409.

PMRs

1. To evaluate the potential for serious risk of contamination, revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. Test three different lots of raw materials in the re-validation runs.

Final Protocol Submission: 04/2013
Study Completion: 08/2013
Final Report Submission: 12/2013

2. To evaluate the serious risk of resistant microorganisms and contamination, conduct a comprehensive risk assessment regarding the microbial control of the cell culture process

and generate an action plan based on the assessment. The risk assessment will consider the feasibility of discontinuing (b) (4), the screening of raw materials for (b) (4) bioburden and endotoxin, (b) (4) the non-sterile media hold time and temperature (b) (4) and the expanded use of (b) (4)

Final Protocol Submission: 09/2012
Final Report Submission: 03/2013

PMC:

Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b) (4). Submit the final study report as a Changes Being Effected-0 (CBE-0).

Final Protocol Submission: 06/2012
Study Completion: 07/2012
Final Report Submission: 12/2012

This review amends the drug substance review memo for Genentech's BLA STN125409/0 by Bo Chi dated 5/22/12 to update the information on post-market commitments (PMCs)/post-market requirements (PMRs). Due to the potential for serious risk of resistant microorganisms and contamination, it is necessary to convert two of the three PMCs to PMRs (see above).

Cc: WO51: Chi
WO51: Hughes
WO22: Tilley

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/s/

WENDY C WEINBERG
06/04/2012

BARBARA L RELAHAN
06/04/2012

PATRICK G SWANN
06/05/2012

PATRICK G SWANN on behalf of KATHLEEN A CLOUSE STREBEL
06/05/2012

From: Tilley, Amy
Sent: Friday, June 01, 2012 2:33 PM
To: 'Josephine Ing'; ing.josephine@gene.com
'Vassia Tegoulia' Tegoulia.vassia@gene.com
Subject: BLA 125409 Perjeta - Follow up email re: PMR Format Telephone Conversation 6-1-12

Josephine & Vassia,

This email is a follow up to our telephone conversation earlier today.

1. There will be 1 or 2 additional PMRs being sent to you later today.
2. We revised the wording of the 3 PMRs which contained language regarding 3rd party oversight.
3. A TCON with Genentech will be scheduled for Thursday, 6-7-12, which must include your upper management as Dr. Janet Woodcock will be present to wrap things up and to discuss any unresolved issues.
4. For now, submit your PMR/PMC milestones via *email* only in the following format:
 - a) 1st document should contain all the PMRs and their milestone dates using our exact language
 - b) 2nd document should contain the following sentence, i.e., "We agree to conduct the following postmarketing commitments.", followed by the exact language of the PMC's and the milestone dates you have proposed

We look forward to receiving via email your proposed milestone dates.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
06/01/2012

From: Tilley, Amy
Sent: Thursday, May 31, 2012 3:31 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: BLA 125409 Perjeta - FDA 2 Minor Revisions to PI 8.1 & 8.6

Importance: High

Follow Up Flag: Follow up
Due By: Friday, June 01, 2012 3:00 PM
Flag Status: Flagged

Attachments: FDA PT revised 5-31-12.doc
Josephine,

Below is the FDA revised PI with 2 minor changes in Section 8.1 and 8.6. See the rationale for these 2 minor changes below.



FDA PT
d 5-31-12.doc

Section 8.1, lines 221-223 - Changed the order of the original second and third sentences, for clarity to the reader. It did not make sense to start off saying that there were no data with PERJETA in pregnant women and then have the second sentence state that the adverse effects would occur during all trimesters of pregnancy (original second sentence). Since the AE occurring during all trimesters is based on the findings in the animal studies, reversing the order of the two sentences now gets the point across that the likelihood that bad things will happen if PERJETA is used during pregnancy is based on the animal data, and that the bad things can happen at any trimester if PERJETA is administered.

Second change - **Section 8.6**, line 265 "PERJETA *can* cause fetal harm..." (originally read (b) (4)). Change is for consistency with the language in the rest of the label, and the CFR required language for a Category D designation.

We respectfully request your response to this email both via email and as an official submission **no later than 3 pm Friday, 6-1-12.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,

CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/31/2012

From: Tilley, Amy
Sent: Thursday, May 31, 2012 1:33 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: **TIME SENSITIVE** BLA 125409 Perjeta - Additional PMRs & PMCs

Importance: High

Follow Up Flag: Follow up
Due By: Friday, June 01, 2012 2:00 PM
Flag Status: Flagged
Josephine,

Below are the PMRs and PMCs for Perjeta relating to product quality. These are in addition to the PMR and PMCs from clinical that have already been agreed to.

We respectfully request your official submission of the milestone dates for both the PMRs and PMCs and your agreement to the PMCs by email **no later than 2 pm EST, on Friday 6-1-12.** Your email must state that the official submission is in progress and will be submitted no later than the following business day. You will note that some milestone dates are already populated as we think these dates are critical.

Wording of some PMR's may or may not change regarding the need for a third party oversight as the action letter undergoes further review. Please focus on the milestones.

Please let me know as soon as possible today if you need a teleconference today or tomorrow to obtain clarification on the PMRs or to discuss the PMCs.

POSTMARKETING REQUIREMENTS UNDER 505(o)

1 Conduct a process validation study to support manufacture of pertuzumab from the Master Cell Bank (MCB (b) (4)) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. Drug substance testing that is part of this qualification must include standard drug substance lot release testing, and analysis of the pertuzumab glycosylation profile, (b) (4), ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the 2012 MCB campaign must be placed into the annual drug substance and drug product stability programs. Concurrent release of process performance qualification (PPQ) batches as per FDA guidance for industry Process Validation: General Principles and Practices must be performed under third party oversight. Submit the final study report as a Prior Approval Supplement (PAS).

Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

2 Conduct a study that tests the stability of the Master Cell Bank (MCB) at more frequent intervals than the currently proposed 10 years. Submit interim reports every four years and a final report after 20 years.

Final Protocol Submission: MM/YYYY
Interim Report 1: MM/YYYY
Interim Report 2: MM/YYYY
Interim Report 3: MM/YYYY
Interim Report 4: MM/YYYY
Final Report Submission: 06/2032

3 Conduct a process validation study under third party oversight to support manufacture of pertuzumab from a new Working Cell Bank (WCB) and to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced from the new WCB must include analysis of the percent (b) (4) ADCC activity, and purity by non-reduced CE-SDS. At least one lot from the new WCB campaign must be placed into the annual drug substance and drug product stability programs. Submit the final study report as a Prior Approval Supplement (PAS).

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

- 4 Conduct process validation studies under third party oversight to support manufacture of pertuzumab from Working Cell Banks by a modified process using (b)(4) in order to ensure that drug substance manufacturing campaigns are able to deliver consistent product with comparable strength, quality, purity, and potency to that used in the phase 3 clinical trial. In addition to standard drug substance lot release testing, extended characterization of the first three lots produced by the (b)(4) process must include analysis of the pertuzumab glycosylation profile, (b)(4), ADCC activity, and purity by non-reduced CE-SDS. Submit the final study report as a Prior Approval Supplement (PAS).

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

- 5 Conduct a stability study that includes real time and stressed stability testing to assess the stability of the drug substance manufactured from thaws #4 and #6 of the Q1/Q2 2012 pertuzumab campaign. The stressed stability testing must be performed prior to release of drug substance arising from thaws #4 and #6 to support comparability of these batches of drug substance to those from the 2010 manufacturing campaign. In addition, one lot of drug substance and drug product arising from both thaws #4 and #6 must be placed on real time stability monitoring. Submit the Interim Report of stressed stability testing as a Changes Being Effected-30 Days (CBE-30).

Final Protocol Submission: 06/2012
Interim Report (Stressed): 08/2012
Study Completion: MM/YYYY
Final Report (Real Time): MM/YYYY

- 6 Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the final study report as a Prior Approval Supplement (PAS).

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

- 7 Conduct a study to establish a drug substance release specification to control for antibody-dependent cellular cytotoxicity (ADCC) activity of pertuzumab (b)(4) and to assess process parameter controls to assure that the process is controlled to maintain ADCC activity within clinical experience. The control strategy must be

updated to include ADCC activity and the drug substance release specifications must be updated to include an assay capable of controlling ADCC activity, with acceptance criteria based on clinical experience. In addition, the (b) (4) manufacturing process will need to be updated to include a list of process parameters, and their ranges, sufficient to assure that ADCC activity will remain within clinical experience. Submit the final report as a Prior Approval Supplement (PAS).

Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

- 8 To evaluate the potential for serious risk of contamination, revalidate the hold time for non-sterile cell culture media with a (b) (4) acceptance criterion that demonstrates microbial control. Test three different lots of raw materials in the re-validation runs.

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: 12/2013

- 9 To evaluate the serious risk of resistant microorganisms and contamination, conduct a comprehensive risk assessment regarding the microbial control of the cell culture process and generate an action plan based on the assessment. The risk assessment will consider the feasibility of discontinuing (b) (4) the screening of raw materials for (b) (4) bioburden and endotoxin, the (b) (4) the non-sterile media hold time and temperature (b) (4), and the expanded use of (b) (4)

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: 03/2013

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

- 11 Conduct a study to assess the ability of a non-reduced CE-SDS assay to detect and quantitate pertuzumab fragmentation. If the CE-SDS assay is determined to be non-redundant to the approved SE-HPLC assay, incorporate the CE-SDS assay into the control strategy for pertuzumab and/or the pertuzumab reference standard. Submit the final report as a Changes Being Effectuated-30 Days (CBE-30).

Final Protocol Submission: MM/ YYYY
Study Completion: MM/ YYYY
Final Report Submission: MM/ YYYY

- 12 Reassess release and stability specifications for pertuzumab drug substance and drug product through June 30, 2013.

Final Protocol Submission: MM/YYYY
Study Completion: MM/ YYYY
Final Report Submission: MM/ YYYY

- 13 Re-qualify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, and the in-house environmental isolate, *Acinetobacter radioresistens* B217VA, to the list of challenge microorganisms and use 10 mL sample volumes. Include in this re-qualification study bioburden samples collected at each pertuzumab chromatography steps (b)(4) Submit the final study report as a Changes Being Effectuated-0 (CBE-0).

Final Protocol Submission: MM/ YYYY
Study Completion: MM/ YYYY
Final Report Submission: MM/ YYYY

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology
Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver
Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/31/2012

From: Kacuba, Alice
Sent: Tuesday, May 29, 2012 1:10 PM
To: 'Josephine Ing' ing.josephine@gene.com
Cc: Tilley, Amy
Subject: Perjeta FDA revised labeling and tcon time

Importance: High

Attachments: 5-29-2012-int-meeting-Spon revised PI rcv 25May2012 (2).doc
Hi,

1. Attached is the revised FDA labeling. Minor issues.
2. The PT reviewer and supervisor and I request to discuss the numbers in Section 8.2 regarding your comment on the doses. We are available at 2:20-3 PM Washington DC time. It will be me, Kimberly Ringgold, Ph.D., and Anne Pilaro, Ph.D. Please have your PT available. Please provide a call in number and passcode.
3. I need to discuss a call that I received from a patient's aunt today.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov

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5-29-2012-in
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following this page

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/s/

AMY R TILLEY
05/31/2012

From: Tilley, Amy
Sent: Thursday, May 24, 2012 2:15 PM
To: 'Josephine Ing' ing.josephine@gene.com
Cc: Kacuba, Alice
Subject: TIME SENSITIVE BLA 125409 Perjeta - FDA revised PI

Follow Up Flag: Follow up
Due By: Friday, May 25, 2012 4:00 PM
Flag Status: Flagged

Attachments: FDA Revised 5-24-12.doc
[Josephine,](#)

Below is the FDA revised PI for Perjeta for Genentech's review and concurrence.



FDA Revised
I-12.doc (2 MI

In the 2 tables please delete the extra column where the Perjeta information was cut and inserted before the Placebo column.

Should Genentech need to discuss any label revisions with the Division, we must know ahead of time the *specifics* of the revisions and which sections. The only time available for the Division is 10 am our time on Tuesday, 5-29-12.

Genentech must also supply us with the call in information should they want to have a brief label discussion.

Please note that I will be out of the office on 5-29-12 and that my Chief, Alice Kacuba will be covering for me so please *Reply to All* when responding to this email.

We respectfully request your revisions to the label **no later than 4 pm on 5-25-12.**

Kindly confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
05/24/2012

From: Vassia Tegoulia [tegoulia.vassia@gene.com]
Sent: Wednesday, May 23, 2012 6:27 PM
To: Tilley, Amy
Cc: Vassia Tegoulia; Welch, Joel
Subject: Re: Submission of pertuzumab product quality data for (b) (4) runs 13, 18, 20 and 21 and updated supply chain slide
Hello Amy,

Originally we would be sending the majority of Product Quality (PQ) data on May 24th, followed by ADCC and Potency data on May 29th. Our teams worked over the weekend and off-hours and were able to expedite PQ data by 1 day and ADCC/potency data by 6 days (staying away from the long weekend break help us achieve this).

As a results what you just received contains both the info that was supposed to be submitted on May 24th and May 29th.

I hope this clarifies the situation.

Please feel free to give me a call on my mobile (b) (6)

Best results,

Vassia

On Wed, May 23, 2012 at 3:21 PM, Tilley, Amy <AMY.TILLEY@fda.hhs.gov> wrote:
[Vassia](#),

[This email is a follow up to my vm from a few moments ago.](#)

[We seek clarification as to what you meant in your email below dated 5-23-12, regarding "This is our last submission of information at this time. Please let me know of any questions or any additional information needed."](#)

[We were of the understanding Genentech was to submit additional information regarding additional runs on or about May 29, 2012.](#)

[Please provide us with an update as soon as possible.](#)

[Thanks.](#)

[Amy](#)

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]
Sent: Wednesday, May 23, 2012 5:09 PM
To: Welch, Joel; Tilley, Amy
Subject: Submission of pertuzumab product quality data for (b) (4) runs 13, 18, 20 and 21 and updated supply chain slide

Dear Joel,

We were able to get all the product quality data for the remaining (b) (4) runs today including potency and ADCC information.

I am sending you a courtesy copy of the report that we will be submitting through the electronic gateway shortly. I am sending you the courtesy first as it's getting 5pm already in East Coast.

As you will see product quality for all four runs is consistent with the historical batches.

We updated our supply chain slide to reflect 4 successful runs out of the Q1/Q2 2012 (b) (4) campaign and I am also attaching it to this email.

We expect that the material generated from this campaign will supply the market till February 2013.

This is our last submission of information at this time. Please let me know of any questions or any additional information needed.

Last item: I received an email from the PLAIR group earlier in which they indicated that they will follow up with either you or Amy. Any updates you can provide on this are appreciated.

Best regards,

Vassia

On Tue, May 22, 2012 at 11:11 PM, Vassia Tegoulia <vassia@gene.com> wrote:
Dear Joel,

Today we submitted the last updated BLA sections, 3.2.S.2.6, 3.2.A.2 and sections from Module 2 (QOS). We believe these are the last remaining sections that needed to be updated to reflect the Q&A during the pertuzumab review. The sections were also submitted through the electronic gateway and the submission has been acknowledged.

With today's submission, we have updated a total of 22 sections from Module 3 and 9 sections from Module 2 since last Wednesday. We believe we incorporated all the changes we discussed throughout the review. Do let us know if there are any other sections that the Agency thinks that need to be updated or if there any questions on the updated sections.

I will be contacting the PLAIR group next to see if there is any more information that they might need. I will cc both you and Amy. I want to make sure that they have all the information to move forward.

We are on track to officially submit the product quality data from the remaining three successful (b) (4) runs on Thursday. We added the results from (b) (4) 0013 along with the three new runs (b) (4) 0018, (b) (4) 0020 and (b) (4) 0021) so we can provide all the information from the Drug Substance generated in (b) (4) from Campaign 2 in a single report. We have

accelerated potency and ADCC testing and we will provide the results in the report as well. Will it also be acceptable to provide the report to you by email tomorrow as well?

Finally, we have started putting together all the commitments that were communicated during the IRs. Should we send you a copy when we finalize them?

As always, do let me know if there is anything else we can do to help the review move forward.

I appreciate your help,

Vassia

On Tue, May 22, 2012 at 10:59 AM, Welch, Joel <Joel.Welch@fda.hhs.gov> wrote:
[Vassia](#),

[At this time, we don't plan on additional teleconferences to discuss the product quality data. I'll remind the team regarding the outstanding PLAIR issue.](#)

[Joel](#)

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]
Sent: Tuesday, May 22, 2012 2:46 AM
To: Welch, Joel
Cc: Vassia Tegoulia; Tilley, Amy
Subject: Re: Submission of updated BLA sections.

Dear Joel,

please find attached submission Sequence No 0053 that contains Part4 of the Updated BLA sections. This submission was transmitted through the Gateway and was acknowledged on Monday afternoon. The sections included in this Sequence are 3.2.S.2.2.3, 3.2.S.7.1, 3.2.S.7.2, 3.2.S.7.3, 3.2.P.8.1, 3.2.P.8.2, 3.2.P.8.3. We will submit the last updated sections (Part 5) on Tuesday.

I would like to ask for your help in the next two questions

a) Will there be a phoneconference to discuss the product quality data for the last three runs ^{(b) (4)} runs?

b) Do you have any updates on the PLAIR? Is there any additional information that the Agency would like to see? As we have discussed during the previous two phoneconferences, we need to bring the unlabeled vials into the country as soon as possible. When should we expect to get a response to our request and is there anything we can do to help the PLAIR decision?

Any information you can provide on the two issues above is much appreciated.
Best regards.

Vassia

On Mon, May 21, 2012 at 7:31 AM, Welch, Joel <Joel.Welch@fda.hhs.gov> wrote:
[Vassia](#),

[Can you send us a list of changes made to each section as well?](#)

[Thanks.](#)

[Joel](#)

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]
Sent: Saturday, May 19, 2012 2:47 AM
To: Welch, Joel
Cc: Vassia Tegoulia; Tilley, Amy
Subject: Re: Submission of updated BLA sections.

Dear Joel,

thanks for the flexibility. Please find attached the .pdfs of the following updated BLA sections.

3.2.S.7.1 Stability Summary and Conclusions

3.2.S.7.3 Stability Data

3.2.P.8.1 Stability Summary and Conclusion

3.2.P.8.3 Stability Data

I will be also sending 3.2.S.2.5 but in another email due to its size.

These sections will be formally submitted to the BLA on Monday.

I am missing the relevant QOS sections from list I sent you earlier in the week (see below) but I will try to complete this over the weekend.

As we are going through the BLA updates, we are identifying some additional sections (3.2.S.2.6, 3.2.A.2) that are also affected, albeit to a much lesser extent. We will submit

these early next week as well. It is difficult to map everything to the BLA but I want to communicate that we are standing behind all of our agreements either through Q&A or through our phoneconferences.

Please let me know of any questions.
Have a good weekend,

Vassia

On Fri, May 18, 2012 at 4:32 AM, Welch, Joel <Joel.Welch@fda.hhs.gov> wrote:
[Vassia](#),

[This suggestion seems acceptable.](#)

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]
Sent: Thursday, May 17, 2012 5:27 AM
To: Welch, Joel; Tilley, Amy
Subject: Submission of updated BLA sections.
Good morning Joel,

I would like to give you some information on the updated (b) (4) section that was submitted earlier and discuss with you our proposal for the updated BLA sections.

You have received already the seven updated sections below. One comment on the (b) (4) plan. We ended up removing the table of the CPPs (Table 3.2.R.2-1) from the revised version and replacing it with references to two tables in the BLA that present the CPPs for DS and DP. The reason for this is that our Cell Culture experts are currently evaluating the Cell Culture process for any Critical Process Parameters due to the introduction of (b) (4) as a CQA. So the Cell Culture CPPs might change and we didn't think it would be appropriate to send you something that we would change again on Friday especially given the urgency to review it. By referencing the Table in the BLA, the (b) (4) section doesn't need to change once the new CPPs are identified. I wanted to provide the clarification in case a question comes up from the reviewers. It also help to explain that the main reasons we haven't submitted updated BLA sections so far is that we wanted to make sure that the sections would not change in the future.

As we working full time on updating the BLA sections, we identified some weak points in our ability to submit all affected sections through the electronic gateway to the BLA by Friday.

a) The new IEX specifications forces us to update 4 addl sections, the stability sections for DS and DP since we have to constrict our expiry dating to 2 years from the proposed (b) (4). Although the change is not significant, publishing all four sections again takes time as all links needs to be established from the beginning. Since this is a minor change and not critical for the submission, I would like to propose that we send you the updated .pdf unofficially by Friday and finalize the publishing/submission early next

week.

b) 3.2.S.2.5 is also running into publishing delays due to its size so I would like to ask if it will be ok to formally update the section in the BLA next week.

c) And finally, this is the same situation for the QOS which needs to come last once everything else is finalized to ensure that all updates are captured.

Just to clarify, we can provide all the sections in .pdf by Friday. Is enabling all the links and formally publishing the sections that delays us.

I wanted to check if this is an acceptable proposal that we can move forward with.

I appreciate your help,

Vassia

Proposal per sections

Part 1 : Formally Submitted on 05/16 (completed)

3.2.S.2.2.3 Purification and Modification Reactions

3.2.S.6 Container Closure System

3.2.P.2.2.1 Formulation Development

3.2.P.2.3 Manufacturing Process Development

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

3.2.P.3.5 Process Validation and/or Evaluation

3.2.P.7 Container Closure System

(b) (4)

3.2.R.3.1 Comparability Protocols (Working Cell Bank) - Removed

3.2.R.3.2 Comparability Protocols (Site Transfer) – Removed

Part 2: To be formally submitted on 05/18 (or earlier if available)

3.2.S.3.2 Impurities

3.2.S.5 Reference Standards or Materials

3.2.S.2.2.2 Cell Culture and Harvest

3.2.S.4.1 Specification

3.2.S.4.5 Justification of Specification

3.2.P.5.1 Specification(s)

3.2.P.5.6 Justification of Specification(s)

Part 3: To email as .pdfs on 05/18 and Publish and formally submit early next week

3.2.S.2.5 Process Validation and/or Evaluation

3.2.S.7.1 Stability Summary and Conclusions

3.2.S.7.3 Stability Data

3.2.P.8.1 Stability Summary and Conclusion

3.2.P.8.3 Stability Data

QOS

--

Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: (b) (6)

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Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: [REDACTED] (b) (6)

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Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: [REDACTED] (b) (6)

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Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: [REDACTED] (b) (6)

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Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: [REDACTED] (b) (6)

--

Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : 650 225 7527

Fax: 650 225 4171

Mobile:  (b) (6)

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/s/

AMY R TILLEY
05/23/2012

From: Abdus-Samad, Jibril
Sent: Friday, May 18, 2012 2:26 PM
To: Tilley, Amy
Cc: Rains, Kimberly E; Bridges, Todd; Fahnbulleh, Frances; Rellahan, Barbara; Graham, Laurie; King, Kathryn; Welch, Joel
Subject: RE: Spon Rev C&C labels and PI re BLA 125409 Perjeta
The Applicant's revisions are acceptable.

Jibril Abdus-Samad, PharmD
Safety Evaluator
Division of Medication Error Prevention and Analysis
Office 301-796-2196

From: Rains, Kimberly E
Sent: Friday, May 18, 2012 11:15 AM
To: Tilley, Amy; Abdus-Samad, Jibril
Subject: RE: Spon Rev C&C labels and PI re BLA 125409 Perjeta

Hi Amy,

The labels are acceptable. Have they been officially submitted? Jibril are they acceptable to you?

Kimberly Rains, Pharm.D
Lieutenant Commander
United States Public Health Service
FDA/CDER/OPS/OBP
301-796-4242

From: Tilley, Amy
Sent: Friday, May 18, 2012 11:03 AM
To: Justice, Robert; Ibrahim, Amna; Cortazar, Patricia; Scher, Nancy; Blumenthal, Gideon; Pilaro, Anne; Ringgold, Kimberly; Zineh, Issam; Garnett, Christine; Sridhara, Rajeshwari; Tang, Shenghui; Chattopadhyay, Somesh; Weinberg, Wendy; King, Kathryn; Kacuba, Alice; Rellahan, Barbara; Graham, Laurie; Chi, Bo; Thomas, Colleen; Hughes, Patricia; Grimstein, Christian; Charlab Orbach, Rosane; Welch, Joel; Swann, Patrick G.; Boone, Hilde *; Krudys, Kevin; Howard, Christopher; CDER OSI PM TRACK; Young, Robert S K; Philip, Reena; Lorick, Kevin; Chan, Maria M; Hu, Yun-Fu; Liu, Qi (CDER); Song, Pengfei; Cullity, Constance; Iacono-Connor, Lauren; Leibenhaut, Susan; Thompson, Susan (CDER); Fahnbulleh, Frances; Bridges, Todd; Abdus-Samad, Jibril; Booth, Brian P; Kim, Tamy; Toscano, Marybeth; Fedenko, Katherine; Jenney, Susan; Rains, Kimberly E; Bewry, Nadine; Pohlman, Janice; Tassinari, Melissa; Ceresa, Carrie M; Epperly, Holly; Wang, Cunlin; Rulli, Karen
Subject: Spon Rev C&C labels and PI re BLA 125409 Perjeta
Importance: High

Review Team,

Below is the CDER Share Drive Link for you to access to review and make ***all revisions*** to the Sponsor revised PI prior to the 5-24 Label Mtg.

Also attached are the Sponsor's revised Carton and Container Labels for your review.

***** **ATTENTION ALL REVIEWERS** *****

All revisions are to be made on the CDER Share Drive version of the PI only.
Link: <\\cdsnas\transfer\DDOP RPM\Amy Tilley\BLA 125409 Pertuzumab>

<< File: Carton 10135204 17May2012.pdf >> << File: Container Label
10135205 17May2012.pdf >>
See everyone ready and prepared at the 5-24 label meeting.

Have a great weekend.

Amy

3 Page(s) of Draft
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/s/

AMY R TILLEY
06/04/2012

From: [Tilley, Amy](#)
To: ["Josephine Ing"](#)
Bcc: [Cortazar, Patricia](#); [Blumenthal, Gideon](#); [Scher, Nancy](#); [Bridges, Todd](#); [Abdus-Samad, Jibril](#); [Kacuba, Alice](#)
Subject: BLA 125409 Perjeta FDA Revised PI & DMEPA Container Comment
Date: Wednesday, May 16, 2012 1:00:00 PM
Attachments: [FDA rev PI 5-15-12.doc](#)
Importance: High

Josephine,

Below is the latest FDA Revised PI for Genentech's review. Also, below is DMEPA's Container Comment.

DMEPA's Container Comment:

Container Label

Revise the presentation of the strength statement to appear similar to the carton labeling by decreasing the font size of the concentration (30 mg/mL) and relocating the concentration (30 mg/mL) to appear directly below the total drug content (420 mg/14 mL). Thus, the strength statement should appear as:

420 mg/14 mL

(30 mg/mL)

We respectfully request any additional PI revisions you may have or your consent to our revisions as soon as possible.

Kindly confirm receipt of this email and let me know the date you will be making any further label submissions.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/16/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 16, 2012
TIME: 2:00 p.m. EST
LOCATION: Telecon
APPLICATION: BLA 125409
DRUG NAME: Pertuzumab
TYPE OF MEETING: C
MEETING CHAIR: Barbara Rellahan
MEETING RECORDER: Joel Welch

FDA ATTENDEES: (Title and Office/Division)

Kathleen Clouse, Ph.D. Division Director, Division of Monoclonal Antibodies
Patricia Cortazar, M.D., Medical Officer, Division of Oncology Products I
Laurie Graham, M.S. Quality Reviewer, Division of Monoclonal Antibodies
Kathryn King, Ph.D., Quality Reviewer, Division of Monoclonal Antibodies
Barbara Rellahan, Ph.D., CMC Team Leader, Division of Monoclonal Antibodies
Nancy Scher, M.D., Medical Officer, Division of Oncology Products I
Patrick Swann, Ph.D. Deputy Division Director, Division of Monoclonal Antibodies
Wendy Weinberg, Ph.D. CMC Team Leader, Division of Monoclonal Antibodies
Joel Welch, Ph.D., Regulatory Project Manager, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES (Genentech):

Dana Andersen, PhD, Senior Director, Pharmaceutical Development
Jesse Bergevin, Associate Director, Vacaville Science and Engineering
Mary Cromwell, PhD, Director, Pharmaceutical Development
Vickie Frydenlund, Senior Director, Pharma Technical Regulatory
Lynn Gennaro, PhD, Scientist, Analytical Development and Quality Control
Martin Gawlitzek, PhD, Senior Group Leader, Late Stage Cell Culture
Reed Harris, Senior Director, Analytical Development and Quality Control
Josephine Ing, Senior Scientist, Product Development Regulatory
Karen Jones, PhD, Head Oncology, Product Development Regulatory
Brian Kelley, PhD, Vice President, Pharma Technical Development, Bioprocessing
Bob Kiss, PhD, Director, Late Stage Cell Culture
Andrew Kosky, PhD, Associate Director, Pharma Technical Development, Team Leader
Charles Morgan, PhD, Senior Product Manager, Pharma Technical Regulatory
Teresa Perney, PhD, Director, Global Regulatory Lead, Product Development Regulatory
Dieter Schmalzing, PhD, Director, Methods Management and Technology
Mary Sliwowski, PhD, Vice President, Pharma Technical Regulatory
Vassia Tegoulia, PhD, Senior Product Manager, Pharma Technical Regulatory

BACKGROUND:

A ninth CMC teleconference with Genentech was held to discuss the Pertuzumab application. This teleconference was called to discuss DMA information request #3 (aka CMC IR#6).

DISCUSSION POINTS:

The discussion focused on DMA IR#3, specifically questions 8, 9, and 11 and the finalization of specifications associated with purity by IEC-HPLC and ADCC Control. The Sponsor began by presenting their proposed specifications, reproduced in Slide 4 of their attached presentation. The Agency stated while it agrees in some cases, it would also request some changes. The Agency noted that the risk assessment presented by the Sponsor did not include ADCC as a mechanism of action. Therefore, the Sponsor had failed to consider all variants which affected ADCC as critical quality attributes. After some discussion it was agreed that the in-process drug substance rejection limit would be (b) (4) for main peak, (b) (4) for acidic peak and (b) (4) for basic peak. The drug product release specification would be (b) (4) main, (b) (4) acidic and (b) (4) basic peaks and the drug product stability specifications would be (b) (4) main, (b) (4) acidic, and (b) (4) basic peaks. As a final agreement, the Agency requested clarification in the BLA that the revision of in-process limits may only be performed with Agency approval. The Sponsor agreed to include the language in the BLA.

Regarding the ADCC control specification, the Sponsor proposed to establish (b) (4) acceptance criteria for (b) (4) which would maintain the product's ADCC activity within a range of (b) (4) relative to the reference material until a drug substance release specification is established. The Agency agreed with this proposal.

A final set of discussions occurred regarding outstanding regulatory questions, including the pre-launch activities importation request (PLAIR) submitted by Genentech. The Sponsor inquired if the above referenced IR was the source of the delay of the approval of the PLAIR. The Agency said that they (DMA) could not comment on the PLAIR at this time. The Agency noted that a complete response to IR6 had been expected on May 11, 2012 and that delay in getting a final response to all the issues in IR6 was still one outstanding issue. The Sponsor noted the request was approaching urgency and that the timeline was very tight.

Regarding the Sponsor's question regarding the adequacy of Section 3.2.S.2.2.3 updates, the Agency noted they were still concerned with the viability and low cell growth, thus weren't satisfied with a (b) (4) final viability at thaw in process control limit. After a brief discussion, a limit of (b) (4) was agreed upon. The Sponsor then restated their commitment to meet the previously mentioned dates for product quality data submission.

DECISIONS (AGREEMENTS) REACHED:

Agreements were reached regarding the specifications for IEC-HPLC, (b) (4) acceptance criteria and final viability at thaw limit.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

The Sponsor included a slide deck to guide the discussion. Those slides are presented as an attachment.

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/s/

JOEL T WELCH
05/29/2012

BARBARA L RELAHAN
05/29/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:

1. In your response to Question 1 of FDA's information request dated 4/20/12, you did not address the additional procedures you plan to implement to prevent (b) (4)

If no additional procedures are in place, remove the option of (b) (4)

2. You indicated in your response to Question 2 of FDA's information request dated 4/20/12 that one of the purposes of having (b) (4)

(b) (4)

- time and hold temperature to prevent bioburden accumulation during (b) (4)
3. The hold time validation for non-sterile cell culture media (b) (4) was inadequate in that the bioburden acceptance criterion of the studies for (b) (4) was set at a (b) (4) level without considering impact on media performance. In addition, the bioburden levels in the media at the end of several hold time validation runs were (b) (4). Please commit as a post-marketing commitment (PMC) to revalidate the hold time for non-sterile cell culture media with an adequate bioburden acceptance criterion at scale at the Vacaville facility. The three validation runs should use three different batches of the raw materials used at a concentration higher than (b) (4) in the media. The PMC should include the date by which the results will be submitted in a CBE30.
4. You committed in your response to 483 observation 6a to perform a comprehensive risk assessment regarding cell culture microbial control and generate an action plan based on the assessment. The risk assessment will consider the current use of (b) (4). In addition, consider the implementation of (b) (4). Provide a date for the submission of the results and action plan in a CBE30.
5. In your response to Question 3 of FDA's information request dated 4/20/12, you intend to retain the option of using (b) (4).
6. With regard to Question 4 of FDA's information request dated 4/20/12, you did not clarify if a bioburden sample is taken prior to (b) (4). If the product pool is held (b) (4) a bioburden sample should be collected (b) (4). Please confirm.
7. You have committed to requalify the bioburden test for the bulk drug substance and in-process bioburden samples with the addition of *S. aureus* ATCC 6538 and *B. subtilis* ATCC 6633 as well as an in-house environmental isolate *Acinetobacter radioresistens* B217VA to the list of challenge microorganisms and to use a 10 mL sample volumes. The (b) (4) bioburden sampling at pertuzumab chromatography steps will be included in this qualification. Please provide a date by which the summary data will be provided in a CBE0.
8. The bioburden data for the (b) (4) for the drug substance registration batches manufactured at Vacaville were not provided in Table 3.2.S.4.4-4. Please provide the summary bioburden data for that step. In addition, you have

established the (b) (4) bioburden alert limit of the (b) (4) (b) (4). Please evaluate the bioburden data to determine if the alert limit is set at a meaningful level taking into consideration the manufacturing capability and readjust the limit as necessary. Update Table 3.2.S.4.1-2 accordingly.

9. Please update Table 3.2.S.4.1-2 to include the endotoxin action limit of (b) (4) (b) (4).
10. The endotoxin specifications for the DS and DP have been revised to (b) (4) (b) (4). Please update Tables 3.2.S.4.1-1 and 3.2.P.5.1-1, respectively.

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
05/15/2012

From: [Tilley, Amy](#)
To: ["Josephine Ing"](#)
Bcc: [Cortazar, Patricia](#); [Blumenthal, Gideon](#); [Scher, Nancy](#)
Subject: BLA 125409 Pertuzumab - Clin IR DFS Results
Date: Monday, May 14, 2012 11:44:00 AM
Importance: High

Josephine,

The Clinical Review Team wants to know when you plan to submit the DFS results from the NeoSPHERE study (WO20697)?

We would like a response by **Tuesday, May 15, 2012**.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/14/2012

From: Tilley, Amy
Sent: Friday, May 11, 2012 12:15 PM
To: 'Josephine Ing'
Cc: Vassia Tegoulia
Subject: BLA 125409 Pertuzumab - FDA Carton & Container Label Revisions

Importance: High

Follow Up Flag: Follow up
Due By: Friday, May 18, 2012 12:00 AM
Flag Status: Flagged

[Josephine,](#)

[Please see the label revisions from the DMEPA and DMA Review Teams.](#)

General Comments for the Container Label, Carton Label, Vial cap, and ferrule:

1. Revise the color scheme to differentiate from Trastuzumab packaging.
2. Revise the proprietary name to appear in Title Case and revise the established name, (Pertuzumab), to have the same font size and weight as the proprietary name. For example:

Tradename
(Pertuzumab)

3. Revise the concentration portion of the strength statement, 30 mg/mL, by slightly increasing the font size and relocating so that it appears within the colored background bar with the total drug content (420 mg/14 mL).
4. Revise the listing of important information on the label in the following order:

Dilute Prior To Use
For Intravenous Infusion Only
Single-Use Vial
Discard Unused Portion

5. Relocate the statement, *No preservative*, to the side panel to provide space for the preceding recommendation in 4.
6. Revise the storage and handling statements on the side panel to read as follows:

Storage: Refrigerate at 2°C to 8°C (36°F to 46°F). Store in original carton to protect from light

Do Not Freeze. Do Not Shake.

Additionally, note the change in case to sentence case and Title case in both statements, respectively.

6. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60.
7. Per USPC Official 5/1/12-8/1/12, USP 35/NF 306, <1091> Labeling of Inactive ingredients, please list the names of the inactive ingredients in alphabetical order on all carton labels. Consider the following format: inactive ingredient (amount)
8. Revise the manufacturer information from [REDACTED] ^{(b) (4)} to “Manufactured by:” to comply with the definition of manufacturer in 21 CFR 601.3(t), 21 CFR 610.60, 21 CFR 610.61, and 21 CFR 610.64.
9. Please provide all proposed printed information on the vial cap and/or ferrule.

We respectfully request your revised labels be officially submitted **as soon as possible** to facilitate our review of this application.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/11/2012

From: [Tilley, Amy](#)
To: ["Josephine Ing"](#)
Bcc: [Cortazar, Patricia](#); [Scher, Nancy](#); [Blumenthal, Gideon](#)
Subject: BLA 125409 Pertuzumab - Clinical IR-Label-Table 1 febrile neutropenia
Date: Thursday, May 10, 2012 5:21:00 PM
Importance: High

Josephine,

Below is a Clinical Information Request (IR) regarding Table 1 in the proposed pertuzumab label.

Please verify the entries for "febrile neutropenia".

We were able to verify "All grades" for placebo arm (7.6%) and pertuzumab arms (13.8%) from dataset AE.

Per CTCAE, febrile neutropenia is, by definition grade ≥ 3 . Please verify the correct values for grade 3-4 febrile neutropenia.

We respectfully request your response to this Clinical IR as soon as possible to continue our review of this application.

Kindly confirm receipt of this email.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/10/2012

From: Tilley, Amy
Sent: Tuesday, May 01, 2012 4:47 PM
To: 'Josephine Ing'
Subject: *TIME SENSITIVE* BLA 125409 Pertuzumab - Teleconference Request

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, May 02, 2012 12:00 AM
Flag Status: Flagged
Josephine,

The Review Team would like to have a TCON with Genentech **on Thursday 4-3-12, from 12:15 pm - 12:30 pm.**

The TCON will last 15 minutes to discuss a potential PMR with regards to a Pregnancy Registry.

FDA attendees will be from the Clinical, Pharm Tox and Safety disciplines.

Robert Justice, M.D., M.S., Division Director
Amna Ibrahim, M.D., Division Deputy Director
Gideon Blumenthal, M.D., Clinical Reviewer
Nancy Scher, M.D., Clinical Reviewer
Anne Pilaro, Ph.D., Supervisory Toxicologist
Kimberly Ringgold, PhD., Pharmacologist/Toxicologist Reviewer
Katherine Fedenko, M.S., C.R.N.P., Deputy Director Safety
Susan Jenney, M.S., Safety Project Manager
Alice Kacuba, RN, MSN, RAC, Chief, Project Management Staff
Amy Tilley, Regulatory Project Manager

As soon as possible, kindly confirm Genentech's Clinical and Pharmacologist/Toxicologist Reviewers availability for this TCON.

Please provide a call in number.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/01/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 9, 2012
TIME: 3:00 p.m. EST
LOCATION: Telecon
APPLICATION: BLA 125409
DRUG NAME: Pertuzumab
TYPE OF MEETING: C
MEETING CHAIR: Wendy Weinberg
MEETING RECORDER: Joel Welch

FDA ATTENDEES: (Title and Office/Division)

Kathleen Clouse, Ph.D. Division Director, Division of Monoclonal Antibodies
Laurie Graham, M.S. Quality Reviewer, Division of Monoclonal Antibodies
Kathryn King, Ph.D., Quality Reviewer, Division of Monoclonal Antibodies
Robert Justice, M.D., Director, Division of Drug Oncology Products I
Barbara Rellahan, Ph.D., CMC Team Leader, Division of Monoclonal Antibodies
Patrick Swann, Ph.D. Deputy Division Director, Division of Monoclonal Antibodies
Amy Tilley, Regulatory Health Project Manager Division of Drug Oncology Products I
Wendy Weinberg, Ph.D. CMC Team Leader, Division of Monoclonal Antibodies
Joel Welch, Ph.D., Regulatory Project Manager, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES (Genentech):

Jesse Bergevin, Associate Director, Vacaville Science and Engineering
Mary Cromwell, PhD ,Director, Pharmaceutical Development
Vickie Frydenlund, Senior Director, Pharma Technical Regulatory
Martin Gawlitzek, PhD, Senior Group Leader, Late Stage Cell Culture
Lynn Gennaro, PhD, Scientist, Analytical Development and Quality Control
Alissa Goodale, PhD, Global Franchise Head for HER and Haem, Product Development Regulatory
Reed Harris, Senior Director, Analytical Development and Quality Control
Josephine Ing, Senior Scientist, Product Development Regulatory
Karen Jones, PhD, Head Oncology, Product Development Regulatory
Brian Kelley, PhD, Vice President, Pharma Technical Development, Bioprocessing
Bob Kiss, PhD, Director, Late Stage Cell Culture
Andrew Kosky, PhD, Associate Director, Pharma Technical Development, Team Leader
Charles Morgan, PhD, Senior Product Manager, Pharma Technical Regulatory
Teresa Perney, PhD, Director, Global Regulatory Lead, Product Development Regulatory
Dieter Schmalzing, PhD, Director, Methods Management and Technology
Roger Symczak, Product Supply Chain Leader, Global Supply Chain Management
Ron Taticek, PhD, Senior Director, Pharma Technical Quality
Vassia Tegoulia, PhD, Senior Product Manager, Pharma Technical Regulatory

BACKGROUND:

An eighth CMC teleconference with Genentech was held. This teleconference was called to provide an update for the investigation into the low cell growth of the 2012 campaign of pertuzumab at the Vacaville facility.

DISCUSSION POINTS:

The Sponsor began by providing an update on the progress of the cell growth action plan. They stated that (b) (4) runs are expected to be successful from the current campaign in Vacaville.

The Sponsor then noted the current timelines for the availability of product quality data (presented in slide 6). The Sponsor inquired if submitting results for batches (b) (4) 0018, (b) (4) 0020, and (b) (4) 0021 individually or together was preferable. The Agency agreed that together was the most efficient. The Sponsor agreed to provide the data by May 24. (b) (4)

The Sponsor then presented the quality data from (b) (4) 0013, noting that it was generated in a developmental laboratory and was not the “official” quality control data. Therefore, the actual submitted results will differ slightly. The Sponsor noted that the general conclusion is the results were within the historical trend of those successfully manufactured from previous campaigns. Some values that were slightly different included a (b) (4) (which the Sponsor stated is actually an “impurity” and therefore not an issue), and the non-reducing CE-SDS (which the Sponsor stated differed by only by (b) (4) which is within the precision of the method). The Agency asked for the ADCC method to be provided as well. The Sponsor agreed.

The Sponsor provided a brief update on the status of the WCB being transferred into (b) (4) noting that a total of 2 WCB thaws were performed and have successfully completed (b) (4). The transfer to the (b) (4) was expected by May 12. The Agency thanked the Sponsor for the update, noting that should any unexpected observations occur, the Agency should be notified as soon as possible. An agreement was reached to have an additional teleconference to discuss CMC IR#6 (also referred to as the Division of Monoclonal Antibodies IR #3) around May 15.

DECISIONS (AGREEMENTS) REACHED:

A decision was reached to have an additional teleconference on May 15 to discuss CMC IR#6. The Sponsor also agreed to submit analytical test results for batches (b) (4) 0018, (b) (4) 0020, and (b) (4) 0021 simultaneously.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

The Sponsor included a slide deck to guide the discussion. Those slides are presented as an attachment.

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/s/

JOEL T WELCH
05/22/2012

WENDY C WEINBERG
05/25/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:

1. The (b) (4) requalification data provided thus far includes only one validation run for (b) (4) 3 and two validation runs for (b) (4) 4. In addition, the (b) (4) locations for load 3 have not been provided. Because items from both loads may be used for pertuzumab manufacturing, additional information is needed to ensure that both load configurations have been validated.
 - a. Please provide summary data from the three most recent validation runs for (b) (4) 3 and 4. This information can include runs performed during initial validation of the (b) (4).
 - b. The amendment dated 26-April-2012 (sequence 0030) included a table (Table Q4-3) describing the items in (b) (4) 4 and the corresponding (b) (4) I placement for validation studies. Please provide a table that lists this information for load configuration 3.
2. Please describe how worst-case locations for (b) (4) placement for (b) (4) validation studies were identified. This information was previously requested, but the response dated 26-April-2012 (sequence 0030) describes identification of worst-case location for (b) (4) placement for (b) (4) studies.
3. Please describe how worst-case locations for placement of (b) (4) were identified. This information was previously requested, but the

response dated 26-April-2012 (sequence 0030) describes identification of worst-case location for (b) (4) placement for (b) (4) studies.

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
05/08/2012

From: [Tilley, Amy](#)
To: ["Josephine Ing"](#)
Bcc: [Cortazar, Patricia](#); [Scher, Nancy](#); [Blumenthal, Gideon](#)
Subject: BLA 125409 Pertuzumab - Clinical IR (CRC)
Date: Tuesday, May 08, 2012 12:09:00 PM
Importance: High

Josephine,

Below is a Clinical Information Request (IR) for BLA 125409 Pertuzumab.

Please summarize the findings of the CRC by treatment arm in WO20698 regarding the number of:

- Probable cardiac deaths, including LVSD deaths
- Non-LVSD cardiac deaths (i.e. due to MI or documented arrhythmia).

Include the deaths during treatment and the deaths in the post treatment period.

Please clarify if the definition of the preferred term LVD (from dataset AE) is patients with symptomatic LVSD (investigator-defined) + patients with protocol-defined significant decrease in LVEF. (Also see Table 54 of the CSR for study WO20698)

Please verify the number of patients in each treatment arm who had no post-baseline Ejection fractions assessed.

We respectfully request your response [no later than 10 am on Thursday, May 10, 2012.](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/08/2012



BLA 125409/0

LABELING PMR/PMC DISCUSSION COMMENTS

Genentech, Inc.
Attention: Josephine Ing
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

Please refer to your Biologics License Application (BLA) dated December 6, 2011, received December 8, 2012, submitted under section 351 of the Public Health Service Act for Pertuzumab.

In accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012, if major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 9, 2012.

Labeling

On March 13, 2012, we received your March 12, 2012, revised labeling submission to this application and have proposed revisions that are included as an enclosure. As discussed in our May 3, 2012, teleconference, the text of the Boxed Warning, if needed, and the text of some of the non-clinical sections are still pending feedback from the Maternal Health Team. Those revisions will be communicated to you at a later date.

Post Marketing Commitments

We request that you agree to conduct the following postmarketing commitment studies/trials:

1. Conduct a trial to test the addition of hormonal therapy to increase the efficacy of pertuzumab-based therapy in the hormone receptor-positive, HER2-positive metastatic breast cancer population. Please respond in the following format.

Description:

Final Protocol Submission: MM/YYYY

Trial Completion: MM/YYYY

Final Report Submission: MM/YYYY

2. Submit the final Overall Survival (OS) analysis of the pivotal study WO20698/TOC 4129g.

Description:

Final Protocol Submission: MM/YYYY

Trial Completion: MM/YYYY

Final Report Submission: MM/YYYY

Post Marketing Requirement

Establish a Pregnancy Registry to collect information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Include in your annual reports the cumulative findings from the Pregnancy Registry. Revise the package insert to include information about the Pregnancy Registry and a telephone contact number.

Description:

Draft Protocol Submission: MM/2012

Final Protocol Submission: MM/2012

Submission of Revised Labeling with the Registry Information: MM/2012

Trial Completion: MM/2022

Final Report Submission: MM/2023

If you have any questions, call me, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley

Regulatory Project Manager

Division of Oncology Products 1

Office of Hematology & Oncology Products

Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

43 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMY R TILLEY
05/07/2012



BLA 125409

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

ATTENTION: Michelle H. Rohrer, PhD.
Vice President, Regulatory Affairs

Dear Dr. Rohrer:

Please refer to your Biologics License Application (BLA) dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act, for Pertuzumab, Injection, 420 mg/14 mL.

We also refer to your correspondence dated and received April 10, 2012, requesting review of your proposed proprietary name, Perjeta. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your April 10, 2012, 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 Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Amy Tilley at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/07/2012

From: Tilley, Amy
Sent: Monday, May 07, 2012 4:00 PM
To: 'Josephine Ing'
Subject: BLA 125409 Pertuzumab - FDA Revised Label

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, May 09, 2012 2:00 PM
Flag Status: Flagged

Attachments: FDA rev 5-4-12.doc
Josephine,

Below is the FDA revised label for Genentech's review. However, please note that any yellow highlighted sections are currently still under review.



FDA rev
-12.doc (673)

We respectfully request Genentech's response **no later than 2 pm on Wednesday, May 9, 2012**, as we have a labeling meeting the following day.

Kindly confirm receipt of this email.

Regards.

Amy

43 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
05/07/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:

1. The revised endotoxin specification (b) (4) does not provide a 2-fold safety factor for the patient because the safety factor was applied to the drug product but not the diluent. Please recalculate the endotoxin specification for the drug substance and drug product using minimum 2-fold safety factor for both the drug product (maximum dose) and diluent and revise the MVD for the endotoxin assay accordingly. Alternatively, provide justification for not including a 2-fold safety factor for the diluent in the calculation even though the diluent is required for administration of the drug product.
2. Please indicate the minimum and maximum capping speeds and crimping forces for the pertuzumab drug product vials. Describe how container closure integrity was verified under worst-case conditions for capping speed and crimping forces (minimum and maximum) and provide summary data.
3. Please indicate whether 100% of vials are tested for container closure integrity by the (b) (4) method during routine production. If not, please describe the sampling and testing plan.
4. Please provide the summary report and data for comparison of the dye ingress test to the microbial ingress test for container closure integrity. Compare the container(s) and closure(s) used for the comparison study to the container closure system for pertuzumab

drug product and explain why the comparison study applies to the pertuzumab container closure system.

5. Table 3.2.P.3.5-28 indicates that the throughput batch size used for microbial retention validation was (b) (4) and that the volume per filter area (ml/cm²) was (b) (4). The throughput batch size of (b) (4) does not appear to include the (b) (4) and would not yield a (b) (4) area of (b) (4). Please clarify and make the appropriate corrections to the BLA.
6. The BLA does not specifically describe the sterile filter used for pertuzumab manufacturing. Please indicate whether the (b) (4) modeled by validation studies (b) (4) is representative of the production filter material. Indicate the size and surface area of the production filter.
7. Please provide the alert limits and action limits for environmental monitoring for each processing area (b) (4).
8. Please provide the alert and action limits for personnel monitoring in (b) (4) areas.
9. There are no in-process limits provided for the bioburden sample taken (b) (4). Please provide alert and action limits for bioburden samples taken (b) (4).
10. Please specify the conditions (e.g., equipment problems) under which (b) (4) of pertuzumab bulk drug substance will be allowed during commercial production at the drug product manufacturing site. Indicate whether a bioburden sample is taken (b) (4) and provide the alert and action limits. (b) (4) should not be used to justify further processing of (b) (4) bioburden material.
11. Please provide the duration for each media fill listed in Table 3.2.P.3.5-25 of the original BLA submission. Indicate the time between (b) (4).
12. Please provide the following information regarding drug product shipping:
 - a. List the performance qualification shipments made for truck and air transport. Include the shipping dates, ambient temperature range, and excursions (temperature and duration) outside of 2-8°C.
 - b. Provide the acceptance criteria (temperature and duration) for temperature excursions during qualification shipments and routine shipments. Justify the acceptance criteria based on product stability data.
 - c. Indicate the minimum and maximum shipping loads for qualification shipments and routine shipments, describe how the loads are packaged, and indicate the locations for temperature monitoring.
 - d. Provide the maximum shipment duration for each shipping route.

- e. Describe the load configuration(s) used for [REDACTED] ^{(b) (4)} testing and justify choice of the configuration(s) as worst-case for mechanical stress testing. Briefly describe the tests that were performed and provide the acceptance criteria (visual inspection, container-closure integrity testing, etc.).

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
05/03/2012

MEMORANDUM OF TELECONFERENCE

DATE: May 3, 2012

APPLICATION NUMBER: BLA 125409/0

BETWEEN:

Josephine Ing, Regulatory Program Director, Product Development Regulatory
Teresa Perney, Director, Product Development Regulatory
Mark (Kip) Benyunes, Senior Group Medical Director, Product Development Clinical Oncology
Colin Neate, Project Statistician, Biostatistics
Graham Ross, Global Science Leader, Product Development Clinical Oncology
Noel Dybdal, Associate Director, Safety Assessment
Simone Kraev, Safety Science Leader, Drug Safety
Laura Chu, Epidemiology
Caroline Trudeau, Clinical Science Associate, Product Development Clinical Oncology
Ana Sousa, Regulatory Program Director, Product Development Regulatory
Lisa Wang, Principal Epidemiologist, Epidemiology
Ru Walker, Senior Medical Director, Product Development Clinical Oncology

Phone: (b) (4)

Representing: Genentech, Inc.

AND

Participants from Division of Oncology Products 1 (DOP1):

Robert Justice, Director
Amna Ibrahim, Deputy Director,
Patricia Cortazar, Clinical Team Leader
Gideon Blumenthal, Clinical Reviewer
Nancy Scher, Clinical Reviewer (Safety)
Anne Pilaro, Supervisory PT Reviewer
Kimberly Ringgold, PT Reviewer
Kathryn Fedenko, Deputy Director Safety
Susan Jenney, Safety RPM
Alice Kacuba, Chief Project Management Staff

BACKGROUND: Genentech submitted BLA125409/0 for the proposed indication: in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The PDUFA action date is Friday, June 8, 2012.

SUBJECT: To begin discussion with Genentech regarding a PMR for a pregnancy registry

TODAY'S PHONE CALL:

-The Division stated concerns found during the non-clinical review. Therefore, we will be listing a PMR in the action letter for a pregnancy registry similar to that for Herceptin.

Establish a Pregnancy Registry to collect and analyze information for ten years on pregnancy complications and birth outcomes in women with breast cancer exposed to a pertuzumab-containing regimen within 6 months of conception or during pregnancy. Submit yearly interim reports, which may be included in your annual reports, on the cumulative findings and analyses from the Pregnancy Registry.

-Genentech agreed.

-FDA will send the PMR description to Genentech to fill in the milestones and return to FDA.

Alice Kacuba
Chief, Project Management Staff, DOP1

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/s/

ALICE KACUBA
06/12/2012

From: Tilley, Amy
Sent: Wednesday, May 02, 2012 5:37 PM
To: 'Josephine Ing' ing.josephine@gene.com
Cc: Kacuba, Alice
Subject: RE: BLA 125409 Pertuzumab - Clinical PMCs milestone dates
Josephine,

Please include the following information in your submission with regards to the milestone dates for the 2 proposed PMC's.

Final Protocol Submission: MM/YY
Study/Trial Completion: MM/YY
Final Report Submission: MM/YY

Thank you.

Amy

From: Tilley, Amy
Sent: Wednesday, May 02, 2012 2:23 PM
To: 'Josephine Ing'
Subject: RE: BLA 125409 Pertuzumab - Clinical PMCs milestone dates

Josephine,

Prior to your submission tomorrow I have some additional information to send to you and will hopefully have it finalized later today.

Thanks.

Amy

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Tuesday, May 01, 2012 6:25 PM
To: Tilley, Amy
Subject: Re: BLA 125409 Pertuzumab - Clinical PMCs milestone dates

Hi Amy,
We are submitting the milestone dates for the 2 proposed PMCs tomorrow. As usual, I will email you an e-copy of the submission.

Thanks
Josephine

On Tue, May 1, 2012 at 2:23 PM, Tilley, Amy <AMY.TILLEY@fda.hhs.gov> wrote:
Josephine,

When will you be submitting the milestone dates for the 2 proposed PMCs?

Thanks.

Amy

--

Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞p: (650) 225-2330 | 📠m:
(415) 297-2695

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/s/

AMY R TILLEY
05/02/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:



- [REDACTED]
- 4) The BLA does not provide sufficient information to demonstrate that, based on the proposed control strategy; the cell culture process will be controlled in a manner that assures consistent cell growth and viability. The manufacturing process description in the BLA needs to be updated to include process parameters [REDACTED] that provide assurance that the cell population propagated to the [REDACTED] stage will produce product that is representative of that used in your clinical trials. [REDACTED] The updated description should delineate differences between expansion from the MCB vs. the WCB. Include details of the expansion process from a vial of MCB such as sizes/types of flasks, volumes of media used and number of passages.
 - 5) For the [REDACTED] update the manufacturing process description in the BLA with a list of parameters including their ranges sufficient to assure glycosylation profiles and pertuzumab ADCC activity remain within a range that is representative of your clinical experience.
 - 6) Update the manufacturing process description in the BLA for the [REDACTED]. The update should include [REDACTED].
 - 7) Update section 3.2.P.7 with information on the manufacturer of the DS and DP container/closure systems.
 - 8) Update the DS in-process testing (Table 3.2.S.4.1-2) to include rejection limits for purity by IE-HPLC as follows: % Main Peak [REDACTED] or > [REDACTED] and % Acidic peak [REDACTED]. Provide confirmation that a BLA supplement would be submitted per 21 CFR 601.12 prior to changes being made to these limits.

- 9) Update the drug product release and shelf-life specifications (Table 3.2.P.5.1-1) as follows:
 - a) Revise the release acceptance criteria to include criteria for purity by IE-HPLC that are based on your clinical experience. Provide data to justify the proposed criteria.
 - b) Revise the shelf-life acceptance criteria for purity by IE-HPLC to be reflective of clinical experience. Provide data to justify the proposed criteria.
 - c) Revise the release and shelf-life acceptance criteria for [REDACTED] (b) (4) to be reflective of clinical experience. Provide data to justify the proposed criteria.

- 10) Provide a post-marketing commitment to incorporate a non-reduced SDS method into the drug product release and shelf-life specifications. Alternatively, data can be submitted that demonstrates that the non-reduced SDS method is not a relevant stability indicating assay. The post-marketing commitment should indicate that the information will be submitted as a CBE-30 and the date by which the specification will be submitted.

- 11) Control of quality attributes that can impact ADCC activity should be incorporated into the control strategy. This could include, for example, incorporation of a specification for [REDACTED] (b) (4) or a specific test for ADCC can be incorporated into the DS release program.

- 12) Update the primary and secondary reference standard acceptance criteria (Table 3.2.S.5-4) as follows:
 - a) Revise the purity by CE-SDS to include acceptance criteria for % heavy chain and % light chain.
 - b) Revise the purity by IE-HPLC acceptance criteria to be reflective of manufacturing experience and to include criteria for % main, acidic and basic peaks.
 - c) Revise the potency assay acceptance criteria to a sufficiently narrow range so as to provide assurance against product drift over time. Include information on how assessment of potency for the reference standards will be performed.
 - d) Revise the acceptance criteria to include a specification with acceptance criteria for product glycosylation.
 - e) Revise the acceptance criteria to include a specification with acceptance criteria for purity by non-reduced SDS method.

- 13) You state in section 3.2.S.2.3.2 that action limits for WCB stability have been established and that MCB and WCB stability must be monitored [REDACTED] (b) (4).
[REDACTED] What are the action limits for WCB stability?
Provide justification of the timeframe for this testing to ensure viability of the cell banks and the ability to consistently achieve viable production cultures.

- 14) In section 3.2.S.2.2.2, Cell Culture and Harvest, acceptable concentration ranges for components of the selective and non-selective cell culture media are listed. What data support the values listed in Table 3.2.S.2.2.2-1?

- 15) Provide copies of [REDACTED] (b) (4)
[REDACTED]

16) Correct the following inconsistencies in your submission. The statement made on page 11 of your IE-HPLC analytical methods validation: (b) (4)

[Redacted]

17) We note from validation reports VP09-240 and VP09-241 that studies to ensure genetic consistency of the MCB were performed (b) (4)
[Redacted] Provide data to support genomic stability of the MCB at manufacturing scale.

18) [Redacted] (b) (4)

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
04/26/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 25, 2012
TIME: 3:00 p.m. EST
LOCATION: Telecon
APPLICATION: BLA 125409
DRUG NAME: Pertuzumab
TYPE OF MEETING: C
MEETING CHAIR: Wendy Weinberg
MEETING RECORDER: Joel Welch

FDA ATTENDEES: (Title and Office/Division)

Kathleen Clouse, Ph.D. Division Director, Division of Monoclonal Antibodies
Patrick Swann, Ph.D. Deputy Division Director, Division of Monoclonal Antibodies
Barbara Rellahan, Ph.D., CMC Team Leader, Division of Monoclonal Antibodies
Wendy Weinberg, Ph.D. CMC Team Leader, Division of Monoclonal Antibodies
Joel Welch, Ph.D., Regulatory Project Manager, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES (Genentech):

Jennifer Mercer, Associate Director, Pharma Technical Regulatory
Vassia Tegoulia, PhD, Senior Product Manager, Pharma Technical Regulatory

BACKGROUND:

A fifth teleconference was held to discuss the low cell growth of the 2012 campaign of pertuzumab at the Vacaville facility. This teleconference was requested by the Sponsor by email on April 25th to ask for additional clarification regarding the Agency's concerns expressed at the April 24th teleconference.

DISCUSSION POINTS:

The Sponsor inquired what the exact nature of the Agency concerns were, specifically if long term supply of pertuzumab or the consistency of the process was the greater issue. The Agency stated that "consistency" was the real core issue, with the underlying assumption that a lack of consistency can impact availability as well as product quality in ways we may not be fully aware of. The Sponsor proposed that additional measures of control could be implemented such as a control strategy that includes additional characterization in the case of poor growth. The Agency then stated that regulatory flexibility is traditionally based on process understanding. The Sponsor then restated that any material generated from production using the Master Cell Bank wouldn't be needed until (b) (4) regardless. The Agency requested a Gantt chart detailing the timelines associated with the use of the Master Cell Bank for production.

DECISIONS (AGREEMENTS) REACHED:

The Agency stated that additional data could be submitted on May 23rd, but that it had no comment on whether or not it will be adequate for approval.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

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/s/

JOEL T WELCH
05/10/2012

WENDY C WEINBERG
05/10/2012

From: Tilley, Amy
Sent: Tuesday, April 24, 2012 6:53 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: RE: BLA 125409 Pertuzumab – Clinical IR

Importance: High
Josephine,

Completion of Protocol MO27775 (PERTAIN) as designed would be acceptable to address the PMC request. Please send in PMC schedule milestone information including date of study completion and final report submission.

In addition, please send PMC schedule milestone information regarding date of CLEOPATRA final OS analysis completion and date of final OS analysis report submission.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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From: Josephine Ing [<mailto:ing.josephine@gene.com>]
Sent: Friday, April 20, 2012 3:09 PM
To: Tilley, Amy
Subject: Re: BLA 125409 Pertuzumab - Clinical IR

Dear Amy,

We would like to request a telecon next week to discuss the following questions. We would like the Agency's feedback as we consider possible options to address the PMC request in the HR+ HER2+ MBC population.

1. We refer to the response to the clinical information request submitted as Serial No. 008 on February, 28, 2012 for Protocol MO27775, A Study Of Pertuzumab in Combination with Trastuzumab Plus an Aromatase Inhibitor in Patients with Hormone-Receptor Positive, Metastatic HER2-Positive Breast Cancer (PERTAIN). Would the completion of this study as designed be

acceptable to address the PMC request? If not, what elements of the protocol would need to be amended in order for this study to be sufficient to address the PMC request?

2. Would a hypothesis generating study, eg, Phase II, IV, or observational study in patients with HER2+ 1st or later line MBC, examining the addition of hormonal therapy to a pertuzumab-based regimen be sufficient to address the PMC request?

3. Would a study in a 2nd or later line HER2+ MBC patient population be acceptable to address the PMC request?

Thanks
Josephine

On Thu, Apr 19, 2012 at 1:00 PM, Tilley, Amy <AMY.TILLEY@fda.hhs.gov> wrote:
[Josephine](#),

[The Clinical Review Team has the following Information Request \(IR\) for BLA 125409 Pertuzumab.](#)

In reviewing Pertuzumab BLA 125409, it appears that the magnitude of PFS effect in the Hormone Receptor positive (HR+) sub-population is not as large as in the ITT population. We are concerned that this is due to continued cross-talk between Estrogen Receptor signaling and HER2 receptor signaling. As a Post Marketing Commitment (PMC), we will request an additional trial to study the addition of hormonal therapy to increase the efficacy of pertuzumab-based therapy in the HR+ HER2+ MBC population. We request that you propose such a post-marketing trial.

We would like a written concept [**no later than Monday, April 23, 2012.**](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

[301.796.3994](tel:301.796.3994) (phone) • [301.796.9845](tel:301.796.9845) (fax) | [✉ amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov)



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Josephine Ing | Product Development Regulatory | Genentech, Inc. | 📞: (650) 225-2330 | [REDACTED] (b)
[REDACTED] [REDACTED] (6)

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/s/

AMY R TILLEY
04/24/2012

From: Tilley, Amy
Sent: Wednesday, April 18, 2012 4:51 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: BLA 125409 Pertuzumab - Additional Clinical Label IRs

Importance: High

Follow Up Flag: Follow up
Due By: Monday, April 23, 2012 12:00 PM
Flag Status: Flagged
Josephine,

Below are 2 additional requests regarding information in the proposed Pertuzumab label.

- In section 6.2 of the draft label, you list paronychia as "a clinically relevant ADR reported in < 10%" (3.5% placebo-treated, 7.1% pertuz-treated). This seems unusual. Would you please comment on the significance of this finding?
- In section 5.2, we agree that the overall frequency of hypersensitivity/anaphylaxis reactions was 9.1% in the placebo-treated group. For the pertuzumab-treated group, we calculated an incidence of 11.5% (47/407 patients). Your incidence was 10.8% (44/407); did you choose to leave out the 3 subjects in the pertuzumab arm that were listed as "cytokine release syndrome?"

We respectfully request your response to the above additional Clinical IRs **no later than Noon on 4-23-12.**

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/18/2012

From: Tilley, Amy
Sent: Wednesday, April 18, 2012 3:46 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: TIME SENSITIVE BLA 125409 Pertuzumab - Clinical Label & PT IR

Importance: High

Follow Up Flag: Follow up
Due By: Monday, April 23, 2012 12:00 PM
Flag Status: Flagged
[Josephine,](#)

[Below are Clinical and Pharm Tox Information Requests \(IR\).](#)

- Regarding section 5.2 of the draft label, we are concerned about your definition of “infusion reactions.” Your definition includes “ADRs occurring during infusion or on the same day as the infusion.” For example, during the second cycle (day 1), you include [REDACTED] ^{(b)(4)} as among “the most common infusion-associated reactions.” Clearly these symptoms are not appropriately characterized. We note that the Herceptin label (section 5.2) defines Infusion Reactions as “a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain, headache, dizziness, dyspnea, hypotension, rash, and asthenia.” We ask you to propose changes in section 5.2 of the pertuzumab label, utilizing some of these ADRs/or ADRs actually observed in study 1 to be the “most common infusion-associated reactions.”
- From section 5.2 of the draft label, please clarify which datasets you used and how you calculated the frequency of pertuzumab vs. placebo infusion-associated reactions (19.2 vs. 14.6%) for treatment 1. Which AEs were encompassed and over what time course?
- We understand monkey data showed increase in oligohydramnios with pertuzumab. From the datasets of Cleopatra, we note 1 patient experienced spontaneous abortion and cycle 2 had to be delayed (CRF pt #8295). Is it possible to get information how far along in pregnancy she was and if there were any fetal findings? Are you aware of pregnancies occurring in other patients in other pertuzumab trials and, if so, is there any information regarding these subjects or their fetuses?

We respectfully request your response to the above IRs [no later than Noon on 4-23-12.](#)

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/18/2012

From: Tilley, Amy
Sent: Thursday, April 19, 2012 4:00 PM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: BLA 125409 Pertuzumab - Clinical IR

Importance: High

Follow Up Flag: Follow up
Due By: Monday, April 23, 2012 12:00 AM
Flag Status: Flagged
[Josephine,](#)

The Clinical Review Team has the following Information Request (IR) for BLA 125409 Pertuzumab.

In reviewing Pertuzumab BLA 125409, it appears that the magnitude of PFS effect in the Hormone Receptor positive (HR+) sub-population is not as large as in the ITT population. We are concerned that this is due to continued cross-talk between Estrogen Receptor signaling and HER2 receptor signaling. As a Post Marketing Commitment (PMC), we will request an additional trial to study the addition of hormonal therapy to increase the efficacy of pertuzumab-based therapy in the HR+ HER2+ MBC population. We request that you propose such a post-marketing trial.

We would like a written concept **no later than Monday, April 23, 2012.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/19/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:

1. In your response to Question 27 in FDA information request dated 3/2/12, you indicate that cell culture media may be (b) (4) It was also (b) (4) communicated during the pre-license inspection (PLI) that if (b) (4)

(b) (4) Please provide information about the additional (b) (4) procedures that will be implemented to (b) (4)

2. The agency does not agree with the response to Question 28 in the information request dated 3/2/2012 with regard to (b) (4) (b) (4)

(b) (4) As cited in Form FDA 483 at the (b) (4) end of the pre-license inspection (PLI) of the Vacaville facility, currently, (b) (4) do not include bioburden (b) (4) and endotoxin specifications. Using (b) (4)

(b) (4) not a good manufacturing practice. You also responded that “although (b) (4)

[REDACTED] (b) (4)

3. It is indicated in Section 3.2.S.2.2. [REDACTED] (b) (4)

4. Please provide conditions for [REDACTED] (b) (4)
[REDACTED] (b) (4). Clarify if a bioburden sample is taken prior to [REDACTED] (b) (4)
due to [REDACTED] (b) (4) bioburden should not be conditions for reprocessing.

5. The agency requested in an information request dated 4/12/12 a revision to the endotoxin specifications of the drug substance and drug product. [REDACTED] (b) (4)

6. You responded to Question 31 in FDA information request dated 3/2/12 that [REDACTED] (b) (4)

7. In your response to Question 32 in FDA information request dated 3/2/12, you committed to revise the bioburden [REDACTED] (b) (4) [REDACTED] (b) (4)
[REDACTED] Please update Table 3.2.S.4.1-2 for the new bioburden alert limits.

8. It was communicated during the PLI that the acceptable hold times and temperatures for [REDACTED] (b) (4) provided in Table 3.2.S.2.2.3-1 are based on chemical stability. Please update the BLA with the acceptable in-process hold times and temperatures at Vacaville that have been validated from microbiology perspective. Please note that these hold times are facility dependent and do not cover future new facilities.

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
04/19/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:

With regard to the [REDACTED] (b) (4) at the Vacaville facility, please provide summary information on the root cause and corrective and preventive action related to the [REDACTED] (b) (4). In addition, provide information on [REDACTED] (b) (4).

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
04/19/2012

From: Tilley, Amy
Sent: Tuesday, April 17, 2012 5:06 PM
To: 'Josephine Ing'
Subject: BLA 125409 Pertuzumab - CDRH IR

Importance: High

Follow Up Flag: Follow up
Due By: Friday, April 20, 2012 12:00 PM
Flag Status: Flagged
[Josephine,](#)

Below are two CDRH (Center for Devices and Radiological Health) Information Requests (IR).

- 1. Please provide line data that includes primary and secondary endpoint data for 8 patients for whom Pertuzumab treatment was based upon FISH results but where IHC results were either missing or negative.**
- 2. Please provide line data that includes primary and secondary endpoint data for 1 patient for whom Pertuzumab treatment was based upon equivocal IHC results but FISH results were negative.**

We respectfully request your response to the above two CDRH IRs **no later than Noon on 4-19-12.**

Please officially submit this information to the BLA and in a courtesy email to myself.

Kindly confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/17/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 12, 2012
TIME: 4:00 p.m. EST
LOCATION: Telecon
APPLICATION: BLA 125409
DRUG NAME: Pertuzumab
TYPE OF MEETING: C

MEETING CHAIR: Wendy Weinberg

MEETING RECORDER: Joel Welch

FDA ATTENDEES: (Title and Office/Division)

Laurie Graham, M.S., Quality Reviewer, Division of Monoclonal Antibodies
Kathryn King, Ph.D., Quality Reviewer, Division of Monoclonal Antibodies
Patrick Swann, Ph.D. Deputy Division Director, Division of Monoclonal Antibodies
Wendy Weinberg, Ph.D. CMC Team Leader, Division of Monoclonal Antibodies
Barbara Rellahan, Ph.D., CMC Team Leader, Division of Monoclonal Antibodies
Joel Welch, Ph.D., Regulatory Project Manager, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES (Genentech):

Vickie Frydenlund, Senior Director, Pharma Technical Regulatory
Lynn Gennaro, PhD, Scientist, Process Analytical Chemistry
Martin Gawlitzek, PhD, Senior Group Leader, Late Stage Cell Culture
Reed Harris, Senior Director, Process Analytical Chemistry
Josephine Ing, Senior Scientist, Product Development Regulatory
Karen Jones, PhD, Global Oncology Therapeutic Head, Product Development Regulatory
Brian Kelley, PhD, Vice President, Process Technical Development
Bob Kiss, PhD, Director, Late State Cell Culture
Andrew Kosky, PhD, Associate Director, Pharma Technical Development
Charles Morgan, PhD, Senior Product Manager, Pharma Technical Regulatory
Teresa Perney, PhD, Director, Global Regulatory Lead, Product Development Regulatory
Qasim Rizvi, Associate Director, Commercial Team Leader
Roger Symczak, Product Supply Chain Leader, Global Supply Chain Management
Vassia Tegoulia, PhD, Senior Product Manager, Pharma Technical Regulatory
Dan Stark, PhD, Director, Technology, Vacaville

BACKGROUND:

A request was made by Genentech to have a brief teleconference on April 12, 2012 to discuss their quality information submitted on April 9, 2012 (serial number 0023, BLA 125409).

The purpose of the submission was to present the action plan and timelines to address concerns regarding the thaw (b) (4) during the 2012 Pertuzumab campaign at the Vacaville facility.

DISCUSSION POINTS:

The Sponsor began with a discussion of the proposal presented in the above referenced submission. The Sponsor noted they plan to have available release test results and additional characterization data for three batches from the current campaign in Vacaville, utilizing thaws 4 and 6, by May 10. The Agency stated this timeline was acceptable, and noted it needed not only these data, but historical trending results, full quantitative values for each test, and when applicable, copies of the individual chromatograms. The Sponsor agreed to this request and noted they planned to summarize the results and trending in histograms.

The Sponsor then described the “additional testing” plan presented in Table 3.2.1.3. The Agency stated it also needed the percentage of each individual glycoform, and the percentage of fragments as determined by non-reducing SDS-PAGE. The Sponsor noted that the monomer is generally (b) (4) and that (b) (4) have been observed. The Agency then inquired how many historical lots were available for comparison from Vacaville for ADCC values. The Sponsor stated an estimate of between (b) (4)

(b) (4)

Finally, the Sponsor summarized the progress on the creation of a new working cell bank. The Sponsor plans (b) (4)

(b) (4)

During the teleconference, the Sponsor was asked to provide the division with the growth metrics of all stages of cell bank preparation. The Agency reminded the Sponsor it wants data to compare the growth of the new

working cell bank with that of the current working cell bank. The Agency also stated that for the May 10th submission it requests not only viability data for the new and established WCBs, but also how the observed viability compares to cell banks for other products. The Sponsor agreed.

In addition, the Sponsor stated

(b) (4)
(b) (4)

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

A slide deck was provided by the sponsor regarding potential Pertuzumab drug supply under various scenarios. The slides are presented as an attachment.

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/s/

JOEL T WELCH
04/27/2012

WENDY C WEINBERG
04/27/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed your application and have determined that the following information is necessary to take a complete action on your application:

Please respond to the following product quality microbiology questions regarding the endotoxin specification, endotoxin method qualification, and sterilization/depyrogenation of equipment and components.

1. The following deficiencies were identified for the calculation of acceptable endotoxin levels in the drug substance (3.2.S.4.5):
 - The calculation for acceptable endotoxin levels in the drug substance does not account for the diluent (250 ml saline) that is administered with the drug product.
 - The calculation should be performed with a safety factor of at least 2.0 to account for variability in the endotoxin assay.
 - Based on the average weights of the North American versus European patient populations from the pivotal clinical trial, the calculation should be performed with 70 kg as an average patient weight to provide a better margin of safety for lower weight patients in the intended markets (North America and Europe).

Please revise the endotoxin specification for the drug substance and drug product. The calculation should include the maximum possible endotoxin contribution from the diluent (based on the USP limit of 0.5 EU/ml for large volume parenterals), a safety factor of at least 2.0, and an average patient weight of 70 kg. In addition, recalculate the MVD for the endotoxin assays using the new specification.

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/s/

JOEL T WELCH
04/12/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 10, 2012

TIME: 3:30-4:00pm

APPLICATION:BLA 125409

DRUG NAME: Pertuzumab

TYPE OF MEETING: T-con

MEETING RECORDER: Frances Fahnbulleh, SRPM

FDA ATTENDEES:

Office of Surveillance and Epidemiology-

Todd Bridges, Team Leader, DMEPA (DOP)

Sean Bradley, Team Leader, Safety Project Management

Frances Fahnbulleh, SRPM, DOP1

EXTERNAL CONSTITUENT ATTENDEES:

Genentech, Inc.-

Josephine Ing

Teres Perney

Liz Homans

Qasim Rizvi

BACKGROUND:

The sponsor submitted a PN review request for [REDACTED]^{(b) (4)} under BLA 125409 on Jan. 6, 2012. The name was reviewed and found unacceptable with a subsequent issuance of a name Denial letter on April 5, 2012.

MEETING OBJECTIVES:

The sponsor requested a t-con to discuss possible options in view of the rapidly approaching PDUFA date of 6/8/12, for this application.

DISCUSSION POINTS:

The sponsor sent in questions with discussion points and comments as listed.

FDA/DMEPA answered the questions, and participated in a dialogue which led to agreements as listed below, under Agreements Reached.

We are concerned that another 90 day review clock for a new request for proprietary name review will complete after the June 8, 2012 PDUFA date for the pertuzumab BLA. Therefore, we would like your feedback on possible options to best collaborate with you to enable approval of a proprietary name for pertuzumab in advance of June 8, 2012.

1) We refer to the request for proprietary name review for [REDACTED]^{(b) (4)} submitted to BLA 125049 on January 6, 2012 as Serial No.

001 and the Proprietary Name Letter dated April 5, 2012 received from FDA.

a) Would it be possible to submit a Request for Reconsideration of the Proprietary Name for (b) (4) along with an Amendment to the Request for Proprietary Name Review for an alternate name in parallel? **NO**

b) Would it be possible submit to 2 new proposed names for simultaneous review? **NO**

c) Would it be possible to accelerate the timelines for review if Look Alike Sound Alike (LASA) reports prepared by Drug Safety Institute are provided for each proposed name? **NO**

2) We also refer to the following:

- Initial submission to Request for Proprietary Name Review submitted to IND 9900 on May 27, 2011 as Serial No. 0606.
- Correspondence dated November 4, 2011, received from FDA stating that the proposed proprietary name, (b) (4) is conditionally accepted.
- Request for Withdrawal for (b) (4) as a proposed proprietary name submitted to IND 9900 on January 3, 2012 as Serial No. 0728.

(b) (4) was also submitted to other Health Authorities and was not globally accepted. Therefore, we requested the withdrawal of (b) (4) as a proposed proprietary name. However, as a contingency plan, in the event a new proprietary name is not accepted by FDA and a global proprietary name is not pursued, what would be the timelines and regulatory steps for approval for (b) (4)? **Same official timeline as with a new submission; however, it may be possible to do quicker since it was reviewed before.**

3) As an alternative contingency plan, would it be possible to launch the drug as pertuzumab similar to how AstraZeneca launched with vandetanib before waiting for the trade name approval of CAPRELSA? **YES**

AGREEMENT REACHED:

FDA/DMEPA encouraged the sponsor to submit the Alternate name for review asap.

DMEPA also made the following points:

- Every effort will be made to review the alternate name, but there is no guarantee that the name will be reviewed by PDUFA date of 6/8/12 (~ 2 months from now); if this be the case, we will promptly inform them.

- DMEPA will make every effort to inform the sponsor within 2 weeks of any issues that would render the alternate name unacceptable.
- DMEPA assured the sponsor that if the name review is not completed by the PDUFA date, the drug may be launched, under the established name “pertuzumab”, without a trade name.

The t-con concluded at 3:50pm (EST).

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/s/

FRANCES G FAHNBULLEH
05/02/2012

MEMORANDUM OF TELECONFERENCE

DATE: April 4, 2012

APPLICATION NUMBER: BLA 125409

BETWEEN:

Name: Josephine Ing, Sr. Scientist Regulatory Affairs
Phone: (b) (4)
Representing: Genentech/Roche

AND

Name: Amy Tilley
DDOP HFD-150

SUBJECT: Discuss recent pertuzumab cell growth issues with Genentech's Clinical and Manufacturing Teams

The Agency told the sponsor they were concerned about recent cell growth issues related to pertuzumab production and wanted confirmation that Genentech was willing to commit sufficient resources to addressing the issue in a timely fashion. Genentech confirmed they were aware of the seriousness of the issue and were committing resources accordingly.

FDA asked if Genentech planned on communicating information on the recent cell growth issues to the EMA. Genentech confirmed they planned to send information to the EMA by April 10, 2012.

Sponsor stated they are on schedule to submit their plans and timeframes regarding actions that will be taken to address the cell growth issue on or about April 09, 2012.

The Agency asked the sponsor to provide an estimate of how much drug product they expect to sell upon launch and how much drug product the sponsor has on hand. Sponsor agreed to submit this information and their contingency plans regarding drug product availability by April 12, 2012

The OBP Review Team agreed with the sponsor to hold bi-weekly teleconferences to further discuss the drug product issues.

Amy Tilley
Regulatory Project Manager

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/s/

AMY R TILLEY
04/20/2012



BLA 125409

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Genentech Inc.
1 DNA Way
South San Francisco, California 94080-4990

ATTENTION: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Rohrer:

Please refer to your Biologics License Application (BLA) dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act, for Pertuzumab Injection, 420 mg/14 mL.

We also refer to your January 6, 2012, correspondence, received January 6, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name (b) (4) is phonetically similar to (b) (4). The phonetic similarity between these names is due to the identical three syllable count and stress pattern (b) (4) that make the first and last syllables sound the same.

(b) (4) was identified as having sound-alike similarity in the external name assessment conducted by (b) (4). (b) (4) concluded (b) (4) and (b) (4) were found to have enough sound-alike and/or look-alike differences, and/or product characteristic differences with (b) (4) and therefore the risk of confusion between the name pair was considered to be minimal. DMEPA acknowledges the product characteristics for these products vary significantly between (b) (4). However, the phonetic similarities between the two names is such that the possibility exist that verbal exchanges between healthcare practitioners such as during product procurement can lead to confusion and wrong drug errors.

Additionally, our post marketing experience with other similar sounding name pairs has shown that differing product characteristics do not sufficiently minimize the risk of name confusion when the proprietary names are nearly identical in sound, such as the case with [REDACTED] ^{(b) (4)} [REDACTED]. Thus, we object to the proposed name based on 21 CFR 201.10 (c)(5), which states “The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.”

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Amy Tilley at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/05/2012

From: Tilley, Amy
Sent: Tuesday, April 03, 2012 6:04 PM
To: Josephine Ing ing.josephine@gene.com
Vassia Tegoulia Tegoulia.vassia@gene.com
Subject: URGENT - TCON scheduled 4-4-12 re BLA 125409 Pertuzumab

Follow Up Flag: Follow up
Due By: Wednesday, April 04, 2012 2:30 PM
Flag Status: Flagged
[Josephine and Vassia,](#)

This email is a follow up to our telephone conversation regarding the teleconference scheduled between DOP1 and Genentech on April 4, 2012, from 3:15 pm - 3:30 pm EST.

As discussed, DOP1 requests the following members of the Clinical and Manufacturing Teams.

Clinical Review Team:

Clinical Vice President
Clinical Review Team
Josephine Ing, Sr. Scientist, Regulatory Affairs

Manufacturing Review Team:

Jesse Bergevin, Associate Director, Vacaville Science and Engineering
Vickie Frydenlund, Senior Director, Pharma Technical Regulatory
Martin Gawlitzek, PhD, Senior Group Leader, Late Stage Cell Culture
John Joly, PhD, Senior Director, Early State Cell Culture
Andrew Kosky, PhD, Associate Director, Pharma Technical Development
Charles Morgan, PhD, Senior Product Manager, Pharma Technical Regulatory
Ron Taticek, PhD, Senior Director, Global Commercial Quality
Vassia Tegoulia, PhD, Senior Product Manager, Pharma Technical Regulatory

As agreed upon, Genentech will provide the call in number for the teleconference and a list of attendees.

Kindly confirm receipt of this email as well as Genentech's availability for the teleconference.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,

CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/03/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 2, 2012
TIME: 4:00 p.m. EST
LOCATION: Telecon
APPLICATION: BLA 125409
DRUG NAME: Pertuzumab
TYPE OF MEETING: C

MEETING CHAIR: Barbara Rellahan

MEETING RECORDER: Joel Welch

FDA ATTENDEES: (Title and Office/Division)

Jeffrey Baker, Ph.D. Deputy Director, Office of Biotechnology Products
Kathleen Clouse, Ph.D., Division Director, Division of Monoclonal Antibodies
Laurie Graham, M.S., Quality Reviewer, Division of Monoclonal Antibodies
Patricia Hughes, Ph.D., Team Leader, Office of Compliance
Steven Kozlowski, M.D., Director, Office of Biotechnology Products
Kathryn King, Ph.D., Quality Reviewer, Division of Monoclonal Antibodies
Barbara Rellahan, Ph.D., CMC Team Leader
Patrick Swann, Ph.D. Deputy Division Director, Division of Monoclonal Antibodies
Wendy Weinberg, Ph.D. CMC Team Leader, Division of Monoclonal Antibodies
Joel Welch, Ph.D., Regulatory Project Manager, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES (Genentech):

Jesse Bergevin, Associate Director, Vacaville Science and Engineering
Vickie Frydenlund, Senior Director, Pharma Technical Regulatory
Martin Gawlitzek, Ph.D., Senior Group Leader, Late Stage Cell Culture
John Joly, Ph.D., Senior Director, Early State Cell Culture
Andrew Kosky, Ph.D., Associate Director, Pharma Technical Development
Charles Morgan, Ph.D., Senior Product Manager, Pharma Technical Regulatory
Ron Taticek, Ph.D., Senior Director, Global Commercial Quality
Vassia Tegoulia, Ph.D., Senior Product Manager, Pharma Technical Regulatory

BACKGROUND:

A request was made by the FDA at the end of the March 30, 2012 teleconference to have a follow-up teleconference to further discuss issues of low growth ^{(b) (4)} of cells in the ^{(b) (4)}. The Sponsor was requested to provide an update on the ongoing investigation and the timeline for its completion prior to the meeting.

DISCUSSION POINTS:

The Agency explained its concern for the low (b) (4) growth of cells in the (b) (4) experienced the issue. Two possibilities were described as potential causes— a failure of the working cell bank, or an unknown issue related to the process. The Sponsor agreed with this assessment, though they stated it was their opinion that the working cell bank was not to blame. The Sponsor also noted they had not experienced the issue with other licensed products in the Vacaville facility. The Agency asked for clarification when the next GMP campaign was expected for Pertuzumab drug product. The Sponsor indicated it anticipated manufacturing in November 2012, (b) (4)

The Agency stated it had a mid May deadline to complete its discipline specific review of BLA 125409 and they needed confirmation that Genentech has a robust process in place for production of pertuzumab. This requirement is unaffected by the nature of the root cause of the (b) (4). The Sponsor stated that additional characterization testing of the master cell bank would be performed, but even if this work were expedited, results wouldn't be available until the end of May. Moreover, a new working cell bank could be made, but not for several months. Agency reiterated that it needs confirmation that the process is controlled, and that pertuzumab can be manufactured consistently at the licensed facility (Vacaville). Finally, the Agency noted that approval of a drug with a high efficacy, but inconsistent manufacturing process often leads to drug shortages.

The disposition of the two production runs that were still underway was also discussed. The Agency stated they had concerns that the quality of these lots may be different compared to the clinical/commercial process due to the overall cell growth issue and the (b) (4) of the two lots soon after they had gone into the (b) (4). Genentech confirmed that a more extended characterization of drug substance produced from these runs would be performed. The Agency stated that they considered ADCC to be a mechanism of action of pertuzumab and that Genentech should take that under consideration when deciding on assays to include in the extended characterization study.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

The Agency concluded the meeting by stating there are substantial unresolved concerns regarding the successful resolution of the (b) (4). The Agency reiterated that it felt that the data generated from (b) (4) were not necessarily representative and useful to support the commercial process. Finally, the Agency restated it does not agree with the sponsor that data indicate the working cell bank is valid. The Agency reiterated the importance of demonstrating stability of the master cell bank.

ACTION ITEMS:

The Sponsor agreed to provide the following items within approximately one week:

- 1). A summary of their approach to address the outstanding issue with respect to (b) (4) performance, including proposed timelines to complete ongoing experiments and supportive data. This includes not only the possible generation of a new working cell bank, but also the use of the master cell for future production needs.
- 2). An assessment of the current amount of drug product in inventory available for launch.
- 3). An evaluation of the success rate for (b) (4) at the Vacaville site for other licensed products.

ATTACHMENTS/HANDOUTS:

A slide deck was provided by the sponsor to guide the discussion. The slides are presented as an attachment.

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/s/

JOEL T WELCH
04/16/2012

BARBARA L RELAHAN
04/16/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 30, 2012
TIME: 4:00 p.m. EST
LOCATION: Telecon
APPLICATION: BLA 125409
DRUG NAME: Pertuzumab
TYPE OF MEETING: C
MEETING CHAIR: Wendy Weinberg
MEETING RECORDER: Joel Welch

FDA ATTENDEES: (Title and Office/Division)

Kathleen Clouse, Ph.D., Division Director, Division of Monoclonal Antibodies
Laurie Graham, M.S., Quality Reviewer, Division of Monoclonal Antibodies
Kathryn King, Ph.D., Quality Reviewer, Division of Monoclonal Antibodies
Patrick Swann, Ph.D., Deputy Division Director, Division of Monoclonal Antibodies
Wendy Weinberg, Ph.D., CMC Team Leader
Joel Welch, Ph.D., Regulatory Project Manager, Office of Biotechnology Products

EXTERNAL CONSTITUENT ATTENDEES:

Vassia Tegoulia, Ph.D. Senior Product Manager, Pharma Technical Regulatory

BACKGROUND:

A request was made by the FDA on March 30, 2012 to have a brief teleconference later that day regarding issues observed during inspection of the Vacaville facility the week of March 19. Specifically, the discussion items relate to [REDACTED] (b) (4) at the Vacaville site in 2010 versus 2012.

MEETING OBJECTIVES:

The objective of the meeting was to obtain further information and a timeline regarding the investigation into poor cell growth [REDACTED] (b) (4)

DISCUSSION POINTS:

The Agency inquired if the investigation into the root cause of the low cell growth was near completion. The Sponsor indicated they needed to confirm, but that it was likely still ongoing. The Sponsor indicated they might be able to provide an interim set of results. The Agency requested that in addition to interim results, timelines for potential outcomes also be included.

DECISIONS (AGREEMENTS) REACHED:

The Sponsor agreed to provide an update on the ongoing investigation and the timeline for its completion prior to the next teleconference meeting scheduled for April 2.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

The Sponsor agreed to provide an update on the ongoing investigation and the timeline for its completion prior to the next teleconference meeting scheduled for April 2.

ATTACHMENTS/HANDOUTS:

There were no attachments or handouts.

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/s/

JOEL T WELCH
04/16/2012

WENDY C WEINBERG
04/16/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have reviewed the sections 3.2.S.4.5, 3.2.P.2, and 3.2.R.2 of your application and have determined that the following information is necessary to take a complete action on your application:

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
03/22/2012

From: Tilley, Amy
Sent: Friday, March 16, 2012 10:55 AM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: BLA 125409 Pertuzumab - Clinical Safety IR sent 3-16-12

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, March 21, 2012 12:00 PM
Flag Status: Flagged
[Josephine,](#)

[Below are two Clinical Safety Information Requests \(IR\) for BLA 125409 Pertuzumab.](#)

In clinical trial WO20698, the incidence of febrile neutropenia is highest for patients from the Asia region, with 12% in the Placebo+T+D treatment group and 26% in the Pertuzumab+T+D treatment group. Based on available data, are you able to explain the findings? Also, are there regional differences in supportive care practices that could be contributory?

According to our analysis, there were 18 deaths within 30 days of study drug in study WO20698, 10 in the placebo +T+D arm and 8 in the Pertuzumab+T+D arm. We appear to be missing 4 narratives, 2 from each group. Please provide the narratives for patients with the following ID numbers:

- 6733 (pl)
- 8435 (pl)
- 8101 (pz)
- 8221 (pz).

[We respectfully request your response to the above Clinical Safety IR's by Wednesday, March 21, 2012 or sooner.](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
03/16/2012

From: Tilley, Amy
Sent: Wednesday, March 14, 2012 11:31 AM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: BLA 125409 Pertuzumab - Clinical Safety IR

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, March 21, 2012 12:00 PM
Flag Status: Flagged
[Josephine,](#)

Below are Clinical Safety Information Requests (IR) for BLA 125409 Pertuzumab.

- With respect to the supportive, neoadjuvant study WO20697, are you able to provide any additional information regarding patient 116963/1747, who died of fulminant hepatitis on study day 69? Is there additional information to support or refute that this is a likely Hy's Law case? Please summarize the data for patients across the pertuzumab trials who experienced fulminant hepatitis/hepatotoxicity.
- Please clarify for the pivotal (Cleopatra) trial how many patients died within 30 days of the last dose of study treatment in each treatment arm. How many of these patients who died within 30 days of the last dose of study treatment had previously discontinued docetaxel?

We respectfully request your response [by Noon on Wednesday, March 21, 2012.](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
03/14/2012

From: CDER-OC-PLAIR
Sent: Monday, March 12, 2012 10:28 AM
To: 'Vassia Tegoulia' Tegoulia.vassia@gene.com
Cc: Tilley, Amy; Welch, Joel; CDER-OC-PLAIR CDER-OC-PLAIR@fda.hhs.gov
Subject: RE: PLAIR submission for pertuzumab
Follow Up Flag: Follow up
Due By: Monday, April 09, 2012 12:00 AM
Flag Status: Red
Dear Vassia

At this time, BLA 125409/0 is denied because the PLAIR submission is too premature. FDA will not exercise enforcement discretion to allow importation of finished product and you do not need to resubmit the request. We will monitor the status of your PLAIR request and will notify you when the PLAIR is acceptable. However, you may check back with us in 30 days.

Thanks,

CDER-OC-PLAIR@fda.hhs.gov

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]
Sent: Friday, March 09, 2012 4:49 PM
To: CDER-OC-PLAIR
Cc: Vassia Tegoulia; Tilley, Amy; Welch, Joel
Subject: PLAIR submission for pertuzumab

Dear PLAIR group,

I am attaching the Pre-Launch Activities Importation Request (PLAIR) for pertuzumab as communicated in my previous email. The PLAIR is attached as both a .pdf and as a .doc file. The second .pdf file provides the senior management letter.

I am cc-ing the pertuzumab CDER project managers to whom I have already communicated our intention to submit the PLAIR.

If you have any questions regarding this request, please contact me.
Best regards.

Vassia

--

Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: (b) (6)

From: Vassia Tegoulia [mailto:tegoulia.vassia@gene.com]

Sent: Thursday, March 08, 2012 2:01 PM

To: CDER-OC-PLAIR

Subject: Information request on PLAIR submission for pertuzumab

Dear PLAIR group,

I am the Genentech product manager for pertuzumab. The BLA was submitted on December 8, 2011 (BLA 125409/0) and the product is under priority review with an action date of June 8th. Pertuzumab DS is manufactured in Vacaville, CA and pertuzumab DP is manufactured in Mannheim, Germany. I am finalizing the PLAIR for importing pertuzumab DP (naked vials) that will allow us to prepare for a US launch.

I have the following list of needed information and I wanted to check with you that the information will be sufficient.

1. Drug Product Name (trade and established) and complete product description
2. Name of CDER Project Manager assigned to the pending application
3. Finished bulk drug NDC number
4. Name and address of foreign manufacturer, including street address, of finished drug product
5. Name and address of US Consignee
6. Pending application number and the PDUFA data
7. The name and street address of the warehouse of distribution center where the imported drug product will be stored pending approval
8. The name and street address, if applicable, of the facility where further processing (i.e., packaging) will occur
9. A description of the further processing activities
10. Anticipated Arrival Date at Port
11. Expected Port of Entry
12. Purchase Order Number(s) and Approximate Quantity
13. Internal control procedure to prevent distribution prior to FDA approval
14. A letter signed by a member of senior management indicating that neither the importer nor its consignee or distributor in the US will sell, offer for sale or distribute the drug product in US Commerce until FDA approval has been granted
15. Entry #

I would also like to inquire whether there is a certain person/department that Item#14 above (letter signed by senior management) needs to be submitted.

Your help is much appreciated. Please let me know if there is anyone I can contact in person to get more information.

Best regards,

Vassia

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/s/

AMY R TILLEY
03/12/2012

From: Tilley, Amy
Sent: Wednesday, March 07, 2012 10:04 AM
To: 'Josephine Ing' ing.josephine@gene.com
Subject: RE: BLA 125409 Pertuzumab – FDA clarification re Exclusivity Information Request Letter

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, March 28, 2012 12:00 AM
Flag Status: Red
[Josephine,](#)

[Below is a revision to Question/Item 1 in the Exclusivity Information Request Letter sent to you via email on 3-1-12, based on your request for clarification.](#)

1. A list of all related products to pertuzumab for which you or one of your affiliates, including any licensors, predecessors in interest, successors in interest or related entities, are the current or previous license holder. This list should include, but is not limited to, products that have the same therapeutic target (i.e., target receptor HER2) and share some, but not necessarily all, of the same principal molecular structural features.

[Please let me know if Genentech still has questions regarding the clarity of the request.](#)

[Regards.](#)

[Amy Tilley](#)

[Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993](#)

[☎ 301.796.3994 \(phone\) • 301.796.9845 \(fax\) | ✉ amy.tilley@fda.hhs.gov](#)

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From: Josephine Ing [<mailto:ing.josephine@gene.com>]
Sent: Friday, March 02, 2012 2:54 PM
To: Tilley, Amy
Subject: Re: BLA 125409 Pertuzumab - Exclusivity Information Request

Amy,

We would like to request feedback regarding 'related products' in Question 1. Does this refer to pertuzumab only, or would it include trastuzumab? Or could it mean any IgG1 monoclonal antibody that is used for cancer (breast cancer)?

Thanks
Josephine

Sent from my iPhone

On Mar 1, 2012, at 1:19 PM, "Tilley, Amy" <AMY.TILLEY@fda.hhs.gov> wrote:

Josephine,

Below is an Information Request Letter regarding your request for exclusivity.

We respectfully request your prompt written response to the items stated in the above Information Request Letter in order to continue our evaluation of your BLA.

Please send us your response both via email and as an official submission to this BLA.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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<BLA 125409 Pertuzumab Exclusivity Information Request_OND ORP.pdf>

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/s/

AMY R TILLEY
03/07/2012

From: Vassia Tegoulia [tegoulia.vassia@gene.com]

Sent: Friday, March 02, 2012 5:02 PM

To: Chi, Bo

Cc: Steven Dawson; Vassia Tegoulia; Graham, Laurie; King, Kathryn; Zhou, Qing; Tilley, Amy; Welch, Joel

Subject: Re: PLI at the Vacaville facility

Dear Dr. Chi,

I am writing to update you and your team regarding a shift in the pertuzumab manufacturing schedule. The campaign started on time; however, technical difficulties have arisen in the thawing of the cells which has delayed (b) (4) the (b) (4)

As a result, the pertuzuma (b) (4)

During the timeframe of the PLI, Herceptin will be manufactured throughout the (b) (4) and pertuzumab will be in (b) (4)

We wanted to inform you prior to the PLI which is scheduled to begin on March 20th, 2012.

Please feel free to contact me with any questions.

Best regards,

Vassia Tegoulia

On Fri, Feb 24, 2012 at 8:40 AM, Chi, Bo <Bo.Chi@fda.hhs.gov> wrote:

Dear Mr. Dawson,

The pre-license inspection (PLI) at the Vacaville facility will be conducted from 3/20/12 to 3/28/12 in support of Genentech's BLA STN125409/0 for pertuzumab. The inspection team will consist of Bo Chi from the Biotech Manufacturing Assessment Branch/Office of compliance/CDER and Laurie Graham, Kathryn King, and Qing Zhou from the Division of Monoclonal Antibodies/Office of Biotechnology Products/CDER.

Please let me know the name and title of the most responsible person on-site.

To facilitate the inspection, we will request that certain documents be ready for review during the inspection. I will send you the list next week.

Best regards,
Bo Chi

--

Vassia A. Tegoulia, Ph.D.
Senior Product Manager
Pharma Technical Regulatory
Genentech - A Member of the Roche Group

Phone : [650 225 7527](tel:6502257527)

Fax: [650 225 4171](tel:6502254171)

Mobile: (b) (6)

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/s/

AMY R TILLEY
03/02/2012

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BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Vassia Tegoulia, Ph.D.
Senior Product Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Tegoulia:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

We have the following comments and information requests with regard to [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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immediately following this page

43. Please describe the routes and shipping containers used to ship drug product from the manufacturing site to the packaging and labeling sites. Provide shipping validation data that demonstrate the ability of the shipping containers to maintain controlled temperatures under worst-case environmental conditions and to protect the drug product from shock and vibration during shipping.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JOEL T WELCH
03/02/2012



BLA 125409/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Josephine Ing
Sr. Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab for Injection.

In reference to your request for exclusivity, we are requesting that you provide the following information.

1. A list of all related products to pertuzumab for which you or one of your affiliates, including any licensors, predecessors in interest, successors in interest or related entities, are the current or previous license holder. This list should include, but is not limited to, products that have similar therapeutic intent and share some, but not necessarily all, of the same principal molecular structural features.
2. Description of the structural differences between the proposed product and any related products identified in Question 1. For purified therapeutic protein products, this should include, but is not limited to, changes in amino acid sequence, differences due to post-translational events, infidelity of translation or transcription, differences in glycosylation patterns or tertiary structure, and differences in biological activities.
3. Description of the change in safety, purity and/or potency between the proposed product and any related products identified in Question 1. This should include, but is not limited to, a description of how the changes identified in Question 2 relate to changes in safety, purity and/or potency.

Please include any other information and data that would assist the FDA in making an exclusivity determination.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
03/01/2012

From: Tilley, Amy
Sent: Monday, February 27, 2012 1:00 PM
To: 'Josephine Ing'
Subject: BLA 125409 Pertuzumab - Clinical IR

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, February 28, 2012 11:00 AM
Flag Status: Completed
Josephine,

The Clinical Review Team requests that you provide the most recent version of the following protocol **by tomorrow, February 28, 2012 at 11 am EST:**

NCT01491737- A Study of Pertuzumab in Combination With Trastuzumab Plus an Aromatase Inhibitor in Patients With Hormone Receptor-Positive, Metastatic HER2-positive Breast Cancer.

Please provide the most recent version of the above protocol both via a courtesy email to myself and as an official submission to this BLA.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
02/27/2012



BLA 125409/0

FILING ISSUES

Genentech, Inc.
Attention: Josephine Ing
Sr. Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Ing:

Please refer to your Biologics License Application (BLA), dated December 6, 2011, received December 8, 2011, submitted under section 351 of the Public Health Service Act for Pertuzumab.

We also refer to our filing notification letter dated February 2, 2012.

We request that you submit the following information:

Please provide information and summary data for the rabbit pyrogen test for pertuzumab as required in 21CFR610.13(b). The rabbit pyrogen test should be performed at least once to demonstrate that your product does not contain pyrogenic substances other than bacterial endotoxin.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. In Highlights and throughout the label, avoid using “IV” as it is commonly mistaken for Roman numeral IV. Instead, use “intravenous.”
2. There should be white space between each major heading in Highlights.
3. In Full Prescribing Information: Contents, delete the un-bolded line “Full Prescribing Information” as it is redundant.
4. Use a two-column format for the TOC, and limit it in length to one-half page.
5. A horizontal line must be located between Highlights and TOC to separate Highlights information from the TOC. A horizontal line must also be located between the TOC and the FPI.
6. TOC section headings must be in bold type and should be in upper-case letters.
7. Renumber subsections in 8 Specific Populations and 12 Clinical Pharmacology as these are required sections/subsections see 21 CFR 201.56 (d)(1). Any required section, subsection, or specific information that is clearly inapplicable may be omitted from the FPI. However, the numbering does not change. This is important to remember for the required subsections in Sections 8 Use in Specific Populations, 12 Clinical Pharmacology and 13 Nonclinical Toxicology.
8. Throughout the label and specifically in Full Prescribing Information under Section 2 Dosage and Administration 2.1 Recommended Doses and Schedules, use active voice instead of “It is recommended”.
9. On line 12 and throughout the label, insert a space before and after a dash, i.e., “30 – 60 minutes”.
10. Under Subsection 2.2 Dose Modification on line 28, after *Left Ventricular Dysfunction* add “(LVEF)”. In the first bullet delete “left ventricular ejection fraction” and the parentheses around LVEF.
11. In Section 3 Dosage Forms and Strengths, reword the sentence so that it does not begin with a number.
12. Throughout the label make sure that the symbols “≤” and “≥” are not bolded.
13. In section 5.2 Infusion-Associated Reactions, Hypersensitivity Reactions/Anaphylaxis, on line 93 spell out the term “2nd” as “second”.
14. On line 98 spell out the acronym “NCI-CTCAE” the first time and then use the acronym thereafter.
15. In Table 1 of Section 6 Adverse Reactions, replace all “-“ with a zero.
16. Also in Section 6 Adverse Reactions and throughout the label, avoid using Pivotal, Phase 1, 2 or 3 and instead, describe the nature of the study. Also, do not use the actual name of a study such as “CLEOPATRA”.
17. In Section 14 Clinical Studies and throughout the label, avoid using “primary” or “secondary” endpoints; instead, describe only those endpoints that were found to be both statistically and clinically significant or demonstrated a meaningful lack of effect.
18. Insert the actual name of the manufacturer after “Manufactured by”.
19. See the FDA Website for fictitious examples of labeling in PLR.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by March 12, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

You submitted establishment information that is not required as part of a BLA for specified products. Please refer to the CMC guidance document, *Guidance for Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In-Vivo Use*, for the information you should include in your application. We will assess this information during the pre-license inspection of your establishment, but not as part of your application. Its inclusion in the file does not constitute approval.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
02/17/2012

From: Tilley, Amy
Sent: Monday, February 13, 2012 2:09 PM
To: 'Josephine Ing' ing.josphine@gene.com
Subject: BLA 125409 Pertuzumab - Clin Pharm IR sent 2-13-12

Importance: High

Follow Up Flag: Follow up
Due By: Thursday, March 01, 2012 12:00 AM
Flag Status: Flagged
[Josephine,](#)

Please refer to the Phase 3 trial W020698/TOC4129g in your BLA 125409 submission for pertuzumab.

Please provide the following immunogenicity related items **by March 1, 2012:**

- 1) Your explanation on the positive anti-therapeutic antibodies (ATA) to pertuzumab in the placebo arm
- 2) Your thoughts on why positive ATA is related with inferior PFS and ORR
- 3) On-treatment HER2 ECD data in the pivotal trial
- 4) Final bioanalytical report for the ATA-assay

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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

/s/

AMY R TILLEY
02/13/2012

From: Tilley, Amy
Sent: Monday, February 13, 2012 11:00 AM
To: 'Josephine Ing'
Subject: RE: *URGENT* BLA 125409 Pertuzumab – Clin Pharm Information Request
[Josephine, yes kindly condense and format for email the datasets requested to help facilitate our review of this application.](#)

Amy

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Sunday, February 12, 2012 1:47 PM
To: Tilley, Amy
Subject: Re: *URGENT* BLA 125409 Pertuzumab - Clin Pharm Information Request

Amy,
Attached please find the response to the clin pharm IR submitted yesterday. In addition, all remaining datasets for 11 studies were submitted. I have not included the datasets by email as they are in xml format and quite large. Let me know if you'd like for me to request for them to be condensed and formatted for email.

Hope you had a nice weekend
Josephine

On Fri, Jan 13, 2012 at 1:36 PM, Josephine Ing <ingjc@gene.com> wrote:

Amy,
I just noticed a typo in my email below. Pls note that the remaining datasets will be provided by February 12, 2012 rather than February 20, 2012.

Josephine

2012/1/13 Tilley, Amy <AMY.TILLEY@fda.hhs.gov>
[Josephine, the Clin Pharm Review Team states that your response below is acceptable.](#)

Amy

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Friday, January 13, 2012 3:49 PM
To: Tilley, Amy
Subject: Re: *URGENT* BLA 125409 Pertuzumab - Clin Pharm Information Request

Hi Amy,

Thank you for your email. The PK parameters for study WO20698/TOC4129g were included in the BLA and are located in Module 5.3.5.1.25.3.1/datasets/wo20698-toc4129g/analysis/patpkp.xpt.

In order to complete your request, we will resubmit the PK parameters dataset for study WO20698/TOC4129g along with the PK parameter datasets for TOC2297g and JO17076 along with the results of the Bayesian *posthoc* analysis used to determine the PK parameter estimates for the individual patients in all twelve studies using the final PopPK model by January 18, 2012. The remaining datasets will be submitted by February 20, 2012.

Thanks
Josephine

2012/1/12 Tilley, Amy <AMY.TILLEY@fda.hhs.gov>
Josephine,

The Clinical Pharmacology Review Team has the following comment to your email dated 1-12-12 below.

Please provide the PK parameters datasets for studies WO20698/TOC4129g, TOC2297g, and JO17076 by January 18, 2012. The remaining datasets should be submitted by February 12, 2012.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • [301.796.9845](tel:3017969845) (fax) |  amy.tilley@fda.hhs.gov

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From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Thursday, January 12, 2012 10:32 AM

To: Tilley, Amy

Subject: Re: *URGENT* BLA 125409 Pertuzumab - Clin Pharm Information Request

Dear Amy,

We'd like to confirm that individual subject PK data along with various demographic factors and covariates from twelve studies (Phase I, II and III studies) are included in the Population PK (PopPK) dataset. The dataset can be sorted by study using the study number variable (STUD) and we can add a column that makes it possible to sort by study phase. In addition, any concentrations and/or subjects that have been excluded from the PopPK analysis are flagged and maintained in this dataset located in Module 5/datasets/WO20698/analysis/poppkall.xpt. Would this be acceptable to address your request for the raw PK dataset?

We understand from your request that the review team is interested in the individual patient PK parameters from each of the twelve studies. Based on our understanding of preBLA agreements from the May 2011 Type C meeting, we prepared only the popPK datasets for the BLA submission and, at this time, we do not have the individual non-compartment analysis (NCA) PK parameters for all twelve studies in a SAS transport file readily available. However, we do have a SAS transport file ready to send that contains the results of the Bayesian *posthoc* analysis used to determine the PK parameter estimates for the individual patients in all twelve studies using the final PopPK model. Would this be acceptable?

I look forward to your response.

Thanks
Josephine

2012/1/11 Tilley, Amy <AMY.TILLEY@fda.hhs.gov>

Josephine,

Upon speaking with you yesterday, I notified the Clinical Pharmacology Team that you would need 4 weeks to respond to their information request below.

The Clin Pharm Review Team states that your proposed timeline of submitting datasets in 4 weeks is **not** acceptable. Submit all required datasets **by January 18, 2012.**

In order for us to make our filing decision regarding this application it is imperative that this information be submitted by the date stated above.

Regards.

Amy Tilley

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consider the environment before printing this e-mail

From: Josephine Ing [mailto:ing.josephine@gene.com]
Sent: Monday, January 09, 2012 7:33 PM
To: Tilley, Amy
Subject: Re: BLA 125409 Pertuzumab - Clin Pharm Information Request

Amy,

I confirm receipt of this email and have shared it with the filing team. We will discuss next steps tomorrow.

Josephine

On Mon, Jan 9, 2012 at 1:59 PM, Tilley, Amy <AMY.TILLEY@fda.hhs.gov> wrote:
Josephine,

Below is a Clinical Pharmacology Information Request (IR).

Please submit pharmacokinetic datasets (raw PK dataset and PK parameter dataset as SAS transport files *.xpt) for each of Phase 1 and 2 trials in your BLA 125409. The raw datasets should include demographic factors and all the relevant covariates for each individual. 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 respond to the above Clinical Pharmacology IR **as soon as possible** both via email and as an official submission to this BLA.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 [301.796.3994](tel:301.796.3994) (phone) • [301.796.9845](tel:301.796.9845) (fax) |  amy.tilley@fda.hhs.gov



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1.11.3 Efficacy Information Amendment

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and 9 January 2012) 2

QUESTION 1

(Received via email from Amy Tilley dated 12 January 2012)

Please provide the PK parameters datasets for studies WO20698/TOC4129g, TOC2297g, and JO17076 by January 18, 2012. The remaining datasets should be submitted by February 12, 2012.

(Received via email from Amy Tilley dated 9 January 2012)

Please submit pharmacokinetic datasets (raw PK datasets and PK parameter dataset as SAS transport files*.xpt) for each of Phase 1 and 2 trials in your BLA 125409. The raw datasets should include demographic factors and all the relevant covariates for each individual. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that been excluded from the analysis should be flagged and maintained in the datasets.

Please respond to the above Clinical Pharmacology IR as soon as possible both via email and as an official submission to this BLA.

Company Response

In response to the request made on 12 January 2012, we refer to the following pharmacokinetic (PK) datasets submitted on 18 January 2012 to BLA 125409/0 as Serial No. 0002:

- Non-compartment analysis (NCA) parameters datasets for studies WO20698/TOC4129g, TOC2297g, and JO17076
- Results of the Bayesian posthoc analysis for the individual patients in all twelve studies using the final population PK (PopPK) model

This submission includes the remaining datasets requested by FDA. [Table 1](#) includes a list of all studies and datasets sent to FDA both on 18 January 2012 and in the current response.

Table 1: Listing of All Study Data Submitted

Study	PK Data Reported	Status
TOC2297g	Concentration data + NCA	Submitted on 1/18/2012*
JO17076	Concentration data + NCA	Submitted on 1/18/2012*
TOC2572g	Concentration data (peaks and troughs)	Included in this submission
BO16934	Concentration data + NCA	Included in this submission
TOC2682g	Concentration data (peaks and troughs)	Included in this submission
TOC2689g	Concentration data (peaks and troughs)	Included in this submission
BO17004	Concentration data + NCA	Included in this submission
BO17003	Concentration data + NCA	Included in this submission
BO17021	Concentration data + NCA	Included in this submission
WO20024	Concentration data + NCA	Included in this submission
TOC3258g	Concentration data (peaks and troughs)	Included in this submission
WO20698/TOC4129g	Concentration data + NCA	Submitted on 1/18/2012*

* NCA parameters dataset was submitted. Raw concentrations datasets are included in this submission.

During the process of collating the requested datasets, it was discovered that two studies had additional data points that were inadvertently omitted from the population pharmacokinetic (PopPK) dataset and analysis submitted with the BLA. Upon finding these missing data, we went on to assess the impact of these data and have found that there is no relevant change in the PopPK analyses presented in the BLA. The following paragraphs provide details on our thinking and actions.

Data were inadvertently omitted from two studies, BO16934 (Phase II study in metastatic breast cancer patients with low HER2 expression) and BO17004 (Phase II study in patients with hormone-refractory prostate cancer). The percentage of patient data that was inadvertently omitted compared to the total patient data that were included in the original PopPK dataset is 8.3% (37 patients compared to a total of 444 patients). The total number of time points missing represents 16.3% of the total time points in the original PopPK dataset (635 compared to 3890 time points).

When we discovered that these data were inadvertently excluded in the original PopPK dataset, we performed due diligence on several fronts:

1. Checked the NCA analyses, PK parameters reported in the clinical study reports (CSR) and PK parameters reported per study in the Summary of Clinical Pharmacology Studies (SCP, [Sections 2.1](#) and [2.2](#)) for accuracy and completeness
2. Re-examined data from all of the studies included in the PopPK for accuracy and completeness

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3/Regional (Q&A Response) (Clin Pharm Information Request)

3. Assessed the impact that the new data might have on the PopPK parameters reported in [Section 3.3](#) of the SCP and in the PopPK report ([Report 11-2998](#)) by conducting a sensitivity analysis of the additional data on the PopPK results reported
4. Planned a root cause analysis to determine why these data were missed in the original PopPK dataset in order to set up corrective actions for the future

The following are the results of these 4 actions:

Action 1:

The NCA analyses (along with the datasets used) and PK parameters reported in the CSRs and the SCP ([Sections 2.1](#) and [2.2](#)) as well as [Table 20](#) in the SCP summarizing key parameters across studies (Section 3.1) are accurate.

Action 2:

All of the data included in the original PopPK analysis were re-checked for accuracy and completeness. With the exception of the two studies mentioned above (BO17004 and BO16934), no additional missing data were discovered. While re-examining all the studies included in this filing, we observed that the data missing from BO17004 were mainly from the 1050 mg cohort (n=34 patients), and that three additional studies (TOC2689, BO17003 and BO17021) included cohorts that also received the 1050 mg dose (n=88 patients). The dose of 1050mg is not the dose intended for use, but data from these 3 studies were used in the original PopPK model. For BO16934 study, data from 3 patients (out of a total of 78) were missing from the original PopPK dataset while 21 patients (who were included in the original PopPK dataset) had some missing data.

Action 3:

Results of the original PopPK analysis reported in [Report 11-2998](#) and the results discussed in [Section 3.3](#) of the SCP were re-examined to determine if the new data would impact any of the conclusions in the original report. As part of this assessment, a new PopPK dataset (n=481 patients) was created that included the recently identified missed patient data (n=37 patients) and this dataset was evaluated for patient characteristics versus the original PopPK dataset (n=444 patients). All covariates such as patient demographics, lab values, and others tested in the original PopPK analyses were examined. This examination did not yield any meaningful patient characteristics differences between the original and new PopPK dataset. A sensitivity analysis using the existing final PopPK model was conducted to evaluate the impact of the new data on the PopPK parameters. [Table 2](#) lists the parameter estimates reported in the original PopPK analysis (Section 3.3 of the SCP and in [Report 11-2998](#)) and the new parameter estimates based on the new PopPK dataset (n=481). The typical values along with the 5th and 95th percentiles are presented. Upon inspection of these parameter estimates and the post-hoc evaluation of covariate effect on key PK parameters, there do not appear to be any clinically relevant differences between the results from the current dataset and the new dataset.

Table 2: Population Pharmacokinetic Parameter Estimates Based on the Original PopPK Dataset (n=444) and the New PopPK Dataset (n=481)

Parameters		Final PopPK Model Estimates		Inter-Individual variability (%)	
		Original [95% CI]	New [95% CI]	Original	New
θ_1	Elimination clearance CL (L/day)	0.239 [0.229, 0.249]	0.235 [0.226, 0.244]	34.5	34.1
θ_5	Influence of LBW on CL	0.519 [0.346, 0.692]	0.516 [0.348, 0.684]		
θ_7	Influence of ALBU on CL	-1.05 [-1.28, -0.821]	-1.06 [-1.28, -0.842]		
θ_2	Volume of central compartment Vc (L)	3.07 [3.00, 3.14]	3.11 [3.04, 3.18]	19.3	18.5
θ_6	Influence of LBW on Vc (L)	0.674 [0.555, 0.793]	0.747 [0.637, 0.857]		
θ_3	Distribution clearance Q (L/day)	0.558 [0.466, 0.65]	0.534 [0.462, 0.606]		
θ_4	Volume of distribution in peripheral compartment Vp (L)	2.36 [2.2, 2.52]	2.46 [2.31, 2.61]	45.3	45.9
θ_8	Influence of LBW on Vp	0.7 [0.402, 0.998]	0.83 [0.516, 1.14]		
$T_{1/2}$	Elimination half-life (day)	17.2	18.0		
δ	Intra-individual variability	17.7%	18.1%		

LBW: Lean Body Weight; ALBU: Albumin

We will report the results of the new PopPK analyses and include the new PopPK dataset in an addendum to the submitted PopPK report (Report 11-2998), by 27 February 2012.

Action 4:

Lastly, as part of this investigation, a root cause analysis is under way to identify where the data processes can be improved. We plan to perform the analysis, document the findings, and implement any needed corrective actions.

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/s/

AMY R TILLEY
02/13/2012

From: Chi, Bo
Sent: Thursday, February 02, 2012 3:01 PM
To: Tilley, Amy
Cc: Hughes, Patricia; Thomas, Colleen
Subject: Microbiology Item to be included in day 74 letter

Follow Up Flag: Follow up
Due By: Friday, February 10, 2012 3:30 PM
Flag Status: Red

Attachments: IR for 74 letter STN125409.doc

Hi Amy,

Please see the attached document for the item to be included in the day 74 letter. We don't have Colleen's items. She will send them out in the next IR. Thanks.

Bo

Please provide information and summary data for the rabbit pyrogen test for pertuzumab as required in 21CFR610.13(b). The rabbit pyrogen test should be performed at least once to demonstrate that your product does not contain pyrogenic substances other than bacterial endotoxin.

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

/s/

AMY R TILLEY
02/17/2012