CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125427Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Kadcyla Full Waiver

- BLA 125427, Kadcyla (trastuzumab) sterile lyophilized single use vial, intravenous infusion, was studied as a single agent for treatment of patients with HER2-Positive Metastatic Breast Cancer.
- The application was submitted on August 27, 2012, and had a PDUFA date of February 27, 2013.
- This application triggers PREA as a new active ingredient and new indication..
- The PeRC agreed with the Division to grant a full waiver because studies are impossible or highly impracticable the disease/condition does not occur in the pediatric population.

From: Greeley, George
Sent: Thursday, December 06, 2012 9:15 AM
Subject: PeRC PREA Subcommittee
When: Wednesday, December 12, 2012 9:00 AM-10:30 AM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WO 1419 conf rm Bldg22 - AR

When: Wednesday, December 12, 2012 9:00 AM-10:30 AM (GMT-05:00) Eastern Time (US & Canada). Where: CDER WO 1419 conf rm Bldg22 - AR

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

NDA/BLA#: 125427 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DOP1 PDUFA Goal Date: February 27, 2013 Stamp Date: 8/27/2012

Proprietary Name: KADCYLA

Established/Generic Name: trastuzumab emtansine

Dosage Form: sterile lyophilized single use vial, intravenous infusion

Strengths: 100 mg and 160 mg vials (20mg/mL)

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: a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

-Received prior therapy for metastatic disease, or

-Developed disease recurrence during or within six months of completing adjuvant therapy.

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]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

e 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).

ıeck 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

e 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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

diatric 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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 ıpropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

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

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

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

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

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

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

☐ Justification attached.

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

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

ıeck 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 failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding ˢtudy plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan ɜmplate); (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 some or all pediatric subpopulations).

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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.

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

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 trastuzumab emtansine (T-DM1) in connection with this Biologic License Application at Genentech, Inc.

Signed by: Michelle Rohrer August 10, 2012

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

Date

From:	Erica Evans
To:	Skarupa, Lisa
Cc:	Erica Evans; Monica Shah; Ahmed Bassyouni; Ahmed Bassyouni; Kathy Francissen; Welch, Joel; Mesmer, Deborah
Subject:	Re: BLA 125427 FDA response on the consolidated list of PMRPMC
Date:	Friday, February 15, 2013 3:01:02 PM

Dear Lisa
We agree with the consolidated list and we will submit to the BLA today.
Kind regards
Erica

On Fri, Feb 15, 2013 at 8:37 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

> Dear Erica,
>
> Please see the attached revised consolidated list based on communications yesterday.
> If Genentech agrees, then please submit to your BLA today.
>
> Sincerely,
> Lisa

--
Erica J. Evans, Ph.D.
Product Development Regulatory - Program Management
Tel: 650-467-2157 (Direct Line); Tel: (b) (6) (Mobile); Fax: 650-467-1844

Genentech
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

PMRs

1. Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to ado-trastuzumab-emtansine 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 February XX, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2013
Final Protocol Submission:	05/2013
Interim Report #1:	05/2014
Interim Report #2:	05/2015
Interim Report #3:	05/2016
Interim Report #4:	05/2017
Interim Report #5:	05/2018
Interim Report #6:	05/2019
Interim Report #7:	05/2020
Interim Report #8:	05/2021
Interim Report #9:	05/2022
Study Completion:	05/2023
Final Report Submission:	05/2024

2. Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of KADCYLA (ado-trastuzumab emtansine conjugate), total trastuzumab, and DM1-containing catabolites. Based on the results of this trial, update the approved KADCYLA labeling with recommendations for appropriate use of KADCYLA in patients with hepatic impairment and submit it as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted
Trial Completion:	06/2014
Final Report Submission:	06/2015
Supplement Submission:	06/2015

   Comment [s1]: FDA does not agree that the description of the PMR needs to be revised to allow you to subsequently amend the trial to include patients with severe hepatic impairment You may submit this amendment regardless of the PMR wording

3. Perform a multivariate characterization study to support the implementation of (b) (4) *trans*-succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) (b) (4) during manufacture of T-DM1.

The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2013
Study Completion:	05/2013
Final Report Submission:	06/2013

4. Develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. Submit the final report as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2013
Study Completion:	11/2013
Final Report Submission:	12/2013

5. Provide quarterly reports on the status of (b) (4) These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the (b) (4) issues during the course of the FDA inspection(s), an update on whether there have been any further instances of (b) (4), and a proposal to prevent (b) (4) managed by each site's quality system.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Quarterly Report #1	05/2013
Quarterly Report #2	08/2013
Quarterly Report #3	11/2013
Quarterly Report #4	02/2014
Interim Report:	04/2014
Quarterly Report #5	05/2014
Quarterly Report #6	08/2014
Quarterly Report #7	11/2014
Quarterly Report #8	02/2015

Final Report Submission: 04/2015

POSTMARKETING COMMITMENTS

6. Conduct ado-trastuzumab emtansine conjugate exposure-response analyses for progression-free survival, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA). The results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with metastatic breast cancer who have lower exposure to ado-trastuzumab emtansine conjugate at the approved dose (3.6 mg/kg q3w). Submit a final report of the exposure-response analyses based on TH3RESA and EMILIA.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Submitted
Study Completion:	06/2016
Final Report Submission:	12/2016

7. Transfer the methodology for validated dye ingress testing developed by Genentech to (b) (4). Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Study Completion:	02/2013
Final Report Submission:	04/2014

8. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4). Submit a final report that includes updated specifications as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

   Final Report Submission: 03/2013

9. If endotoxin masking is observed in the drug product [redacted] (b) (4), develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product [redacted] (b) (4) using routine production conditions. Submit a final report on any changes in the analytical methods as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: 09/2013
   Final Report Submission: 12/2013

10. Dedicate [redacted] (b) (4) for ado-trastuzumab emtansine drug product manufacture and submit a final report of the results from sterilization validation and 3 media fill simulations as a Changes Being Effected Supplement (CBE-0).

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Final Report Submission: 06/2013

11. Conduct cleaning verification [redacted] (b) (4) until use of [redacted] (b) (4) is implemented and report the updated [redacted] (b) (4) procedures in the 2014 Annual Report.

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Study Completion: 06/2013
    Final Report Submission: 04/2014

12. Conduct endotoxin spiking and recovery studies [redacted] (b) (4) Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30).

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Final Report Submission: 05/2013

13. Develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection

of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzumab emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay final report will be submitted as a Prior Approval Supplement by June, 2015.

The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission (Assay and Methodology) Date: 06/2015

14. Reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through the end of February, 2015. Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Final Report Submission: 05/2015

15. Provide a material compatibility assessment (b) (4) Provide a toxicological risk assessment (b) (4) If significant (b) (4) are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality.

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Material Compatibility Assessment Completion: 04/2013
    (b) (4) Assessment and Toxicological Risk Assessment: 05/2013
    Final Report Submission: 06/2013

From: Skarupa, Lisa
To: "Ahmed Bassyouni"; Erica Evans
Cc: Monica Shah
Subject: RE: BLA 125427 FDA summary of PMRs and PMCs
Date: Wednesday, February 13, 2013 4:09:00 PM
Attachments: FDA_summary of PMR and PMC_BLA125427(B).doc

Oh, Thank you Ahmed, that was removed.
Here is a version with that corrected.

From: Ahmed Bassyouni [mailto:bassyouni.ahmed@gene.com]
Sent: Wednesday, February 13, 2013 4:02 PM
To: Erica Evans
Cc: Skarupa, Lisa; Monica Shah; Ahmed Bassyouni
Subject: Re: BLA 125427 FDA summary of PMRs and PMCs

Dear Lisa,

In looking at the PMR list, it looks like (b) (4) in the list of PMRs and PMCs. Can you clarify that this is intentional and that the PMR was intentionally removed.

Thanks
Ahmed

On Wed, Feb 13, 2013 at 12:56 PM, Erica Evans <evans.erica@gene.com> wrote:

> Lisa
> Do you want us to add in the correct dates for when we submitted each timetable to the BLA or will that be done at FDA's end?
> Erica
>
> On Wed, Feb 13, 2013 at 12:53 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
>
> > Thank you Erica. Yes agree COB **PST.**
> >
> > ---
> >
> > **From:** Erica Evans [mailto:evans.erica@gene.com]
> > **Sent:** Wednesday, February 13, 2013 3:39 PM
> > **To:** Skarupa, Lisa
> > **Cc:** Erica Evans; Monica Shah; Patrick Leong; Ahmed Bassyouni; Ahmed Bassyouni; Kathy Francissen; Welch, Joel; Mesmer, Deborah
> > **Subject:** Re: BLA 125427 FDA summary of PMRs and PMCs
> >
> > Dear Lisa
> > We acknowledge receipt and will endeavor to respond by COB PST today.
> > Erica
> >
> > On Wed, Feb 13, 2013 at 12:33 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
> >
> > > Good afternoon,

Please see attached list of PMRs and PMCs. Most of them are modified to provide clarity, most of the dates were the original agreed dates which you submitted to your BLA 125427.

Please review these PMR/PMC descriptions and milestones.

Since most of these were already reviewed, **we request that Genentech respond by COB today.**

Please acknowledge receipt and provide response by COB today.

Sincerely,
Lisa

Lisa Skarupa
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research
(301) 796-2219
Fax (301)796-9845
lisa.skarupa@fda.hhs.gov

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Erica J. Evans, Ph.D.
Product Development Regulatory - Program Management
Tel: 650-467-2157 (Direct Line); Tel: (b) (6) (Mobile); Fax: 650-467-1844

Genentech
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

--
Erica J. Evans, Ph.D.
Product Development Regulatory - Program Management
Tel: 650-467-2157 (Direct Line); Tel: (b) (6) (Mobile); Fax: 650-467-1844

Genentech
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

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--
Ahmed Bassyouni
T-DM1 Technical Regulatory Leader
Office (650) 467-3951
Mobile (b) (6)
Email bassyouni.ahmed@gene.com

PMRs

1. Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to ado-trastuzumab-emtansine 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 February XX, 2013, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2013
Final Protocol Submission:	05/2013
Interim Report #1:	05/2014
Interim Report #2:	05/2015
Interim Report #3:	05/2016
Interim Report #4:	05/2017
Interim Report #5:	05/2018
Interim Report #6:	05/2019
Interim Report #7:	05/2020
Interim Report #8:	05/2021
Interim Report #9:	05/2022
Study Completion:	05/2023
Final Report Submission:	05/2024

2. Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of KADCYLA (ado-trastuzumab emtansine conjugate), total trastuzumab, and DM1-containing catabolites. Based on the results of this trial, update the approved KADCYLA labeling with recommendations for appropriate use of KADCYLA in patients with hepatic impairment and submit it as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2013
Trial Completion:	06/2014
Final Report Submission:	06/2015
Supplement Submission:	06/2015

3. Perform a multivariate characterization study to support the implementation of a (b) (4) *trans*-succinimidyl 4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) (b) (4) during manufacture of T-DM1.

The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2013
Study Completion:	04/2013
Final Report Submission:	06/2013

4. Develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. Submit the final report as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2013
Study Completion:	11/2013
Final Report Submission:	12/2013

5. Provide quarterly reports on the status of [redacted] (b) (4) These reports should include, at a minimum, a summary of the root cause analyses, associated corrective actions, and disposition of all affected DM1 batches. Also, provide the disposition of any potentially affected finished product batches using these affected DM1 batches. Submit an interim report documenting that the manufacturing processes have been appropriately controlled at the manufacturing facilities according to Genentech's evaluation. The interim report should include a request for follow-up inspection(s). Submit a final report with a statement concerning the follow-up performed on the [redacted] (b) (4) issues during the course of the FDA inspection(s), an update on whether there have been any further instances of [redacted] (b) (4), and a proposal to prevent [redacted] (b) (4) managed by each site's quality system.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Quarterly Report #1	05/2013
Quarterly Report #2	08/2013
Quarterly Report #3	11/2013
Quarterly Report #4	02/2014
Interim Report:	04/2014
Quarterly Report #5	05/2014
Quarterly Report #6	08/2014
Quarterly Report #7	11/2014
Quarterly Report #8	02/2015

Final Report Submission: 04/2015

POSTMARKETING COMMITMENTS

6. Conduct ado-trastuzumab emtansine conjugate exposure-response analyses for progression-free survival, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA). The results of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with metastatic breast cancer patients who have lower exposure to ado-trastuzumab emtansine conjugate at the approved dose (3.6 mg/kg q3w). Submit a final report of the exposure-response analyses based on TH3RESA and EMILIA.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: submitted
   Study Completion: 06/2016
   Final Report Submission: 09/2016

7. Transfer the methodology for validated dye ingress testing developed by Genentech to (b) (4). Conduct a study to confirm filling and crimping conditions for container closure integrity using the validated transferred dye ingress method and provide a final report in the 2014 annual report.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

   Study Completion: 02/2013
   Final Report Submission: 04/2014

8. Conduct a study to assess the risk of endotoxin masking (b) (4) using endotoxin spiked ado-trastuzumab emtansine drug product (b) (4) Submit a final report that includes updated specifications as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

   Final Report Submission: 03/2013

9. If endotoxin masking is observed in the drug product [redacted] (b) (4), develop an alternative method to quantitate endotoxin in the finished ado-trastuzumab emtansine drug product [redacted] (b) (4) using routine production conditions. Submit a final report on any changes in the analytical methods as a Prior Approval Supplement.

   The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

   Final Protocol Submission: 09/2013
   Final Report Submission: 12/2013

10. Dedicate [redacted] (b) (4) for ado-trastuzumab emtansine drug product manufacture and submit a final report of the results from sterilization validation and 3 media fill simulations as a Changes Being Effected Supplement (CBE-0).

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Final Report Submission: 06/2013

11. Conduct cleaning verification [redacted] (b) (4) until use of [redacted] (b) (4) is implemented and report the updated [redacted] (b) (4) procedures in the 2014 Annual Report.

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Study Completion: 03/2013
    Final Report Submission: 04/2014

12. Conduct endotoxin spiking and recovery studie [redacted] (b) (4) Submit the final report as a Changes Being Effected in 30 days Supplement (CBE-30).

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Final Report Submission: 05/2013

13. Develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ado-trastuzumab emtansine, including procedures for accurate detection

of neutralizing antibodies to ado-trastuzumab emtansine in the presence of ado-trastuzumab emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling. The assay final report will be submitted as a Prior Approval Supplement by June, 2015.

The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission (Assay and Methodology) Date: 06/2015

14. Reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through the end of February, 2014. Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Final Report Submission: 05/2014

15. Provide a material compatibility assessment (b) (4) Provide a toxicological risk assessment (b) (4) If significant (b) (4) are identified during these assessments, initiate action to mitigate the source(s) of risk to product quality.

    The timetable you submitted on February XX, 2013, states that you will conduct this study according to the following schedule:

    Material Compatibility Assessment Completion: 04/2013
    (b) (4) Assessment and Toxicological Risk Assessment: 05/2013
    Final Report Submission: 06/2013

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/s/

LISA M SKARUPA
02/15/2013

From:	Erica Evans
To:	Skarupa, Lisa
Cc:	Monica Shah; Patrick Leong
Subject:	Re: Package Insert from FDA Feb 11 BLA 125427 Kadcyla
Date:	Monday, February 11, 2013 1:42:34 PM

Dear Lisa
We acknowledge receipt and we concur with the PI as provided. We will resubmit a clean copy of this PI to the BLA.
Kind regards

Erica

On Mon, Feb 11, 2013 at 10:17 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

> Dear Erica,
>
> We resumed the package insert indication as before. Please see attached. Please acknowledge receipt and if you concur with the package insert.
>
> We do not foresee any further changes to this package insert.
>
> Sincerely,
> Lisa

--
Erica J. Evans, Ph.D.
Product Development Regulatory - Program Management
Tel: 650-467-2157 (Direct Line); Tel: (b)(6) (Mobile); Fax: 650-467-1844

Genentech
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

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

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/s/

LISA M SKARUPA
02/11/2013

From:	Ahmed Bassyouni
To:	Skarupa, Lisa
Cc:	Ahmed Bassyouni; Erica Evans; Monica Shah; francissen.kathy@gene.com; Welch, Joel; Mesmer, Deborah; Shiber, Andrew J
Subject:	Re: Feb42013 PMC CMC BLA 125427 TDM1
Date:	Monday, February 04, 2013 5:48:14 PM

Dear Lisa,

I acknowledge receipt.

Ahmed

On Mon, Feb 4, 2013 at 2:26 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

> Dear Ahmed,
>
> Please see the final PMC from CMC. Please acknowledge. Please provide concurrence and milestone by **COB February 5th.**
>
> To reassess release and stability specifications for ado-trastuzumab emtansine drug substance and drug product through Feb 28, 2014.
>
> Submit the Final Report as a Changes Being Effected-30 Supplement (CBE-30).
>
> Final Report Submission (CBE-30):
>
> Sincerely,
> Lisa
>
> ---
>
> **From:** Skarupa, Lisa
> **Sent:** Tuesday, January 29, 2013 11:55 AM
> **To:** 'Ahmed Bassyouni'
> **Cc:** Ahmed Bassyouni; Erica Evans; Monica Shah; francissen.kathy@gene.com; Welch, Joel; Mesmer, Deborah; Shiber, Andrew J
> **Subject:** RE: Followup: January 28 2013 PMR 2 Genentech's response
>
> Dear Ahmed, can you tell me which sequence number?
>
> ---
>
> **From:** Ahmed Bassyouni [mailto:bassyouni.ahmed@gene.com]
> **Sent:** Tuesday, January 29, 2013 11:53 AM
> **To:** Skarupa, Lisa
> **Cc:** Ahmed Bassyouni; Ahmed Bassyouni; Erica Evans; Monica Shah; francissen.kathy@gene.com; Welch, Joel; Mesmer, Deborah; Shiber, Andrew J
> **Subject:** Re: Followup: January 28 2013 PMR 2 Genentech's response
>
> Dear Lisa,
>
> The impacted sections CMC section for the accelerated stability were updated last night to reflect the FDA's request.
>
> Ahmed
>
> On Jan 29, 2013, at 8:43 AM, Skarupa, Lisa wrote:

Dear Ahmed and Erica,
I understand that each of you is responsible for a section of the Jan28th email.
Can you give us an update on this? Can we get a response today?

Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Monday, January 28, 2013 4:29 PM
To: Skarupa, Lisa
Cc: Ahmed Bassyouni; Erica Evans; Monica Shah; francissen.kathy@gene.com; Welch, Joel; Mesmer, Deborah; Shiber, Andrew J
Subject: Re: January 28 2013 PMR 2 Genentech's response

Hi Lisa
These are actually in my domain. We acknowledge receipt.
Kind regards
Erica

Sent from my iPhone

On Jan 28, 2013, at 1:24 PM, "Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov> wrote:

> Dear Ahmed,
>
> Please see the following response regarding the cancelled tcon Friday afternoon.
>
> - As stated in the FDA guidance "Assay Development for Immunogenicity Testing of Therapeutic Proteins", you should address the functional or physiological consequences of product immunogenicity. Therefore, you should develop and validate a neutralizing antibody assay. The potential neutralizing effect of ATA on any positive samples identified to date (including the 44/836 patients identified in the draft label) should be determined. We recommend you expedite the development and validation of the neutralizing antibody assay so samples from planned and ongoing clinical studies can be analyzed. Please coordinate milestone-dates of the validation and neutralizing assay with the timelines of your planned clinical trials.
>
> PMC: To develop a validated, sensitive, and accurate assay

for the detection of neutralizing antibodies to trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to trastuzumab emtansine in the presence of trastuzuamb emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC Schedule Milestones: Final Report Submission
(Assay and Methodology) Date: MM/DD/YYYY

- Additionally, we note that, in your response to the Agency's information request issued on Jan 23, 2013, you propose to include accelerated stability testing (b) (4) Retain accelerated stability testing (b) (4) for drug substance and drug product (b) (4) Update the related BLA sections to reflect this change.

Sincerely,
Lisa

On Jan 18, the following PMR2 was sent to Genentech:

Optimize the assays used for the detection of anti-trastuzumab emtansine antibodies in human serum:

1) Provide an assessment of the ATA response to trastuzumab emtansine with a validated ELISA binding assay capable of sensitively detecting ATA responses in the presence of trastuzumab emtansine levels that are expected to be present at the time of patient sampling.

Genentech response on Jan 24: With respect to request (1) above, as the validated ATA screening ELISA submitted to the BLA was designed to be capable of detecting ATA responses in the presence of trastuzumab emtansine, we consider that no additional assay development is required.

2) Develop a validated assay to assess the neutralizing activity of anti-trastuzumab emtansine antibodies.

Genentech response on Jan 24: With respect to request (2) above, based on the ATA observations to date, the sponsor considers that a neutralizing antibody assay will not provide additional data to inform ATA impact on patient

outcomes.

--
Ahmed Bassyouni
T-DM1 Technical Regulatory Leader
Office (650) 467-3951
Mobile (b) (6)
Email bassyouni.ahmed@gene.com

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/s/

LISA M SKARUPA
02/06/2013

Memo to File
Minutes to teleconference
February 1, 2013 from 8:20 am to 9:00 am

FDA Attendees:

Office of Compliance
Regina Brown, Consumer Safety Officer
Tara Gooen, Acting Branch Chief
Linda Ng, Ph.D., Senior Policy Advisor

Division of Monoclonal Antibodies
Joel Welch, Ph.D. Regulatory Project Manager

(b) (4) Attendees

(b) (4)

Hendrik Moorlag (Global drug substance project coordinator- ROCHE)

The teleconference was requested by FDA on January 30, 2013 to request an update on the investigation into DM-1 drug substance intermediate.

The following list of questions was conveyed to the Sponsor/CMO.

(b) (4)

The Agency agreed to submit these questions by email (to be handled by the Office of Compliance). (b) (4) agreed to submit a response by Monday, February 4, 2013 with a final response a week from the telecon.

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/s/

JOEL T WELCH
02/06/2013

LINDA L NG
02/06/2013

From: Skarupa, Lisa
To: Ahmed Bassyouni; "Erica Evans"; Monica Shah; francissen.kathy@gene.com
Cc: Welch, Joel; Mesmer, Deborah; Shiber, Andrew J
Subject: January 28 2013 PMR 2 Genentech"s response
Date: Monday, January 28, 2013 4:24:00 PM

Dear Ahmed,

Please see the following response regarding the cancelled tcon Friday afternoon.

- As stated in the FDA guidance "Assay Development for Immunogenicity Testing of Therapeutic Proteins", you should address the functional or physiological consequences of product immunogenicity. Therefore, you should develop and validate a neutralizing antibody assay. The potential neutralizing effect of ATA on any positive samples identified to date (including the 44/836 patients identified in the draft label) should be determined. We recommend you expedite the development and validation of the neutralizing antibody assay so samples from planned and ongoing clinical studies can be analyzed. Please coordinate milestone-dates of the validation and neutralizing assay with the timelines of your planned clinical trials.

PMC: To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to trastuzumab emtansine, including procedures for accurate detection of neutralizing antibodies to trastuzumab emtansine in the presence of trastuzuamb emtansine levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC Schedule Milestones: Final Report Submission (Assay and Methodology)
Date: MM/DD/YYYY

- Additionally, we note that, in your response to the Agency's information request issued on Jan 23, 2013, you propose to include accelerated stability testing (b) (4) [redacted] Retain accelerated stability testing (b) (4) [redacted] for drug substance and drug product (b) (4) [redacted] Update the related BLA sections to reflect this change.

Sincerely,
Lisa

On Jan 18, the following PMR2 was sent to Genentech:
Optimize the assays used for the detection of anti-trastuzumab emtansine antibodies in human serum:

1) Provide an assessment of the ATA response to trastuzumab emtansine with a validated ELISA binding assay capable of sensitively detecting ATA

responses in the presence of trastuzumab emtansine levels that are expected to be present at the time of patient sampling.

Genentech response on Jan 24: With respect to request (1) above, as the validated ATA screening ELISA submitted to the BLA was designed to be capable of detecting ATA responses in the presence of trastuzumab emtansine, we consider that no additional assay development is required.

2) Develop a validated assay to assess the neutralizing activity of anti-trastuzumab emtansine antibodies.

Genentech response on Jan 24: With respect to request (2) above, based on the ATA observations to date, the sponsor considers that a neutralizing antibody assay will not provide additional data to inform ATA impact on patient outcomes.

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/s/

LISA M SKARUPA
01/28/2013

From: Skarupa, Lisa
To: Ahmed Bassyouni; "Erica Evans"; Erica Evans; Monica Shah; francissen.kathy@gene.com
Cc: Welch, Joel; Mesmer, Deborah; Shiber, Andrew J
Subject: BLA 125427 CMC Information Request Jan 28 2013
Date: Monday, January 28, 2013 4:15:00 PM

Dear Ahmed,

Based on what has been submitted, you have not submitted the final specifications for DM1. We need for you to provide this information **today.** The current specifications are missing (attribute, method and acceptance criteria) for:

- Optical rotation
- Particulate (b) (4)
- Color (b) (4)

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/28/2013

From: Skarupa, Lisa
To: "Erica Evans"; Monica Shah; Ahmed Bassyouni; "francissen.kathy@gene.com"
Subject: FDAresponseJanuary28PackageInsertlabel/ BLA 125427
Date: Monday, January 28, 2013 1:04:00 PM
Attachments: FDAresponseJanuary28PackageInsertlabel.doc

Good afternoon,
Please see attached package insert which includes changes to Section 14 and geriatric section as well.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/28/2013

From: Ahmed Bassyouni
To: Skarupa, Lisa
Cc: Ahmed Bassyouni; Welch, Joel; shah.monica@gene.com; evans.erica@gene.com; francissen.kathy@gene.com; Patrick Leong
Subject: Re: CMC PMR sent January 23rd for BLA125427/0
Date: Friday, January 25, 2013 7:10:29 PM

Dear Lisa,

We agree to the addition.

Ahmed

On Fri, Jan 25, 2013 at 12:41 PM, Ahmed Bassyouni <abassyou@gene.com> wrote:

> Dear Lisa,
>
> I had sent these to you yesterday and am resending them now. I have reattached them in the event that we did not get them. I will look into the update and provide you an update later today.
>
> Ahmed
>
> On Fri, Jan 25, 2013 at 12:14 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
>
> > Dear Ahmed,
> >
> > FDA understands that you plan to respond today to the following CMC PMR sent Jan 23, 2012 at 3:04pm. We would like to add the following PMR language (see red font):
> > To develop and validate an iCIEF method to use as a drug substance and drug product regulatory method for monitoring the unconjugated antibody content and propose a specification limit for the unconjugated antibody content based on clinical and commercial batch data. The final report will be submitted as a Prior Approval Supplement (PAS).
> >
> > Sincerely,
> > Lisa
> >
> > _____
> > **From:** Welch, Joel
> > **Sent:** Friday, January 25, 2013 2:15 PM
> > **To:** Welch, Joel; 'Ahmed Bassyouni'
> > **Cc:** Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
> > **Subject:** CMC IR #28 for BLA125427/0
> > **Importance:** High
> >
> > Ahmed,
> >
> > Below is an additional information request. Please confirm receipt. We request a response by January 28, 2013.
> >
> > Please amend the BLA to include bacterial endotoxin release specification from

finished product [redacted] (b) (4) and from [redacted] (b) (4) bulk [redacted] (b) (4) Both endotoxin release specifications should be included in the CofA.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

--
Ahmed Bassyouni
T-DM1 Technical Regulatory Leader
Office (650) 467-3951
Mobile [redacted] (b) (6)
Email bassyouni.ahmed@gene.com

--
Ahmed Bassyouni
T-DM1 Technical Regulatory Leader
Office (650) 467-3951
Mobile [redacted] (b) (6)
Email bassyouni.ahmed@gene.com

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/s/

LISA M SKARUPA
01/28/2013

From:	Skarupa, Lisa
To:	Erica Evans; Monica Shah; Patrick Leong
Subject:	Package Insert FDA Responses January 25 2013 BLA 125427
Date:	Friday, January 25, 2013 5:33:00 PM
Attachments:	redlined-label-text.FDAresponseJan25_2013.doc

Dear Erica,

We are not finished reviewing the Package Insert; Section 14 is still under review.

Please see attached package insert for your review. We accepted most changes, we made some formatting changes to Section 2.3, comments to Section 11.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/28/2013

From:	Skarupa, Lisa
To:	"Erica Evans"
Cc:	Patrick Leong; Monica Shah
Subject:	RE: Clinical IR for Genentech BLA 125427 TDM1 January 23, 2013
Date:	Thursday, January 24, 2013 8:20:00 AM

Dear Erica,

Clinical Team says the OS analysis question is for the overall population not the population that crossed over.

sincerely,

Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, January 23, 2013 5:55 PM
To: Skarupa, Lisa
Cc: Patrick Leong; Monica Shah
Subject: Re: Clinical IR for Genentech BLA 125427 TDM1 January 23, 2013

Hi Lisa
We have a request for clarity on the questions from the clinical review team.

Is it accurate to assume that the question "Do you plan to follow patients for OS?" refers to the full study cohort and not to the subgroup of crossover patients? While we plan to follow patients for OS from time of randomization, we do not plan to analyze a point estimate for median OS after crossover to T-DM1.

Can you please ask the clinical team to address this for us.

Thanks and kind regards

Erica

On Wed, Jan 23, 2013 at 2:07 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

> Dear Erica,
>
> Please see the following questions from the Clinical Review Team:
> Please let us know how many patients in the EMILIA trial crossover to the TDM1 arm. Do you plan to follow patients for OS? Are you still going to perform the protocol planned final OS analysis? If you are still planning to perform this analysis, when are you expecting to have the results?
>
> Sincerely,
> Lisa

--
Erica J. Evans, Ph.D.
Product Development Regulatory - Program Management
Tel: 650-467-2157 (Direct Line); Tel: (b) (6) (Mobile); Fax: 650-467-1844

Genentech
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

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/s/

LISA M SKARUPA
01/28/2013

From:	Skarupa, Lisa
To:	Erica Evans; "Monica Shah"; Patrick Leong
Cc:	Ahmed Bassyouni; Kathy Francissen; Welch, Joel; Mesmer, Deborah
Subject:	BLA 125427 carton and containers Jan 24th two more recommendations
Date:	Thursday, January 24, 2013 5:54:00 PM
Attachments:	2013-01-18 - Carton and Container Labels.pdf

Dear Erica,
Based on the January 18, 2013 submission, we have the following recommended revisions:

DMEPA Comments to the revised Container Labels and Carton Labeling

A. Container Label

Remove the large band of yellow color on the upper portion of the principal display and the right panels so it matches the color scheme of the carton labeling.

B. Carton Labeling

Delete [redacted] (b) (4) from the reconstitution statement on the bottom panel.

Please let us know if you agree, or sooner if you have any questions.
We will plan to provide the package insert tomorrow morning.
Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/28/2013

Welch, Joel

From: Welch, Joel
Sent: Wednesday, January 23, 2013 4:10 PM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #27 for BLA125427/0

Ahmed,

Below is an additional information request. Please confirm receipt. We request a response by January 24, 2013.

Please submit information about the status of all clinical lots of T-DM1 that were manufactured (b) (4) We have information about the disposition of those lots, but we would like to know if the lots are within expiry, within inventory, if they have been already used, etc.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
01/23/2013

Welch, Joel

From: Welch, Joel
Sent: Wednesday, January 23, 2013 11:57 AM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #26 for BLA125427/0

Importance: High

Ahmed,

Below is an additional information request. Please confirm receipt. We request a response by Jan 24, 2013.

IR – DMA

1. We note that you have provided updated BLA sections to reflect responses to the CMC information requests to date on January 17, 2013. Please update the related BLA sections to reflect the removal of Roche Penzberg from the BLA as a manufacturing site for trastuzumab, as described in your response to the Agency's IR issued on November 21, 2012. Please be aware that validated studies to support your ability to adequately ship and freeze/thaw trastuzumab BDS produced from Roche Penzberg will be required for the implementation of Roche Penzberg as a manufacturing site for trastuzumab.

2. We note that you have committed to amend (b) (4) (response to IR issued on November 2, 2102). Please define (b) (4) and update the related BLA sections to reflect this implementation.

3. Retain accelerated stability testing (b) (4) for drug substance and drug product. Update the related BLA sections to reflect this change.

4. Based on the 18-months real time stability data provided on three batches of 100 mg/vial trastuzumab emtansine drug product in the BLA submission, a 24-months shelf life will be granted for 100 mg/vial trastuzumab emtansine drug product when stored at 2-8°C, as per ICH Q1E.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
01/23/2013

Welch, Joel

From: Welch, Joel
Sent: Friday, January 18, 2013 2:57 PM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #24 for BLA125427/0

Importance: High

Ahmed,

Below is an additional information request. Please confirm receipt. We request a response by Jan 21, 2013.

1. Submit a list of the planned manufacture dates for (b) (4) TDM1 and indicate when (b) (4) cleaning verification results will be submitted to the Agency (results should be submitted as soon as they are available). Provide rinse and swab results. Rinse data should be provided as ppb and converted to mg of product and should be justified in accordance to the new acceptance limits determined using toxicology data. In addition, indicate the limit of detection of the TOC method used for rinse samples.

2. Provide ADE calculations based on toxicology data for (b) (4) clinical TDM1 lot 64540, which is still in inventory and within expiry.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
01/18/2013

Memo to File
Minutes to teleconference
January 17, 2013 from 1:30pm to 2:20pm

FDA Attendees:

Clinical Team, DOP1
Robert Justice, MD, MS, Director
Amna Ibrahim, MD, Deputy Director
Patricia Cortazar, MD, Clinical Team Leader
Todd Palmby, Ph.D., Nonclinical Team Leader

Chemistry Team
Division of Monoclonal Antibodies
Kathleen Clouse, Ph.D., Director
Wendy Weinberg, Ph.D., Team Leader
Linan Ha, Ph.D., Reviewer

Office of Compliance
Patricia Hughes, Ph.D., Team Leader
Peter Zhihao Qiu, Ph.D., Supervisory
David Doleski, Ph.D., Supervisory
Bo Chi, Ph.D., Reviewer
Maria Candauchacon, Ph.D., Reviewer
Francisco Borrego, Ph.D., Reviewer
Linda Ng, Ph.D., Acting Branch Chief
Tara Gooen, Ph.D., Reviewer

Office of New Drug Quality Assessment
Ali Al Hakim, Ph.D., Branch Chief
Anne Marie Russell, Ph.D., Reviewer
Haripada Sarkar, Ph.D. CMC Lead

Regulatory Project Managers
Lisa Skarupa, DOP1
Susan Jenney, Safety PM, DOP1
Joel Welch, Ph.D., DMA
Andrew Shiber, DMA

Genentech Attendees

Lynne Krummen, Ph.D, Vice-President, Biologics, Technical Regulatory
Kathy Francissen, Ph.D., Director, Biologics Development, Technical Regulatory
Ahmed Bassyouni, Product Manager, Biologics Development, Technical Regulatory
Fred Jacobson, Ph.D. Principal Scientist, Protein Analytical Chemistry
Adam Pinkert Principal Technical Manager, External Quality

Alexandra James, Head, External Quality CMO Steriles, North America
Nick Beaumont, Head, External Quality Validation
Brian Freeman Director, T-DM1 Marketing
Roger Symzak Product Supply Chain Leader
Erica Evans, Ph.D. Senior Manager, Product Development Regulatory Program Management
Jolene Leathers Head, External Quality CMO Drug Substance
Glenn Brame Vice-President, External Quality
(b) (4) Representatives:
(b) (4)

The teleconference today was requested by DOP1 to assure that all necessary information will be submitted to all CMC disciplines in a timely manner.
Many of the CMC Information Requests sent to Genentech January 11, 16 (two) continue to focus on the condition of the lots (DM1 and TDM1) based on the inspections of the manufacturing sites.

This is a bullet summary of the teleconference:

- Genentech agreed to provide responses to all the information requests sent out Jan 11, and 16 and planned for this afternoon.
- Genentech's presentation showed that they have enough supply for 18 weeks at which point they will need to re-supply.
- Genentech reiterated that they need both the (b) (4) manufacturing sites to meet these projected supplies for future demands.
- FDA informed Genentech that additional IR letter will be sent which includes comments related to GMP, Micro and CMC.
- FDA clarified the requests for
  - the genealogy of the Drug Product lots (DM1 batch number, trastuzumab batch number, T-DM1 drug substance batch number),
  - the source of DM1 (b) (4)
  - the condition of DM1 lots (b) (4) and
  - the dates of Drug Substance and Drug Product manufacture
  - also to investigate (b) (4) to prevent any recurrence in the future

    (Genentech reported they had no reports since 2009, however, FDA requested for investigation to prevent any recurrence, and to review current specs provided to FDA (b) (4).)

Conclusion:

Genentech agreed to provide responses to all Information Requests and should all be submitted to FDA by January 25th due to the time constraints of the BLA 125427 review.

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/s/

LISA M SKARUPA
01/28/2013

WENDY C WEINBERG
01/28/2013

From:	Skarupa, Lisa
To:	"Ahmed Bassyouni"; Ahmed Bassyouni
Cc:	"Erica Evans"; Erica Evans; Monica Shah; Patrick Leong; Welch, Joel; Shiber, Andrew J; Mesmer, Deborah
Subject:	CMC Information Request Jan 17 2013 Post TCON BLA 125427
Date:	Thursday, January 17, 2013 4:49:00 PM

Dear Ahmed,

Here is the CMC Information Request we mentioned we would send today.

As usual with all the past CMC I.R.s, please respond to Joel Welch the CMC RPM, and copy me.

Please acknowledge and, due to our time constraints, provide your response by next week January 23rd .

Sincerely,

Lisa

1. At the facility where TDM-1 is manufactured (b) (4) propose in-process testing with acceptance criterion (b) (4) In addition, propose an (b) (4) test with acceptance criterion in the Release Specification at all DM1 facilities. Describe the proposed plan with disposition of failed lots of DM1.

2. It does not appear that appropriate controls are in place (b) (4) at the DM1 manufacturing sites and the associated investigations appear incomplete. Corrective action should be implemented (b) (4) Until this (b) (4) is fully resolved and found satisfactory during onsite FDA inspections, interim tests/controls should be implemented (b) (4) Propose an in-process test with acceptance criterion (b) (4) at the site of the TDM-1 manufacturing (b) (4) The test can be performed (b) (4) In addition, propose a test (b) (4) as part of the Release Specification at the DM1 facilities. Describe the proposed plan with disposition of failed lots of DM1.

3. Perform a risk assessment (b) (4)

4. Update the BLA regarding the sterilization process for the (b) (4) container/closure for the drug product at (b) (4).

5. Include a statement confirming that the BLA contains all submitted information that are consistent with your current manufacturing processes. Otherwise, provide appropriate amendments to the BLA.

6. The proposal provided in your response to IR#15 regarding the timing of adding a specification for optical rotation to DM1 [redacted] (b) (4) is not sufficiently timely. Provide the proposed information by 25-Jan-2013.

7. Since specifications for DM1 starting materials [redacted] (b) (4) and DM1 have been recently revised, confirm that all T-DM1 lots in current inventory have been both:

a. Manufactured using DM1 which meets current specifications

b. Manufactured using DM1 which was manufactured using starting materials which meet current specifications within expiry.

Also, describe plans for disposal of T-DM1 lots which do not comply.

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/s/

LISA M SKARUPA
01/17/2013

From:	Skarupa, Lisa
To:	"Erica Evans"; Monica Shah; Patrick Leong; Erica Evans
Cc:	"Ahmed Bassyouni"
Subject:	Package Insert and prefix/ Jan 16/ BLA 125427
Date:	Wednesday, January 16, 2013 10:11:00 PM
Attachments:	PackageInsertFDAResponseon_Jan16.doc

Dear Erica,
Please see the attached package insert.

1) There are two areas that we still need to respond to later:

- Section 5.8 HER2 Testing, we are waiting for data requested by CDRH
- Section 16.1, we are still reviewing the section referenced regarding KADCYLA (b) (4)

2) Please note that the Table of Contents are not fitting into the one page, please assist in placing into one page.
3) We also removed the bolded and capitalized DO NOT FREEZE or DO NOT SHAKE and formatted to be italicized and underlined.

4) Please be sure the spacing is uniformed throughout the package insert.

Regarding your three proposed prefixes for the established name, FDA accepts the "ado-" prefix, i.e. ado-trastuzumab emtansine.

Please let me know if you have any clarifications.
Please let us know as soon as possible when you can respond to this attached package insert.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/17/2013

From: Ahmed Bassyouni
To: Skarupa, Lisa
Cc: Ahmed Bassyouni; Erica Evans; Monica Shah; Patrick Leong; Mesmer, Deborah; Welch, Joel; Shiber, Andrew J
Subject: Re: Jan16 second CMC Information Request following Genetech"s response to Jan11thIR
Date: Wednesday, January 16, 2013 1:04:07 PM

Dear Lisa,

We acknowledge receipt. I would like to clarify if the request is for all currently available batches that would be used clinically or commercially. Therefore we would not include batches that have already been exhausted.

Ahmed

On Jan 16, 2013, at 9:26 AM, Skarupa, Lisa wrote:

> Dear Ahmed,
>
> Regarding Genentech's response to FDA's Information Request sent January 11th, the response was lacking data, therefore we have this additional request:
>
> Please provide in tabular form a list of **all** TDM1 lots manufactured to date, and indicate for each lot the intended use (clinical or commercial) and the disposition (released, rejected, pending). In accordance with our previous request 1/16, indicate the source of the DM1 (b) (4) for all lots of TDM1 manufactured and the findings (b) (4)
>
> Sincerely,
>
> Lisa

From: Ahmed Bassyouni [mailto:bassyouni.ahmed@gene.com]
Sent: Wednesday, January 16, 2013 12:01 PM
To: Skarupa, Lisa
Cc: Ahmed Bassyouni; Erica Evans; Monica Shah; Patrick Leong; Mesmer, Deborah; Welch, Joel; Shiber, Andrew J
Subject: Re: CMC Information Request following Jan 14 afternoon teleconference_Jan162013

Good Morning Lisa,

I acknowledge receipt of the request. We will work with the team to get responses as soon as possible.

Ahmed

On Wed, Jan 16, 2013 at 8:46 AM, Skarupa, Lisa

<Lisa.Skarupa@fda.hhs.gov> wrote:

Good morning Ahmed,

Please see the following Information Request based on the January 14, 2013 teleconference held between FDA and Genentech.
This topic will also be discussed on the Jan 17th 1pm EST teleconference to cover the CMC I.R. sent Jan 11th by Joel Welch.
Please respond by COB January 17th due to the urgency of the situation.

As per conversation last Monday January 14, 2013, **please submit the following information:**

- List of all TDM1 lots (commercial and IND) with endotoxin results after thaw and bioburden results (b) (4)
- List of all TDM1 lots (commercial and IND), with manufacturing dates, indicating which of them are (b) (4) manufactured (b) (4)
- All (b) (4) cleaning verification data (b) (4) indicating when the verification was conducted
- Cleaning validation results from swab and rinse samples (b) (4) (we have (swab + rinse) results from all equipment and swab results (b) (4) We need (swab + rinse) results (b) (4))
- Information about how often cleaning verification (b) (4) is conducted
- List of all TDM1 lots manufactured (commercial and IND) (b) (4) and indicate the source of the DM1 (b) (4) or verify that this information was already provided in your response to the IR sent on 1/11/2013.

In addition, and after consulting with our colleagues in the toxicology and the clinical division, **we ask you to implement the following as soon as possible**

- Cleaning verification (b) (4)
- Dedicated (b) (4) for TDM1

We will follow up on the last two items on Thursday (T-con) for possible implementation dates.
We understand that some of this information has to come from (b) (4). However due to the urgency of the situation, we would like to have your response by COB January 17, 2013.

Sincerely,
Lisa

--
Ahmed Bassyouni
T-DM1 Technical Regulatory Leader

Office (650) 467-3951
Mobile (b) (6)
Email bassyouni.ahmed@gene.com

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/s/

LISA M SKARUPA
01/16/2013

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Tuesday, January 15, 2013 1:31 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah; Patrick Leong; Lisa Kelsey
Subject: Re: BLA 125427 carton and containers/ additional comments

Dear Lisa
We anticipate all of these changes being acceptable to Genentech. Will we need to formally accept changes by resubmitting updated PDF and Word documents of cartons and container labels to the BLA? If so, we would like to coordinate with the addition of the FDA approved prefix to xxx-trastuzumab emtansine once we receive notification of that and make one formal submission. Is this acceptable?

Kind regards
Erica

From: Skarupa, Lisa
Sent: Tuesday, January 15, 2013 1:11 PM
To: 'Erica Evans'; Monica Shah; Patrick Leong
Subject: BLA 125427 carton and containers/ additional comments

Dear Erica,

Regarding your modifications to the carton and container labels (1.14.1.1. Draft), please see DMEPA Comments to the revised Container Labels and Carton Labeling.
Please let us know if you concur as soon as possible.

A. Container Label

1. De-bold the dosage form, For Injection, so that it has equal prominence with the non-proprietary name, xxx-trastuzumab emtansine.
2. Revise the temperature range in the storage information, (b) (4) to read, 2ºC - 8ºC (36ºF - 46ºF).

B. Carton Labeling

1. See comments A1 and A2.
2. Delete (b) (4) from the reconstitution statement on the back panel. Thus, the volumes (b) (4) should read, *5 mL* and *8 mL*, respectively.
3. Revise the reconstitution statement on the back panel by deleting the statement, (b) (4)

Sincerely,

Lisa

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/s/

LISA M SKARUPA
01/15/2013

Welch, Joel

From: Welch, Joel
Sent: Friday, January 11, 2013 2:47 PM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #22 for BLA125427/0

Importance: High

Ahmed,

Please see below for an additional information request. Please confirm receipt. We request a response by Tuesday January 15, 2013.

1. Provide a listing in tabular format of trastuzumab emtansine Drug Product lots currently available for commercial launch. This information should include the genealogy of the Drug Product lots (DM1 batch number, trastuzumab batch number, T-DM1 drug substance batch number), the source of DM1 (b) (4) the condition of DM1 lots (b) (4) and the dates of Drug Substance and Drug Product manufacture.

2. Provide information on the anticipated market demand for trastuzumab emtansine and comment on your ability to meet the anticipated market demand and maintain an adequate supply for ongoing or anticipated clinical studies, if the clinical trial material would be the same as that approved for commercial distribution.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
01/11/2013

December 2012 Information Requests

From: Skarupa, Lisa
Sent: Monday, December 10, 2012 12:45 PM
To: 'Erica Evans'
Cc: Monica Shah; Liang Fang
Subject: Followup Dec10th: BLA 125427 Clinical Information December 3 2012

Dear Erica,
As per Clinical team, below is a description of the code. Please let me know if this helps.
Sincerely,
Lisa

Patient Population:
DEMOG.Safety Evaluable (YES/NO) =YES

Filters:
LABHEML.Lab Test Description <parm>
LABHEML.Baseline Record Flag (YES,NO) =NO
LABHEML.Test Has NCI Grade Defined (YES,NO) =YES
Abnormal NCI Grade (1-4) is not missing

Column: Actual treatment arm by Row of lab test and NCI tox grade

% denominator is total N subjects treated in each arm (assigned safety population)

Same filters apply to labchem

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, December 05, 2012 1:03 PM
To: Skarupa, Lisa
Cc: Monica Shah; Liang Fang
Subject: Re: BLA 125427 Clinical Information December 3 2012

Dear Lisa
I am following up from my Dec 3 2012 email. Would it be possible for us to receive the program FDA used to generate the % values below. Without this it is very difficult for our team to replicate the FDA data and be able to reconcile the differences between FDA values and our values in table 7 of the draft label. This dataset we are working with has 170,000 data points.

Please advise if we can receive the program in order for us to be able to address the FDAs request by Dec 7.

Thanks
Erica

From: Skarupa, Lisa
Sent: Monday, December 03, 2012 2:07 PM
To: 'Erica Evans'
Cc: Monica Shah
Subject: RE: BLA 125427 Table 6_Clinical Information December 3 2012

Dear Erica,

Please see the addition request on **Table 6** in the draft labeling:

For ADR terms encompassing more than one basket/group of preferred terms (PT), please tell us which PTs were included.

We would like responses no later than COB 12/7/2012.

Sincerely,

Lisa

From: Skarupa, Lisa
Sent: Monday, December 03, 2012 10:46 AM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Clinical Information December 3 2012

Dear Erica,
Please see the following Clinical Information Request:
Reference is made to table 7 of the draft labeling. We note the following discrepancies with your numbers below. Please reconcile no later than COB 12/7/12.

Increased bilirubin TDM1: (b) (4)
Increased AST L + C: (b) (4)
Increased ALT L + C: (b) (4)
Decreased Platelets T-DM1: (b) (4)
Decreased Platelets L + C, grade 3: (b) (4)
Decreased Platelets L + C, grade 4: (b) (4)
Decreased Hemoglobin: (b) (4)
Decreased Neutrophils TDM1: (b) (4)
Decreased Neutrophils L + C: (b) (4)
Decreased potassium TDM1: (b) (4)
Decreased potassium L + C: (b) (4)

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/04/2013

Memo to File
Minutes to teleconference
January 14, 2013 from 3:00pm to 4:00pm

FDA Attendees:

Clinical Team, DOP1
Patricia Cortazar, MD, Clinical Team Leader
Laleh Amiri Kordestani, MD, Reviewer

Division of Monoclonal Antibodies
Wendy Weinberg, Ph.D., Team Leader
Joel Welch, Ph.D., Regulatory Project Manager

Office of Compliance
Patricia Hughes, Ph.D., Team Leader
Bo Chi, Ph.D., Reviewer
Reyes Candau-Chacon, Ph.D., Reviewer

Genentech Attendees

Kathy Francissen, Ph.D.	Director, Biologics Development, Technical Regulatory
Ahmed Bassyouni	Product Manager, Biologics Development, Technical Regulatory
Fred Jacobson, Ph.D.	Principal Scientist, Protein Analytical Chemistry
Joseph Chen, Ph.D	Sr. Principal Scientist, Method Management Technology
Anthony Chen, Ph.D.	Principal Scientist, IMP Quality Control
Adam Pinkert	Principal Technical Manager, External Quality
Alexandra James	Head, External Quality CMO Steriles, North America
Nick Beaumont	Head, External Quality Validation

The teleconference was requested by FDA on January 11, 2013 to discuss two issues: masking of endotoxin (b) (4) of TDM-1 drug product (b) (4).

The Sponsor agreed to provide the following action items by the end of the week:

- List of all TDM1 lots (commercial and IND) with endotoxin results after thaw and bioburden results (b) (4).The Sponsor agreed to provide the following data:
- List of all TDM1 lots (commercial and IND), with manufacturing dates, indicating which of them are (b) (4) manufactured (b) (4)
- All (b) (4) cleaning verification data (b) (4), indicating when the verification was conducted
- Cleaning validation results from swab and rinse samples (b) (4) (we have (swab + rinse) results from all equipment and swab results (b) (4) We need (swab + rinse) results (b) (4))

- Please provide in tabular form a list of all TDM1 lots manufactured to date, and indicate for each lot the intended use (clinical or commercial) and the disposition (released, rejected, pending). In accordance with our previous request 1/16, indicate the source of the DM1 (b) (4) for all lots of TDM1 manufactured and the findings (b) (4)

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/s/

JOEL T WELCH
01/24/2013

PATRICIA F HUGHES TROOST
01/24/2013

From: Erica Evans
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: January 9 PMR Milestones Request BLA 125427
Date: Wednesday, January 09, 2013 12:31:31 PM

Dear Lisa
We acknowledge receipt of your request. We will work with the team to provide a response.
Kind regards
Erica

On Wed, Jan 9, 2013 at 9:12 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

> Good morning,
> Please let me know if these PMR milestone dates are acceptable to Genentech. Thank you, Lisa
>
> | | | |
> |---|---|---|
> | PMR Description: | Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women with breast cancer exposed to xxx-trastuzumab-emtansine 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. | |
> | PMR Schedule Milestones: | Final Protocol Submission: | 04/2013 |
> | | Study/Trial Completion: | 04/2023 |
> | | Final Report Submission: | 04/2024 |
> | | Other: | MM/DD/YYYY |

--
Erica J. Evans, Ph.D.
Product Development Regulatory - Program Management
Tel: 650-467-2157 (Direct Line); Tel: (b)(6) (Mobile); Fax: 650-467-1844

Genentech
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

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/s/

LISA M SKARUPA
01/09/2013

From:	Erica Evans
To:	Skarupa, Lisa
Cc:	Erica Evans; Monica Shah; Patrick Leong; Ahmed Bassyouni; Mesmer, Deborah; Kacuba, Alice
Subject:	Re: Dec 26th: BLA 125427/ FDA response to established name change
Date:	Wednesday, December 26, 2012 12:26:30 PM

Dear Lisa
We acknowledge receipt. We will get back to you regarding the response date.

Kind regards
Erica

Sent from my iPhone

On Dec 26, 2012, at 9:15 AM, "Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov> wrote:

> Good morning Erica, Monica, Patrick, Ahmed,
>
> Please see attached letter regarding the request to modify the established name.
>
> Please acknowledge receipt and if you can provide us a response by COB January 4th.
>
> Sincerely,
> Lisa
>
> <EstablishedNameModification_BLA125427.pdf>

3 Page(s) has been Withheld in Full as duplicate copy of General Advice/Information Request 12.21.12 immediately following this page

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/s/

LISA M SKARUPA
12/26/2012

From:	Erica Evans
To:	Skarupa, Lisa
Cc:	Erica Evans; Monica Shah; Patrick Leong; Ahmed Bassyouni; Mesmer, Deborah; Kacuba, Alice
Subject:	Re: Dec 26th: BLA 125427/ FDA sending PackageInsert/ carton+container comments/ PMR/PMC
Date:	Wednesday, December 26, 2012 12:20:01 PM

Dear Lisa
We acknowledge receipt. We will get back to you regarding the response date of January 2.

Kind regards
Erica

Sent from my iPhone

On Dec 26, 2012, at 9:03 AM, "Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov> wrote:

> Good morning Erica, Monica, Patrick, Ahmed,
>
> I wanted to let you know that in the following days Dec 26 through Dec 28th, we do not foresee any information requests from our division.
> We do have the following documents for you to review and request that you provide your comments/edits/response back to us in one week, by COB January 2nd.
>
> - Package insert Dec26
> - DMEPA comments for the carton and containers
> - FDA requests for agreement on language of PMR and PMC and for dates on the milestones
>
> Please note the following for the Package Insert. We have requested that you assist us in modifying the Table of Contents under Highlights to align with the modifications made in the package insert.
> We also placed comments to assist us throughout the PI with spacing, formatting, and fixing all references to be consistent with this formatting : *[see Warnings and Precautions (5.9)]*.
>
> Regarding the PMR and PMC, please review the language of the PMR/PMC description and let us know if you agree with the language. Lastly, please provide dates on the necessary milestones for each the PMR and the PMC.
>
> Please acknowledge receipt and if you can provide us your edits/comments on each of those documents by COB January 2nd.
>
> Sincerely,
>
> Lisa
>
> <BLA 125427 PMRPMC_needmilestones.pdf>
>
> <DMEPAcomments_CartonContainers.pdf>

<BLA125427_PackageInsert_Dec26.doc>

Regarding BLA 125,427 for Kadcyla™, FDA requests that the applicant provide milestone dates for Study/Trial Completion and Final Report Submission for the post-marketing commitment (PMC) and post-marketing requirement (PMR) described below.

PMC Description: To conduct exposure-response analyses for overall survival, progression free survival, response rate, and safety endpoints utilizing data from trial TH3RESA. The results of the exposure-response analyses from TH3RESA and TDM4370g will determine the need for a post-marketing trial to optimize the dose in patients with lower exposure at the approved dose.

PMC Schedule Milestones:	Final Protocol Submission (TH3RESA):	submitted
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

PMR Description: To evaluate the impact of hepatic impairment on KADCYLA (antibody drug conjugate, total antibody, and DM1) pharmacokinetics.

PMR Schedule Milestones:	Final Protocol Submission (BO25499):	submitted
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
	Other: _____	MM/DD/YYYY

BLA 125427
DMEPA comments for the carton and containers

A. General Comments

1. Your proposed education plan should be revised to include Pharmacy Technicians:

   Pharmacy technicians compound chemotherapeutic products and may be less likely than pharmacists, nurse and practitioners to understand the differences between Trastuzumab and Trastuzumab Emtansine. Therefore, it is essential to include this group in your education plan.

2. Revise the purple color used in the 160 mg strength container label and carton labeling to a different color. This purple color is similar to color used on Herceptin (trastuzumab). It is imperative that these products are distinguished.

B. Container Label

1. Revise the strength, xxx mg, to read, xxx mg per vial.

2. Add the dosage form, For Injection, to appear below the nonproprietary name, trastuzumab emtansine.

3. Add a statement that conveys reconstitution and dilution are required prior to use.

4. Revise the single-use vial statement to read "Single-Dose Vial – Discard Unused Portion". Thus, the principal display panel should appear as:

Kadcyla
(trastuzumab emtansine)
For Injection

xxx mg per vial
For Intravenous Infusion Only

Reconstitute and Dilute prior to administration
Single-Dose Vial – Discard Unused Portion

C. Carton Labeling

1. See Comments B1 through B4.

2. Revise the statement, [redacted] (b) (4) to read as, Do not use if vacuum does not pull diluent into the vial.

3. Replace the abbreviation, *IV*, with the word, *intravenous*.

4. Delete recommendations [redacted] (b) (4)

5. Per 610.61(e), revise the statement, [redacted] (b) (4) to "No preservative."

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

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/s/

LISA M SKARUPA
12/26/2012

Welch, Joel

From: Welch, Joel
Sent: Friday, December 14, 2012 11:10 AM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #21 for BLA125427/0

Importance: High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt.

Reviewer Comments to Information Request for Trastuzumab emtansine STN 125427/0 - Drug product, Microbial Quality

1. P.3.5.4.2. Validation (b) (4)

Please submit the (b) (4) results pre- and post-use from consecutive studies from your 30 most recent production batches.

Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
12/14/2012

Welch, Joel

From: Welch, Joel
Sent: Wednesday, December 12, 2012 2:53 PM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #20 for BLA125427/0

Importance: High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by December 19 , 2012 .

CMC IR#6

1. We note in the drug substance stability section (section 3.2.S.7) that you have designated three registration batches (Batch 921094, 946013 and 946010) that were manufactured using DM-1 (b) (4) . Provide process validation data for the three (b) (4) DM1 derived trastuzumab emtansine registration batches, similar to those provided for the (b) (4) DM1-derived trastuzumab emtansine registration batches (see section 3.2.S.2.5).

2. We acknowledge your response to Question 1 of the information request issued on November 30, 2012, indicating that the identity of the final labeled trastuzumab emtansine drug product vials will be confirmed by Genentech's internal tracking system and the unique configuration of the vials at the Hillsboro Fill Finish Facility. Provide a complete list of products that are currently labeled and packaged at Genentech Hillsboro Fill Finish Facility. Include information on how the configuration of trastuzumab emtansine drug product (both 100 mg and 160 mg) will distinguish trastuzmab emtansine from all other products manufactured in the same facility.

3. We note that you have provided results of a photostability study for trastuzumab emtansine drug product (Table P.8.3-8). Provide detailed information on the conditions used for the study.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
12/12/2012

Welch, Joel

From: Welch, Joel
Sent: Monday, December 03, 2012 7:48 AM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #19 for BLA125427/0

Importance: High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by December 7 , 2012 .

For the in-use dilution stability study, you did not test for Purity by RP-HPLC due to the concentration (b) (4) following dilution into an IV bag (b) (4) the limit of quantification (LOQ) for this method. However, the method validation study for RP-HPLC shows that the LOQ is (b) (4) (See 3.2.P.4.3). The concentration of the diluted drug product in the infusion bag is approximately (b) (4) (See 3.2.P.2.6). Therefore, the calculated (b) (4) content would be (b) (4) as shown below:

Diluted drug concentration: (b) (4)

Total (b) (4) concentration: (b) (4)

Total concentration (b) (4): (b) (4)

Based on the method validation study for Purity by RP-HPLC and also based on the above calculation, please confirm whether the (b) (4) content can be measured in diluetd solution. If this is the case, include this test in the in-use dilution stability studies.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

Reference ID: 3224586

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/s/

JOEL T WELCH
12/04/2012

Welch, Joel

From: Welch, Joel
Sent: Friday, November 30, 2012 3:08 PM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: RE: CMC IR #18 for BLA125427/0

Importance: High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by December 7 , 2012 .

IR DMA #5

21 CFR 610.14 requires an identity test after final labeling operations, as below:

> *The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.*

Provide information regarding the identity testing performed on trastuzumab emtansine following final labeling operations at Genentech Hillsboro Fill Finish (HFF) Facility, as per 21 CFR 610.14.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

Reference ID: 3224261

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/s/

JOEL T WELCH
11/30/2012

November 2012 Information Requests

From: Skarupa, Lisa
Sent: Friday, November 30, 2012 9:58 AM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Clinical Information Request November 30, 2012 Financial Disclosures

Dear Erica,

Please clarify if you obtained the financial disclosures from the independent radiology reviewers and the oncology reviewers.

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Wednesday, November 28, 2012 4:57 PM
To: 'Erica Evans'
Cc: Monica Shah
Subject: FDA responses: BLA 125427 Clinical Pharmacology Information Request November 20 2012

Dear Erica,
Regarding your clarifications sent on Wed November 21, 2012. Here are the ClinPharm team's responses. Sincerely, Lisa

•Population PK (PopPK) predicted Cmin at Cycle 1 Day 21 ($C_{min,C1D21}$):

1) Was the Final PopPK model used for the PopPK prediction? (Appendix 7.10 of the Population Pharmacokinetic Report 12-0489) 2) Was IPRED from PopPK fitting used to predict $C_{min,C1D21}$ for E-R analysis? 3) how were BQL data handled (LLOQ= 60 ng/mL).

FDA response: Yes. Your final PopPK model was used to simulate individual $C_{min,C1D21}$. IPRED from PopPK fitting was used to predict $C_{min,C1D21}$ for E-R analysis. For the simulated $C_{min,C1D21}$, only two patients had concentration < 60 ng/mL which are included in the first exposure quartile for the PFS and OS exposure-response analysis.

•E-R analysis for PFS and OS:

1) In Figures 1 and 2, how were OS and PFS curves adjusted for baseline covariates? 2) Were 4 separate multivariate cox models used to obtain the 4

hazard ratios, one per quartile, in Table 1? 3) What approach was used to select baseline covariates? 4) Were any interaction terms used when adjusting for baseline covariates? 5) How were patients with missing covariates handled?

FDA response: The baseline covariates were not adjusted in Figures 1 and 2. These figures are based on univariate analysis of exposures vs. survival. Four separate multivariate Cox models were used to obtain the hazard ratios, one per quartile. No interaction terms were used for baseline covariates. Baseline covariates were selected based on the statistical significance in the Cox model and clinical relevance. Cox regression analysis identified four significant baseline risk factors for OS: Baseline HER2 ECD (>=median, < median), ECOG performance status (>=1 vs. 0), measurable disease (Yes vs. No) and tumor burden (>= median, < median). For PFS, three significant baseline risk factors were identified: ECOG performance status, measurable disease and tumor burden. However, baseline HER2 ECD was included as it is clinically relevant. Other baseline covariates such as number of disease sites, prior anthracycline use, prior trastuzumab treatment and visceral disease were also selected based on clinical relevance. The patients with missing values were excluded from the multivariate analysis.

• E-R analysis for ORR:
1) Did the analysis include baseline covariates?
Was the ORR p value ($p<0.01$) based on Emax?

FDA response: The baseline covariates were not adjusted in Figures 3. The p-value reported is for Emax. Please note that this analysis for this secondary endpoint was conducted to provide supportive evidence that the E-R relationship is in the same direction as for OS and PFS.

On Nov 26, 2012, at 2:46 PM, "Skarupa, Lisa" <Lisa.Skarupa@fda.hhs.gov> wrote:

Dear Erica,

The Clinical Pharmacology Team feels that December 5 submission date appears reasonable. They will provide response to your request for clarifications by COB tomorrow.

Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, November 21, 2012 7:35 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 Clinical Pharmacology Information Request November 20 2012

Dear Lisa

The team met today to discuss the November 20 2012 Clinical Pharmacology Information Request. The team have some clarifying questions to the to the FDA reviewers that will help us in preparing our response.

The sponsor appreciates the exposure-response (E-R) analysis conducted by the FDA. To better understand, we would appreciate if FDA can clarify the following questions:

•Population PK (PopPK) predicted Cmin at Cycle 1 Day 21 ($C_{min,C1D21}$):

1) Was the Final PopPK model used for the PopPK prediction? (Appendix 7.10 of the Population Pharmacokinetic Report 12-0489)

2) Was IPRED from PopPK fitting used to predict $C_{min,C1D21}$ for E-R analysis?

3) how were BQL data handled (LLOQ= 60 ng/mL)

•E-R analysis for PFS and OS:

1) In Figures 1 and 2, how were OS and PFS curves adjusted for baseline covariates? 2) Were 4 separate multivariate cox models used to obtain the 4 hazard ratios, one per quartile, in Table 1?

3) What approach was used to select baseline covariates?

4) Were any interaction terms used when adjusting for baseline covariates?

5) How were patients with missing covariates handled?

•E-R analysis for ORR:

1) Did the analysis include baseline covariates?

2) Was the ORR p value ($p<0.01$) based on Emax?

The team will require answers from FDA to the above questions in order for Genentech to submit a full and complete response to this information request. In addition, in order to provide a comprehensive written response to the Agency's proposal, the team requires additional time to evaluate the FDA's analysis and

findings as presented in the November 20 2012 email, along with the responses to the above clarifying question. As a consequence, Genentech proposes to submit our response to this clinical pharmacology information request by December 5, 2012.

Please confirm the Agency agreement on this revised submission date.

We look forward to receipt of responses to our questions and confirmation of the revised submission date.

Kind regards

Erica

On Tue, Nov 20, 2012 at 2:01 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Good afternoon,

Please see attached Exposure-Response Analysis Summary which has the following request for a written response. Please provide the response by November 28, 2012 COB.

Based on FDA analysis and findings presented below, please provide a written response on the feasibility of a dose optimization study in patients with lower exposures. This trial could potentially be done post marketing.

Sincerely,
Lisa

EXPOSURE RESPONSE ANALYSIS FOR T-DM1

This document describes the exposure-response analysis conducted by the FDA. The exposure-response analysis for efficacy was conducted using trial TDM4370g data for the three efficacy endpoints (OS, PFS and ORR). The exposure-OS analyses indicates that after accounting for known baseline confounding factors, the patients with lower exposures have lower probability of survival (Figure 1). Similar conclusions were reached when PFS or ORR was used as the response variable (Figures 2-3). Thus, the subgroup of patients with low exposures may receive additional benefit with a higher dose.

Based on FDA analysis and findings presented below, please provide a written response on the feasibility of a dose optimization study in patients with lower exposures. This trial could potentially be done post marketing. Provide your response by November 28, 2012.

Summarized below in brief are the analysis methodologies along with the main findings.

Exposure-efficacy:
Population PK predicted T-DM1 trough concentration on Day 21 in Cycle 1 ($C_{min,C1D21}$) was available for 68.2% patients (N=334) in the T-DM1 arm (N=490). Kaplan-Meier survival analysis for OS was performed with these patients stratified according to quartiles of $C_{min,C1D21}$ (≤1.29, 1.29–1.99, 1.99–2.75 and >2.75 μg/mL). Hazard ratio (HR) for each quartile of $C_{min,C1D21}$ vs. the control arm was estimated using a Cox proportional hazards model adjusted by the following baseline covariates: ECOG (0 vs. 1), number of disease sites (< 3 vs. ≥3), prior anthracycline use (yes vs. no), prior transtuzumab treatment for MBC (yes vs. no), visceral disease (yes vs. no), measurable disease (yes vs. no), tumor burden, and HER2 shed antigen. Similar analysis was conducted for PFS and the results are shown in Figure 2. The relationship between $C_{min,C1D21}$ and objective response rate (ORR), the secondary efficacy endpoint in trial TDM4370g, was analyzed with logistic regression of an E_{max} model.

The datasets utilized for the analysis are listed below:

- OS: second interim analysis (patos.xpt)
- PFS: final analysis (patirf.xpt)
- ORR: final analysis(expreff1.xpt)

Overall, the analysis indicated that the higher the T-DM1 exposure, the greater the OS or PFS improvement. Furthermore, T-DM1 exposure ($C_{min,C1D21}$) was significantly related to objective response rate (ORR, $P < 0.01$) (**Figure 3**), using a logistic regression analysis of an E_{max} model.

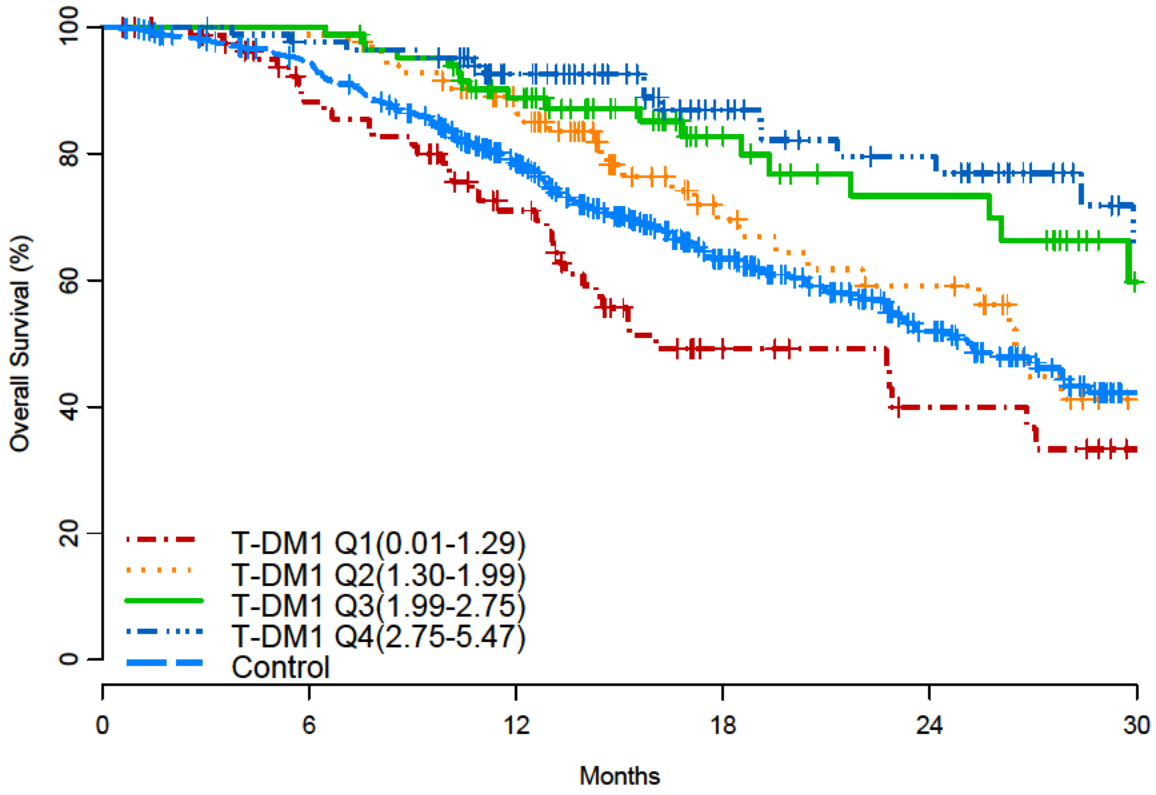

Figure 1. Kaplan-Meier curve of overall survival (OS) for the T-DM1 arm (N=334) by quartiles of $C_{min,C1D21}$ and for the active control arm (N=488) of Trial TDM4370g/BO21977.

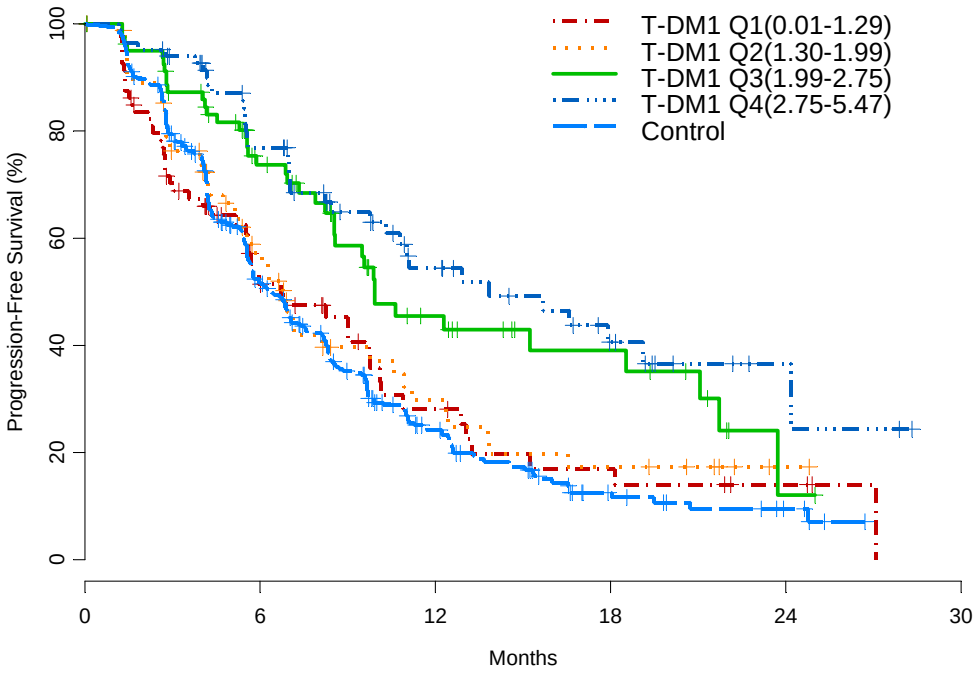

Figure 2 Kaplan-Meier curve of progression free survival (PFS) for the T-DM1 arm (N=334) by quartiles of $C_{min, C1D21}$ and for the active control arm (N=488) of Trial TDM4370g/BO21977.

Table 1. Hazard ratio (HR) for each of $C_{min,C1D21}$ quartiles vs. the active control arm (capecitabine + lapatinib) after adjusting baseline covariates including ECOG, number of disease sites, prior anthracycline use, prior transtuzumab treatment, visceral disease, measurable disease, HER2 ECD and tumor burden.

Efficacy Endpoint		HR (95% CI)	P-value
PFS	TDM1 Q1 vs. Control	0.82 (0.57, 1.16)	0.25
	TDM1 Q2 vs. Control	0.73 (0.52, 1.02)	0.066
	TDM1 Q3 vs. Control	0.57 (0.39, 0.83)	0.0032
	TDM1 Q4 vs. Control	0.36 (0.24, 0.53)	< 0.0001
OS	TDM1 Q1 vs. Control	0.97 (0.65, 1.46)	0.89
	TDM1 Q2 vs. Control	0.68 (0.44, 1.05)	0.080
	TDM1 Q3 vs. Control	0.40 (0.22, 0.72)	0.0024
	TDM1 Q4 vs. Control	0.35 (0.20, 0.63)	0.0005

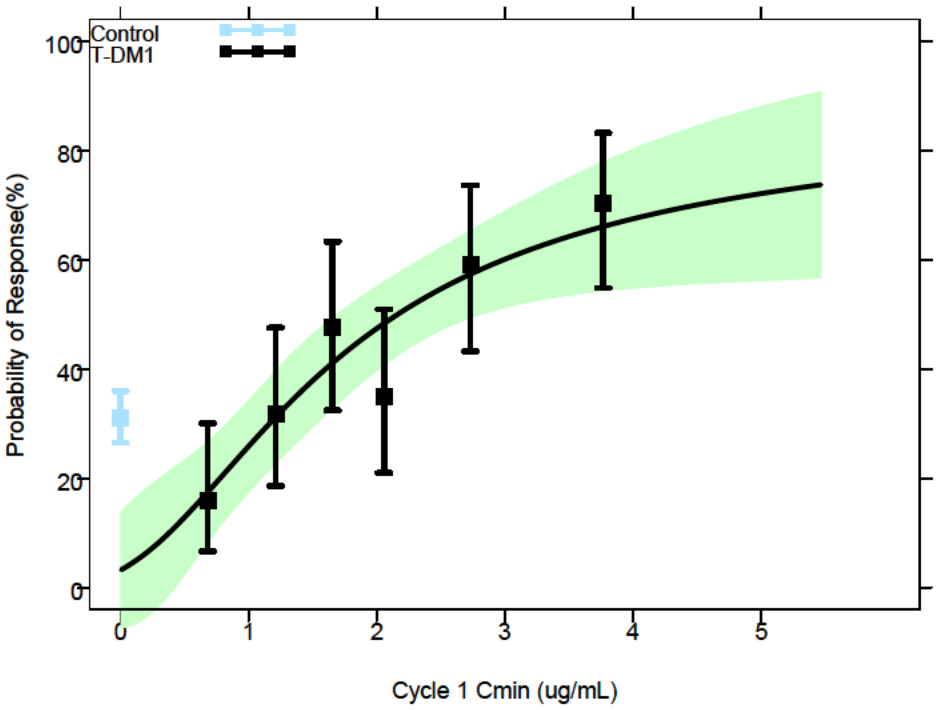

Figure 3. Logistic regression analysis between objective response rates (ORR) and T-DM1 $C_{min,C1D21}$ using an E_{max} model for Trial TDM4370g/BO21977 . Solid black squares represent the proportion of responders grouped by quantiles of T-DM1 $C_{min,C1D21}$ and plotted at the median exposure of each quantile. Solid blue square represents the response treated with active control (lapatinib plus capecitabine). Centered curves and shaded area represent predicted values and 95% of model predicted response probability, respectively.

Exposure-Safety:

No significant exposure-response relationships were identified for individual adverse events (Grade 3 or worse) including thrombocytopenia, hepatotoxicity, and peripheral neuropathy. Logistic regression analysis was conducted to evaluate the relationship between these adverse events and exposures.

In addition, Grade 3 or above AEs and dose adjustments (dose interruption, early discontinuation, and dose reduction) were evaluated in the four C_{min} exposures quartiles. These results are presented below showing slightly higher Grade 3+ AEs patients whose exposure $\leq$ median (Figure 4). In general, dose adjustments appeared to be similar between Q1-4, with the exception of the highest exposure quartile, Q4, having fewer dose interruptions & stops (Figure 5).

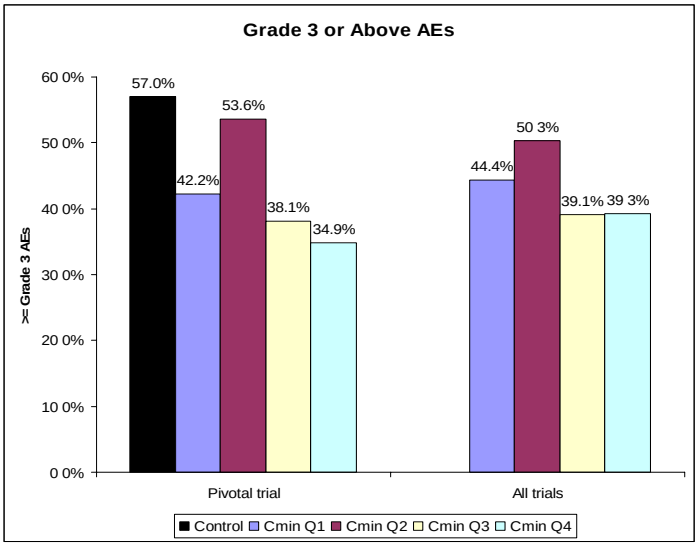

Figure 4. The bar graph represents the incidence of Grade 3+ AEs in the patient safety populations for Trial TDM4370g/BO21977 and for Trials 3569, 4258, 4370, 4374, and 4450 combined.

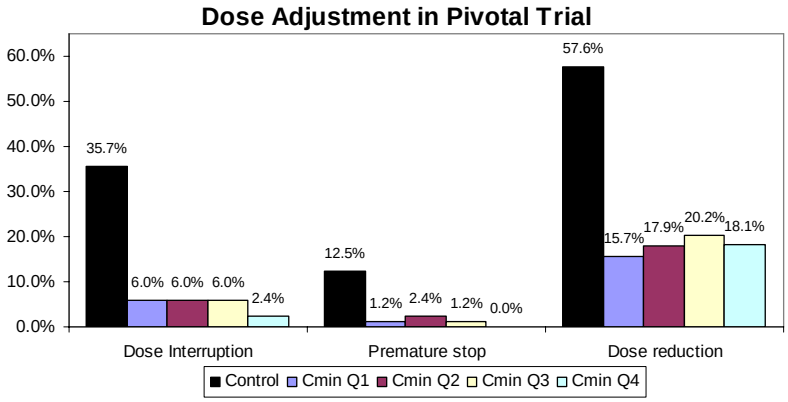

Figure 5. The bar graph represents dose adjustments (dose interruption, early discontinuation, or dose reduction) in Trial TDM4370g/BO21977.

From: Skarupa, Lisa
Sent: Tuesday, November 20, 2012 5:01 PM
To: Erica Evans; Monica Shah
Subject: BLA 125427 Clinical Pharmacology Information Request November 20 2012

Good afternoon,

Please see attached Exposure-Response Analysis Summary which has the following request for a written response. Please provide the response by November 28, 2012 COB.

Based on FDA analysis and findings presented below, please provide a written response on the feasibility of a dose optimization study in patients with lower exposures. This trial could potentially be done post marketing.

Exposure-Response _TDM1_ v3.doc...

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Monday, November 19, 2012 11:41 AM
To: Erica Evans; Monica Shah
Subject: BLA 125427 Clinical Information Request Nov 19th

Dear Erica,

Please see the following Clinical Information requesting response by COB November 20th:
Please submit the AE and lab datasets to support the changes you made to Tables 6 and 7 of the draft label with your 90 day safety update submission.

Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Monday, November 19, 2012 11:54 AM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 Clinical Information Request Nov 19th

Dear Lisa
We acknowledge receipt of the request below. I am checking with the biostats team on a timeline for delivery of the datasets. It takes several days to put datasets into a format for submission to the eCTD BLA.
I will get back to you on when the requested datasets will be submitted.

Kind regards

Erica

On Mon, Nov 19, 2012 at 8:41 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

Dear Erica,

Please see the following Clinical Information requesting response by COB November 20th:

Please submit the AE and lab datasets to support the changes you made to Tables 6 and 7 of the draft label with your 90 day safety update submission.

Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Tuesday, November 06, 2012 7:08 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 November 6 2012 ClinPharm IR

Dear Lisa
November 13th is acceptable as response date for this information request.
Erica

On Tue, Nov 6, 2012 at 2:24 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Dear Erica,

Please acknowledge receipt, and if the timeline for response by 10:00am EST November 13th is acceptable:

Clinical Pharmacology Information Requests
Please provide:

1.An update to Table ataeff in Module 2.7.3 entitled "Efficacy Summary of Subjects with ATA Positive Results Post Baseline Randomized Subjects who received trastuzumab emtansine" to include OS results.
2.Information as to why patients randomized to the control arm in trial TDM4370g/BO21977 had samples analyzed for immunogenicity at various time-points during the trial. Furthermore, within the ABCONC data listing for this trial we identified 2 subjects in the control arm that tested positive for ATA, which were both T-DM1 specific (Subj ID# 17954 and 23301). Please provide your interpretation of this finding.

3.Justification behind your proposed labeling statement: [redacted] (b) (4)

Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, November 07, 2012 6:09 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah; Sandhya Girish; Meghna Samant
Subject: Re: TDM1_ IRT information/ BLA 125427 QT-IR Team November 5, 2012

Dear Lisa
With regard to the request for submission of datasets for the QTc study as detailed below, these will be submitted to the BLA by COB Monday 12 November (SSF time).

Kind regards
Erica

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Monday, November 05, 2012 5:52 PM
To: Skarupa, Lisa
Cc: Monica Shah; Sandhya Girish; Meghna Samant
Subject: Re: TDM1_ IRT information/ BLA 125427 QT-IR Team November 5, 2012

Dear Lisa
We can send the ClinPharm table by Nov 8. We will need more time to prepare the datasets for submission. I will get back to you tomorrow on the proposed adte for submission of the datasets.
Kind regards
Erica

On Mon, Nov 5, 2012 at 1:54 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Dear Erica,

I did not see the summary "ClinPharm table".
So can I ask that you send me the ClinPharm table, the raw triplicate ECG dataset, and let me know if the demographic dataset is in that module?
Can we please have this by November 8th COB?

Let me know if the timeline is acceptable.

Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Thursday, November 08, 2012 1:56 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 Clinical I.R. November 5th/Update target nov 16th

Dear Lisa
Thanks for the response. We will include narratives for other overdoses cases with our response on November 16 as requested. We have a total of 4 cases of overdose for the total clinical development plan with T-DM1. 2 cases from the same clinical site in Chile for TDM4450g/BO21976. In addition we have one case on MARIANNE (TDM4788g/BO22589) and one case on THERESA (TDM4997g/BO25734). These studies are not included with the 7 clinical studies included in the BLA. Can you confirm that we should still submit narratives for overdose cases on MARIANNE and THERESA.

In the meantime, we can propose the end of November (between 26-30 Nov) as the target date for submission of the translated source documents relating to the sudden death case on TDM4450g.

Kind regards
Erica

On Thu, Nov 8, 2012 at 6:15 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Dear Erica,
This plan is acceptable. In addition, please submit narratives on any other patient that received accidental T-DM1 overdose with this submission.

Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, November 07, 2012 5:57 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 Clinical I.R. November 5, 2012

Dear Lisa
We met today to discuss the clinical information request below. In the process of further evaluating this clinical case to fully adddress the FDA's request we have received some clinical documents that were not previously available to us. Therefore the team require some additional time to review this new information and to fully assess its impact on the original narrative written for the patient and its impact on our interpretation of the case, if any. As a consequence we would appreciate an extension to the response time for this request. We propose to submit our response, including our interpretation of the role, if any, of T-DM1 in the patient's death by Friday November 16 2012. Can you please confirm that this is acceptable.

In the meantime we are also gathering all relevant source documents from the site in Chile. As mentioned below these will need to be translated into English for submission to the BLA. We are currently establishing the timeline for completion of that activity - I will get back to you on the proposed date for submission of the source documents.

Kind regards
Erica

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Thursday, November 08, 2012 11:10 AM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 Clinical information Request November 8 2012

Dear Lisa
We acknowledge receipt. I will confirm the response date later today.

Erica

On Thu, Nov 8, 2012 at 7:26 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

Dear Erica,
Please see the following Clinical Information Request. Please acknowledge receipt and if can respond **by COB November 13, 2012:**

Reference is made to the cardiac safety committee for the EMILIA trial. You submitted the CSC minutes, but no final adjudication of symptomatic LVSD was submitted. Did the CSC conduct final adjudication?

Also the following subjects were deemed non evaluable:
15051
11203
16552
19502
21501
22801
17451
20556
21353
21354

What was the committee's final assessment of these patients?

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Tuesday, November 06, 2012 5:24 PM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 November 6 2012 ClinPharm IR

Dear Erica,

Please acknowledge receipt, and if the timeline for response by 10:00am EST November 13th is acceptable:

Clinical Pharmacology Information Requests
Please provide:

1. An update to Table ataeff in Module 2.7.3 entitled "Efficacy Summary of Subjects with ATA Positive Results Post Baseline Randomized Subjects who received trastuzumab emtansine" to include OS results.
2. Information as to why patients randomized to the control arm in trial TDM4370g/BO21977 had samples analyzed for immunogenicity at various time-points during the trial. Furthermore, within the ABCONC data listing for this trial we identified 2 subjects in the control arm that tested positive for ATA, which were both T-DM1 specific (Subj ID# 17954 and 23301). Please provide your interpretation of this finding.
3. Justification behind your proposed labeling statement: (b) (4)

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Monday, November 05, 2012 10:31 AM
To: 'Erica Evans'; Monica Shah
Subject: TDM1_ IRT information/ BLA 125427 QT-IR Team November 5, 2012

Dear Erica,

Can you verify which submission (either to the BLA or to the IND) are the ClinPharm Table and the raw triplicate ECG dataset and demographic dataset?

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Monday, November 05, 2012 10:28 AM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Clinical I.R. November 5, 2012

Dear Erica,

Please see the following Clinical I.R. Please send response by COB November 9, 2012:

Reference is made to patient 9249 on study 4450g who experienced sudden death 19 days after receiving an erroneous T-DM1 dose of 6 mg/kg. Please provide your (sponsor) interpretation of the possibility of T-DM1 contributing to this patient's death. In addition, please provide all source documentation for this patient, including the cardiology and neurology assessments, relevant laboratory and diagnostic data, etc.

Please confirm receipt and if you agree to timeline.

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Monday, November 05, 2012 10:28 AM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Clinical I.R. November 5, 2012

Dear Erica,

Please see the following Clinical I.R. Please send response by COB November 9, 2012:

Reference is made to patient 9249 on study 4450g who experienced sudden death 19 days after receiving an erroneous T-DM1 dose of 6 mg/kg. Please provide your (sponsor) interpretation of the possibility of T-DM1 contributing to this patient's death. In addition, please provide all source documentation for this patient, including the cardiology and neurology assessments, relevant laboratory and diagnostic data, etc.

Please confirm receipt and if you agree to timeline.

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Thursday, November 01, 2012 12:43 PM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 November 1 Clinical Information Request

Dear Erica,

Please see the following Clinical IR. Please confirm that the timeline is acceptable. Reference is made to your draft labeling, Warnings and Precautions, section 5.3, Left Ventricular Dysfunction. (b) (4) FDA review of the preferred term LV Dysfunction yielded an incidence of 1% on T-DM1 and 1.2% on L+C. Please explain this discrepancy no later than COB November 6, 2012.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/04/2013

Welch, Joel

From: Welch, Joel
Sent: Friday, November 30, 2012 10:27 AM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR #17 for BLA125427/0

Importance: High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by December 7 , 2012 .

Reviewer Comments to Information Request Response for Trastuzumab emtansine STN 125427/0 sequence 0052 - Microbial Quality

1. P.5.2. Microbial Attributes - Container closure integrity test
   Indicate the number of samples that you will use to confirm the integrity of the container closure at (b) (4) using the Genentech method. Your response indicates that your comparison between microbial and dye ingress was performed (b) (4). However, your container closure validation report GC-QCM-05-89 describes different conditions for the microbial ingress test (b) (4) and for the dye ingress test (b) (4) Justify this discrepancy. If the comparison was performed (b) (4), perform a study correlating the dye ingress to the microbial ingress test using the same challenge conditions and determine the sensitivity of the method as a function of breach size.
2. P.3.5.4.2. Validation (b) (4)
   Provide validation report showing the adequacy of your (b) (4) integrity testing. Include T-DM1-specific data (b) (4).
3. P.3.5.11 Shipping Validation
   Clarify if both trastuzumab emtansine configurations (100 mg and 160 mg) have been qualified for bulk shipping. Indicate which ASTM D4169 distribution cycle was used and provide justification. In addition, include a brief description of the specific mechanical tests used. Submit a detailed plan describing the mechanical impact studies that you intend to perform to demonstrate container closure integrity (CCI) during shipment. In addition, include number of vials that will be tested for CCI, CCI challenge conditions, and number of positive and negative controls. Mechanical impact studies should include worst-case conditions for bulk vials and finished goods.
4. P.5.3. Validation of Analytical Procedures
   Submit endotoxin results for the six samples of DP batch 760576 indicating approximate (b) (4) for each sample. Table P.5.4-8 indicates that an out of specification result (b) (4) was obtained from DP batch 760576. The endotoxin acceptance criterion for drug product was at the time (b) (4) However, this result is in disagreement with your statement that (b) (4) was obtained from DP batch 760576 (Amendment 0052 page 13). Please, justify the discrepancy. Your endotoxin masking study (b) (4) should include endotoxin spiked DP samples (b) (4) If endotoxin recovery is adequate in those samples (b) (4) production (b) (4) used in the study.
5. Drug Substance
   Results in your interim report on root cause analysis for endotoxin masking in T-DM1 stored in (b) (4) containers suggest (b) (4). Please

conduct endotoxin spiking and recovery studies [redacted] (b) (4)

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
11/30/2012

Welch, Joel

From: Welch, Joel
Sent: Thursday, November 29, 2012 2:55 PM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR#16 for BLA 125427/0
Importance: High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by December 7 , 2012 .

1. In your response dated 02 November 2012 regarding developing an assay for unconjugated antibody content, you requested that "you be allowed up to 12 months post-approval to develop, validate, and transfer the method …… During the interval until this work is complete, the Sponsor commits to test all batches in an R&D lab using the characterization method that is currently available and to include these results in the Annual Report." Clarify which characterization method will be used to test unconjugated antibody content. The Agency recommends that you test using both MS and iCIEF methods. In addition, due to semi-quantitative nature of the iCIEF method and stated challenges associated with validation of iCIEF method for QC analysis, the Agency recommends that you use a validated LC-MS method to measure unconjugated antibody content and for QC analysis.

2. Your revised drug substance and drug product acceptance criteria for (b) (4) content is neither supported by clinical batch analysis data nor by stability data. As you are aware, (b) (4) the limited toxicology study alone cannot justify your proposed drug substance and drug product shelf life acceptance criteria (b) (4) . Please (b) (4) the shelf life acceptance criteria for (b) (4) contents (b) (4) . In addition, the Agency has the following comments:

   a. In your response to FDA Question #3 dated October 25, 2012, you showed (b) (4) content in a Phase I drug product lot (b) (4) It is noted that the early development lot (b) (4) and the proposed drug product is a lyophilized formulation that is more stable. In addition, stability data for the Phase III clinical lots and registration lots showed (b) (4)

   b. Your proposed (b) (4) limit for the drug product acceptance criterion (b) (4) is not supported by the batch release and stability data.

   c. The temperature cycling study showed (b) (4)

3. Regarding statistical modeling for Trastuzumab Emtansine distribution submitted in the amendment dated Oct 17, 2012, the Agency has the following comment: The review of the data submitted showed that the (b) (4) modeling assumption is not appropriate and the correlation between DAR and free drug content appears weak. Submit all numeric data for drug distribution by MS, and DAR by UV for the small scale characterization study runs (Figure S.3.1-5). In addition, provide all available data for the clinical lots that you have measured for both DAR and drug distribution.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
11/30/2012

Welch, Joel

From: Ahmed Bassyouni [bassyouni.ahmed@gene.com]
Sent: Wednesday, November 21, 2012 2:39 PM
To: Welch, Joel
Cc: Ahmed Bassyouni; Skarupa, Lisa; shah.monica@gene.com; evans.erica@gene.com; francissen.kathy@gene.com
Subject: Re: CMC IR#15 for BLA 125427/0

Dear Joel,

We acknowledge receipt.

Ahmed

On Wed, Nov 21, 2012 at 11:34 AM, Welch, Joel <Joel.Welch@fda.hhs.gov> wrote:

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by November 28, 2012 .

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JOEL T WELCH
11/26/2012

Welch, Joel

From: Welch, Joel
Sent: Wednesday, November 21, 2012 11:50 AM
To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR#14 for BLA 125427/0

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by November 30 , 2012.

DMA IR # 4

1. We acknowledge your response to Question 1 of the information request issued on November 2, 2012. We note that Table 1 included in your response provided a comparison of the operating range and the multivariate acceptable range (MAR) (b) (4) Provide a table presenting a comparison of the multivariate acceptable range and the **restricted** operating range obtained from the restricted operating range study (as shown in Table S.2.6-11) (b) (4)

2. We acknowledge your response to Question 6 of the information request issued on November 2, 2012. We note that you commit to performing freeze/thaw validation studies and to filing them to the BLA prior to the use of Roche Penzberg-supplied trastuzumab bulk drug substance (BDS) in the manufacturing of trastuzumab emtansine. Remove Roche Penzberg as one of the manufacturers for trastuzumab BDS until such information is available and deemed adequate by the Agency. In addition, comment on your ability to meet the anticipated market demand for trastuzumab emtansine without utilizing Penzberg-supplied trastuzumab BDS.

3. Regarding process characterization and validation studies for the freeze/thaw process of trastuzumab emtansine BDS:
   a. Provide data to support the MARs identified in Tables P.2.3-8 and P.2.3-10.
   b. We note that data were provided (b) (4)

4. Regarding the lyophilization process characterization study at full scale:
   a. We note that Tables P.2.3-19 and P.2.3-21 provided the mean value of product quality attributes obtained from vials distributed at different locations within the lyophilizer. Provide the min-max range of each test to ensure that the operating parameters assessed in this study resulted in consistent product quality throughout the lyophilizer.
   b. Provide stability data on the drug product obtained from lyophilization runs performed at lower and upper limits (b) (4)

5. Regarding the trastuzumab emtansine drug product compatibility study:
   a. We note the following statement in the EMILIA (4370) protocol: [redacted] Please clarify this discrepancy. [redacted] Please submit the study.
   b. We note that visible particulates were observed after trastuzumab emtansine drug product is diluted in 0.9% sodium chloride (Table P.2.6-5) and, therefore, you state that an in-line filter is required when using 0.9% sodium chloride as diluent for the IV solution. The in-line filter compatibility study submitted in the BLA included testing [redacted] (Table P.2.6-7). Provide any additional data, such as impact on potency, DAR, SE-HPLC, and levels [redacted], to support the use of an in-line filter with 0.9% sodium chloride as IV solution. [redacted]

6. We note that you have provided data to support stability through [redacted] cycles of freeze/thaw of trastuzumab emtansine drug substance at scale, and that a study evaluating the [redacted] cycle of freeze/thaw of trastuzumab emtansine drug substance has been planned. Until the final data are available, revise the MAR for freeze/thaw cycles of trastuzumab emtansine BDS [redacted].

7. We note that 33 drug product vials have been tested in the fill volume/weight consistency validation study. Clarify how these vials were selected and whether these 33 vials cover the entire fill duration, including the beginning, middle, and end of the fill process.

8. Regarding drug product release and shelf-life specifications:
   a. Retain the tests on reconstitution time [redacted] for DP lot release and stability studies.
   b. We note that the manufacturing range of the [redacted] value for phase III batches [redacted] was defined [redacted] The acceptance criterion is set [redacted] the release specification [redacted] to be consistent with your manufacturing experience.

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/s/

JOEL T WELCH
11/21/2012

Welch, Joel

From: Welch, Joel
Sent: Monday, November 19, 2012 6:50 AM
To: 'Ahmed Bassyouni'
Cc: Kathy Champion; Erica Evans; Monica Shah; Skarupa, Lisa
Subject: RE: CMC IR#12 for BLA 125427/0

Ahmed,

Please see comments regarding IR#11 as requested.

IR #11 - Question 3 is fine . Alert limits should be provided in the response.
IR #11 - Question 1. The sponsor states the following:

(b) (4) T o test will be more conducive to bacterial growth (b) (4)

We do not agree. (b) (4)

As we have already indicated, the sponsor should use the label's recommended solutions, i.e. the reconstituted vial (we agree with the use of only the 160 mg), the reconstituted vial diluted in 0.9% saline, (b) (4)
We agree with the use of a low and high dose concentration (b) (4)

From: Ahmed Bassyouni [mailto:bassyouni.ahmed@gene.com]
Sent: Tuesday, November 13, 2012 10:51 PM
To: Welch, Joel
Cc: Ahmed Bassyouni; Kathy Champion; Erica Evans; Monica Shah; Skarupa, Lisa
Subject: Re: CMC IR#12 for BLA 125427/0
Importance: High

Dear Joel,

We would like to confirm that we will provide the responses to IR#12 on November 14 as per the Agency's request.

At this point in the Agency's review we also feel that it is very important to have mutual understanding and alignment on any remaining open items and have the opportunity to engage in dialogue with the Agency in order to help to address outstanding issues and concerns. We recognize that there are some recent compliance concers from 1) the recent PAI observations (b) (4) and 2) questions raised in IR#7 regarding control (b) (4) in the Intermediate, DM-1, manufactured (b) (4). We want the Agency to know we take these issues seriously and are committed to closing these GMP gaps. We believe that these items are being effectively addressed, and will continue to take additional steps and collect additional information to support effectiveness. However, if there are outstanding concerns within the Agency due to compliance or other topics from

the BLA review, we would respectfully appreciate the opportunity to discuss these issues in the near future, so that appropriate options can be evaluated and we can align to ensure these issues are satisfactorily addressed. One consideration is to use the already requested telecon for discussing specifications for the (b) (4) starting materials to also discuss these other open points. Alternatively, we could have a separate telecon at the Agency's convenience. We completely recognize and fully appreciate that outstanding Quality topics are extremey difficult to manage during the BLA review cycle and want to ensure we are being as engaged and cooperative as possible.

Finally, the team would like to seek further clarity from FDA to assist in developing responses to IR#11, Questions 1 and 3 so that our final response, required on November 22, is acceptable. We would very much appreciate feedback on the suitability of the draft study design proposed to address Question 1 as outlined in the first attachment. In addition, we would like to ensure that the table in the second attachment would appropriately address the Agency's request for Question 3.

We highly value your consideration on these issues,

Ahmed

On Nov 13, 2012, at 5:13 AM, Welch, Joel wrote:

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by November 14 , 2012.

FDA response:

Before a meeting can be granted, additional information is needed to evaluate your proposal in the pre-meeting package submitted on 02-Nov-2012. Please provide responses to the following information requests as soon as possible, but no later than Wed 14-Nov-2012.

(b) (4)


(b) (4)

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/s/

JOEL T WELCH
11/20/2012

Welch, Joel

From:	Welch, Joel
Sent:	Tuesday, November 13, 2012 8:13 AM
To:	Welch, Joel; 'Ahmed Bassyouni'
Cc:	Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject:	CMC IR#12 for BLA 125427/0
Importance:	High

Ahmed,

Please find below an additional CMC information request. Please confirm receipt. We request a response by November 14 , 2012.

FDA response:

Before a meeting can be granted, additional information is needed to evaluate your proposal in the pre-meeting package submitted on 02-Nov-2012. Please provide responses to the following information requests as soon as possible, but no later than Wed 14-Nov-2012.


(b) (4)

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/s/

JOEL T WELCH
11/13/2012

Welch, Joel

To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR#11 for BLA 125427/0

Importance: High

Please find below an additional CMC information request. **Please confirm receipt. We request a response by November 22, 2012.**

Reviewer Comments to Information Request for Trastuzumab emtansine STN 125427/0 - Drug product, Microbial Quality

1. Comment to Amendment 0038, Response to IR 8
   Your labeling indicates that the product may be stored (b) (4) after reconstitution and (b) (4) after dilution. Please submit the data in support of your label claim using an inoculum of 10-100 CFU within the BLA review timeline. Without supporting data, the product labeling should recommend storage of no more than 4 hours at 2° to 8°C after reconstitution and no more than 4 hours at 2° to 8°C after dilution.

2. Comment to Amendment 0019, Response to IR 1.b and c
   Validation of the container closure integrity test method is inadequate (b) (4) . In addition, the correlation between the microbial and dye ingress tests was performed (b) (4) Submit data to validate container closure integrity using the container closure system intended for trastuzumab emtansine and compare the sensitivity of both the dye ingress to the microbial ingress method under the similar challenge conditions.

3. Comment to Amendment 0019, Response to IR 4
   (b) (4) has manufactured (b) (4) batches of trastuzumab emtansine. Therefore, enough historic trend data should be available to establish thawed BDS alert limits. Please establish alert limits for thawed BDS. In addition, our request for eliminating (b) (4) applies (b) (4)

4. Comment to Amendment 0019, Response to IR 11.a
   Indicate the volume of (b) (4) integrity testing and provide data demonstrating that the product (b) (4). Alternatively, determine the product-specific (b) (4).

5. Comment to Amendment 0019, Response to IR 17
   Provide mechanical impact studies as part of your shipping validation and demonstrate container closure integrity under worst-case conditions.

6. Comment to Amendment 0019, Response to IR 19.c
   Your risk assessment does not ensure that endotoxin results from drug product batches are not impacted by glass endotoxin masking. Submit the root cause investigation of endotoxin masking interim report. In addition, your (b) (4) bulk may be stored (b) (4) Submit recovery data from endotoxin-spiked samples (b) (4) Submit data showing endotoxin recovery from samples (b) (4) using your production conditions. In the event that low endotoxin recoveries are demonstrated (b) (4) endotoxin testing may be performed (b) (4) If the sterile hold impacts endotoxin recovery, a different method

must be developed and used for endotoxin release test of drug product.

7. Clarify if your bulk sterility testing occurs (b) (4) (P.3.3.2.4) (b) (4) (P.5.2.Sterility.1.2).

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
11/08/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125427

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Erica J. Evans, Ph.D.
Regulatory Program Management

Dear Dr. Evans:

Please refer to your Biologics License Application (BLA), dated and received August 24, 2012, submitted under section 351 of the Public Health Service Act for Trastuzumab Emtansine, 100 mg/vial and 160 mg/vial.

We also refer to your correspondence, dated and received August 27, 2012, requesting review of your proposed proprietary name, Kadcyla. We have completed our review of the proposed proprietary name, Kadcyla and have concluded that it is acceptable.

The proposed proprietary name, Kadcyla, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 27, 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, Lisa Skarupa at (301) 796-2219.

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
11/06/2012

Welch, Joel

To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: CMC IR#10 for BLA 125427/0

Importance: High

Please find below an additional CMC information request (DMA IR#3). **Please confirm receipt. We request a response by November 13, 2012.**

We acknowledge your response to Question 5 of the Information Request issued on October 23, 2012. We note that Table 3 provided a comparison of in-process controls for DM-1 between conformance batches 107, 108, and 109 and all commercial manufacturing lots. Please provide a table presenting the in-process controls implemented from the start of manufacturing through final formulation of BDS. The table should compare the in-process controls performed as part of the validation protocol for drug substance conformance lots 107, 108, and 109 manufactured using (b) (4) DM1 *vs.* those implemented during manufacture of all drug substance lots derived specifically from (b) (4) DM1.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
11/06/2012

Welch, Joel

To: Welch, Joel; 'Ahmed Bassyouni'
Cc: Skarupa, Lisa; 'shah.monica@gene.com'; 'evans.erica@gene.com'; 'francissen.kathy@gene.com'
Subject: RE: CMC IR#9 for BLA 125427/0

Please find below an additional CMC information request. **Please confirm receipt. We request a response by November 12, 2012.**

1. Provide a table comparing the restricted operational range and multivariate acceptable range (b) (4)

2. Regarding release specifications and stability for both DS and DP:
   a. HER2 binding ELISA assay:
      We note your response to the information request sent on October 2, 2012 regarding your intent to remove the HER2 binding ELISA as one of two potency assays. Please retain the HER2 binding ELISA as a second potency assay for lot release and stability studies for both DS and DP.
   b. Osmolality:
      i. Provide information on osmolality of T-DM1 following dilution in the infusion solution.
      ii. We note that the manufacturing range of the osmolality value (b) (4) The acceptance criterion is set (b) (4) the release specification for osmolality to be consistent with your manufacturing experience.

3. It is stated that the levels (b) (4) observed by SE-HPLC (*section S.4.5 Justification of Specification, page 14*). Provide data to support this conclusion. We note that (b) (4) is not included in the stability protocol for DS and DP. We also note your statement (b) (4) (*section P.2.2.1 Formulation Development, page 6*). Provide an explanation (b) (4)

4. We note that the reference standard batch TMCCDM11208-2 is placed (b) (4) for long-term storage. However, the stability data provided in the submission support long-term storage (b) (4) (Table S.5-4). Justify the discrepancy.

5. The shelf-life acceptance criteria for potency by bioassay and potency by ELISA listed in Tables S.7.1-3 and S.7.1-4 (b) (4) differ from those presented in Table S.4.1-1 (b) (4) Explain this discrepancy.

6. We note that Genentech Vacaville, Roche Singapore, and Roche Penzberg are listed as manufacturing sites for trastuzumab intermediate. Provide a validation study to support your ability to adequately freeze and thaw trastuzumab BDS produced from Roche Singapore and Roche Penzberg during the manufacture of T-DM1.

7. Regarding the validation report of an ELISA method for the detection of anti-trastuzumab emtansine antibodies in human serum (validation report: BA.MET.HERc.008.AVR_1):
   a. Provide information on the determination and validation of the ULOQ (Upper Limit of

Quantification) for the detection of anti-T-DM1 antibodies in human serum. The information should include %CV and SD.

b. Regarding the immunodepletion assay:
   i. Provide a justification for targeting a (b) (4) untreated positive rate in the immunodepletion cutpoint assessment study.
   ii. We note that sample #45 is excluded from the assay cutpoint determination study as an outlier. This sample is not excluded in the cutpoint study for immunodepletion, although the decreased signal after pre-incubating this sample with 50µg/mL T-DM1 and trastuzumab is determined to be 75% and 67%, respectively. Provide a justification for not excluding this sample as an outlier in the study to determine the immunodepletion cutpoint. Provide a summary of statistical analyses which comparing the immunodepletion cutpoint before and after the removal of sample #45.
   iii. We recommend (b) (4)
c. Provide validation data for the recovery study performed across concentrations of anti-T-DM1 antibodies. Include LLOQ, ULOQ, and % CV for every concentration tested.
d. Provide validation data (b) (4)
e. Provide information on the concentration of anti-T-DM1 antibodies used in the HER2 ECD cross reactivity study and whether the concentration used in the study is clinically relevant.
f. Regarding the validation data for T-DM1 drug interference:
   i. Provide information on patient T-DM1 serum concentrations at the time of sampling.
   ii. We note that, at serum concentration as low as 10 µg/mL, T-DM1 will interfere with the assay unless high levels of ATA (anti-therapeutic antibody) are present in patient serum. Therefore, there is no assurance that this assay is sensitive enough to be able to detect anti-T-DM1 antibodies. Please comment.
   iii. Provide information on the positive ATA response rate for patients in the control arm group.
g. Provide a validated neutralizing assay.

Joel Welch, Ph.D.
Regulatory Health Project Manager
FDA/CDER/OPS/OBP
WO-Building 21, Room 1521
(301) 796-2017
joel.welch@fda.hhs.gov

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/s/

JOEL T WELCH
11/02/2012

Oct 2012 Information Requests

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, October 31, 2012 1:15 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: Clinical I.R. BLA 125427 October 31

Dear Lisa
We acknowledge receipt of this request and submission by Nov 2 is acceptable.
Kind regards
Erica

On Wed, Oct 31, 2012 at 7:23 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Dear Erica,

Reference is made to EMILIA CSR. In table 50, (b) (4) TDM1 pts experienced AE leading to dose reduction. In table 42, 16.3% of TDM1 pts had dose reduction. Please explain this discrepancy no later than COB November 2, 2012.

Please confirm if the timeline is acceptable.

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Friday, October 19, 2012 2:23 PM
To: 'Erica Evans'; Monica Shah
Subject: Stats Information Request: BLA 125427 October 19, 2012

Dear Erica,

Please see the following Statistician Team's Information Request, please respond by October 24th:

Please demonstrate the derivation of datasets RESPIRF2 and IRFONC and provide related SAS program.

Please acknowledge and if the timeline is acceptable.

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Friday, October 19, 2012 1:30 PM
To: 'Erica Evans'; Monica Shah
Subject: Clinical Information Request BLA 125427 October 19, 2012

Good afternoon Erica,

Please see the following Clinical Information Request, please respond by Tuesday October 23, 2012.

It appears that you have 40 patients with liver disease and 75 patients with lung disease that are categorized as non-visceral.

Please define how you grouped patients into visceral and non-visceral?

Please acknowledge this Clinical IR and if the target date is acceptable.

Sincerely,

Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Thursday, October 18, 2012 3:22 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: Clinical Information Request BLA 125427 Oct 18th

Thank you Lisa

We will provide our response by next week as requested.
Erica

On Thu, Oct 18, 2012 at 12:07 PM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:

Good afternoon,
Please provide the following Clinical Information Request by COB EST October 23, 2012:

Reference is made to Section 4.5.1 'Baseline Demographic Data' of the EMILIA CSR. You state that 3.4% and 1.4% of T-DM1 pts and 5% and 2.7% of L/C patients had segmental wall abnormalities by local and central assessments, respectively. Please provide subject ID and all LVEF data for these subjects. In addition, please report any grade 3-5 cardiac events in this cohort.

Sincerely,
Lisa

DMEPA

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Tuesday, September 25, 2012 8:14 PM
To: Fahnbulleh, Frances
Cc: Skarupa, Lisa; Monica Shah
Subject: Fwd: Please review: Trastuzumab emtansine BLA 125427

Dear Frances
Please find below a list of items that will form the basis of the discussion at the t-con planned for this Friday Sept 28:

1) The USAN/INN approved established name is for T-DM1 is trastuzumab emtansine. In the first sentence of the "Comments to the Applicant" received Sept 7 2012, the Agency makes reference to Kadcyla (**Herceptin Trastuzumab**). Can the Agency confirm that the reference to Herceptin Trastuzumab in this context was a typographical error?
2) The USAN/INN approved established name trastuzumab emtansine was included in a previous request for review of a proprietary name (KADCLYA) as submitted to IND 71072 as S0604 (Oct 31 2011). Following review of this submission, we gained conditional acceptance of the name KADCYLA on April 27 2012. We would appreciate if the Agency could help us understand why the recommendation that for the conduct a Human Factors Study was not made following this initial review of the proprietary name request?
3) Can the Agency advise us on the required timing for submission and review of the information requested in the Comments to the Applicant sent Sept 7 2012 (i.e., Human Factors validation study protocol as well as results of formative study) as it relates to review and potential approval of KADCYLA under BLA125427? Specifically,
a) Will the Agency require the results of a Human Factor study to be submitted and reviewed by the FDA as part of the initial BLA review and approval process?
b) Further to 3a above, can the Agency advise us on how the information gained from a Human Factor study could impact the labeling of Kadcyla?
c) In addition, can the Agency comment on the potential for FDA to request a change in the established name for trastuzumab emtansine akin to that recently requested for Zaltrap as reviewed under BLA 125418?
4) The similarity between the established names for Kadcyla and Herceptin has been recognized by the Sponsor and plans to mitigate the risk of medication errors between the two products have been ongoing in preparation for the potential launch of Kadcyla. Genentech plans to outline the risk mitigation steps we have planned or implemented to date in our response to the Sept 7 2012 Information Request. In the meantime, any guidance the FDA can share with us on the conduct of Human Factors studies for a therapeutic agent (versus a medical device) would be much appreciated.

Kind regards
Erica

From: Skarupa, Lisa
Sent: Tuesday, October 09, 2012 4:01 PM
To: 'Erica Evans'
Cc: Monica Shah
Subject: FDAResponseOct9th: BLA 125427 October 3 2012 Clinical Safety Update/date of submission

Dear Erica
To clarify, the global safety update referred to your proposal of updated safety data from EMILIA, 4450g and 4529g. The updated narratives for study TDM4529g are not necessary unless requested by FDA. The updated CRFs for EMILIA are also not necessary unless requested by FDA. The most critical safety data for this BLA review is the updated data from EMILIA.

Would an interim submission of strictly the updated EMILIA data be possible by October 25? This submission should contain updated exposure data, deaths (<30 days and > 30 days), AEs (gr 1-5), AEs (gr 3-5), discontinuations, SAEs, AEs of special interest (hepatotoxicity, cardiotoxicity, pneumonitis, neurotoxicity). This updated data would be critical in finalizing the BLA review.

Please provide us your response on the timeline by COB Eastern Standard Time Wednesday October 10th.

Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Friday, October 05, 2012 12:51 AM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 October 3 2012 Clinical Safety Update/date of submission

Dear Lisa
We are meeting tomorrow morning to discuss this clinical information request. Do you have any feedback regarding our request for clarity below?

*In the meantime can the reviewers please provide clarity around the request "**and in a separate document safety updates on the global database**." We will need to be clear on the expectations of this request before we can evaluate timing for delivery to the BLA.*

We can work towards potentially providing a revised timeline for the 90D safety update. However, we cannot incorporate timelines for the above request without fully understanding the reviewers expectations of this request.

Kind regards
Erica

On Wed, Oct 3, 2012 at 11:06 AM, Erica Evans <ericae@gene.com> wrote:
Dear Lisa
The request below is for delivery the 90D safety report a full month before it was originally scheduled and agreed by FDA for submission (target date Nov 21) - so this is in fact a 60 day safety report. The potential for this request of a 60 day report was not raised by the Agency as part of the preBLA meeting held 30 May 2012. At this meeting Genentech made it very clear we were planning to submit a 90D safety report and all of internal planning has been driving towards that. At this time we cannot agree to the Oct 25 deadline, especially in light of the other requests for clinical/safety information the team is currently working towards addressing which have BLA submission dates in October.

We will need to meet with the full clinical and drug safety team to discuss this request. Unfortunately I would anticipate the maximum we can do is bring the delivery date of the safety update forward by 1 to 2 weeks. We will get back to you by the end of the week on a revised November delivery date for the safety update.

In the meantime can the reviewers please provide clarity around the request "**and in a separate document safety updates on the global database**." We will need to be clear on the expectations of this request before we can evaluate timing for delivery to the BLA.

Kind regards
Erica

On Wed, Oct 3, 2012 at 9:33 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Good afternoon Erica,

Regarding the future submission of the 90-day safety update, clinical would like to request:

Given expedited review timelines, we will need the safety update by October 25, 2012. In one submission, please include updates on the EMILIA trial and in a separate document safety updates on the global database.

Please confirm receipt and if the timeline is acceptable.

Sincerely
Lisa

From: Skarupa, Lisa
Sent: Friday, October 05, 2012 5:49 PM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Clinical Information Request Oct 5 2012

Dear Erica,
Please see the following Clinical Information Request:

Reference is made to EMILIA CSR Table 43 'Adverse Events Occurring in > 10% of patients in either treatment group (safety population)'

FDA analysis of the AE dataset revealed the following discrepancies with your table:

Nausea L/C Arm: Genentech 218 (44.7%); FDA 220 (45.1%)
Dry Mouth TDM1 Arm: Genentech 77 (15.7%); FDA 78 (15.9%)
Abdominal Pain Upper L/C Arm: Genentech 41 (8.4%); FDA 42 (8.6%)
Fatigue L/C Arm: Genentech 136 (27.9%); FDA 137 (28.1%)
Asthenia TDM1 Arm: Genentech 86 (17.6%); FDA 87 (17.7%)
Pyrexia TDM1 Arm: Genentech 85 (17.3%); FDA 86 (17.6%)
Decreased Appetite TDM1 Arm: Genentech 101 (20.6%); FDA 102 (20.8%)
Dizziness TDM1 Arm: Genentech 48 (9.8%); FDA 49 (10%)
Insomnia TDM1 Arm: Genentech 54 (11.0%); FDA 55 (11.2%)
Epistaxis L/C Arm: Genentech 39 (8.0%); FDA 40 (8.2%)
Dyspnoea L/C Arm: Genentech 36 (7.4%); FDA 37 (7.6%)
Dyspnoea TDM1 Arm: Genentech 56 (11.4%); FDA 57 (11.6%)
Rash L/C Arm: Genentech 130 (26.6%); FDA 131 (26.8%)
Dry Skin L/C Arm: Genentech 49 (10.0%); FDA 50 (10.3%)

In each case, the FDA computation revealed one extra patient (with the exception of L/C nausea, which revealed 2 extra patients). Please repeat your analysis and explain differences between FDA and your numbers.

We would like responses no later than COB-Eastern standard time zone-
October 12, 2012.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/04/2013

Sept 2012 Information Requests

From: Skarupa, Lisa
Sent: Wednesday, October 03, 2012 11:22 AM
To: Erica Evans; Monica Shah
Subject: Response to submission 0014/ BLA 125427 Information Request: Sept 24, 2012 Clinical requesting Tables

Dear Erica,
Regarding submission Serial No. 0014, EMILIA Trial (TDM4370g/BO21977), we have the following clarification questions:

· Provide the rationale for OS censoring of subjects who withdrew from study. Were these patients lost to follow-up?

· Define "early study termination "as one of the PFS censoring reasons.

· What were the reasons that 27 patients in Lap+Cap arm and 14 patients in T-DM1 arm had no post-baseline scans?

Sincerely,

Lisa

From: Monica Shah [mailto:shah.monica@gene.com]
Sent: Friday, September 28, 2012 4:02 PM
To: Skarupa, Lisa
Cc: Monica Shah; Erica Evans
Subject: Re: BLA 125427 Information Request: Sept 24, 2012 Clinical requesting Tables

Dear Lisa,

Please find attached our response to the FDA Request for Information below. In addition, we have formally submitted this response to BL 125427 today September 28th, as Sequence No. 0014.

Please kindly confirm receipt of this email.

Kind Regards,
Monica

From: Skarupa, Lisa
Sent: Friday, September 28, 2012 2:15 PM
To: 'Erica Evans'; 'Monica Shah'
Subject: Second I.R.: BLA 125427 Clinical Information Request Sept 28 2012

Dear Erica,

Second Clinical Information Request:

Reference is made to the patients with grade 3-5 nervous system disorder/ peripheral neuropathy on T-DM1. Please provide narratives for these patients, as well as data on duration of neuropathy, and any de-challenge and re-challenge data for these patients. We would like responses no later than cob October 8, 2012 (EST).

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Friday, September 28, 2012 11:52 AM
To: Erica Evans; 'Monica Shah'
Subject: BLA 125427 Clinical Information Request Sept 28 2012

Dear Erica,

High Priority:
Your proposal to submit the hepatotoxicity data by October 31, 2012 will not allow sufficient time to adequately review this data. Please propose an interim report by mid October.
October 31 is acceptable for a final report. Please include an edish analysis, as you did in the original hepatotoxicity report.

Sincerely,
Lisa

From: Skarupa, Lisa
Sent: Monday, September 24, 2012 6:50 PM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Information Request: Sept 24, 2012 Clinical requesting Tables

Dear Erica,
Please see SECOND Sept 24th Clinical Information Request: Please provide this data no later than COB Friday September 28.

Please provide the following information in regards to the Trastuzumab emtansine BLA 125427:
1) Provide a table with details of post progression therapies.
2) Provide a table with details of censoring.

Please confirm receipt of Information request.
Sincerely,
Lisa

Microbiology Quality Team
IR#1 through IR #20

From: Skarupa, Lisa
Sent: Monday, September 24, 2012 6:30 PM
To: 'Erica Evans'; Monica Shah
Subject: BLA 125427 Information Request Sept 24, 2012 Microbial Quality

Dear Erica,

Please see the following Information Requests (20 main items) from Microbial Quality Team. Please confirm once received and if Genentech will provide **response by October 9th.**
Sincerely,
Lisa

IR 1: Container Closure Integrity Test:

1. Clarify if the samples used in the container closure integrity tests (microbial and dye ingress) have been validated outside the normal operating range for crimping speed and crimping forces. Crimping speed and crimping forces should reflect worse case operating conditions.
2. Provide number and type of positive and negative controls for the microbial and dye ingress tests (how controls were prepared), and sensitivity of both methods correlated to breach size.
3. Provide the bacterial challenge concentration at the end of the microbial ingress test.
4. The number of samples to validate the dye ingress test (30 vials) appears to be insufficient. Please justify your sample size.

IR 2: Facility Overview

Indicate which other products are manufactured (b) (4)

IR 3: Description of Manufacturing Process and Process Controls

[redacted] (b) (4)

IR 4: Control of Critical Steps and Intermediates

An investigation should be conducted any time an action limit is exceeded and may result in batch rejection. Please eliminate the [redacted] (b) (4) You should use a two tier system with action limits based on risk assessment and process understanding and alert limits based on historical trend data.

IR 5: Registration Batches

Submit in-process pool bioburden and endotoxin results from your registration batches.

IR 6: [redacted] (b) (4) **Process Equipment**

[redacted] (b) (4)

IR 7: [redacted] (b) (4) **Vials**

1. Describe the routine [redacted] (b) (4) procedure and describe the routine production and validation conditions. Submit summary report demonstrating efficacy of the

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

2. Include a lot of each DP configuration (100 mg and 160 mg) in your annual stability program if both are manufactured in a given year.

From: Skarupa, Lisa
Sent: Monday, September 24, 2012 3:31 PM
To: 'Erica Evans'
Cc: Monica Shah
Subject: RE: BLA 125427 Ongoing Information Requests: new Clinical and Hepatotoxicity 105828

Dear Erica,
The Clinical Team's response is:
It would be helpful to report any additional cases that transpired beyond the December 2011 clinical and March 2012 global data cut-off, since several months have passed.

Let me know if this is helping address your clarification.

Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Monday, September 24, 2012 1:39 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah
Subject: Re: BLA 125427 Ongoing Information Requests: new Clinical and Hepatotoxicity 105828

Dear Lisa
Can you confirm that what the reviewers are asking that we provide is AST>3XULN and TBL>2XULN from clinical database with cut off of Dec 31 2011 but the same from the global safety database with a more recent cut-off date than March 9 2012?

Erica

On Mon, Sep 24, 2012 at 10:02 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Dear Erica and Monica,

Please see response to your questions regarding Sept 21st Clinical Information on Hepatotoxicity 105828:
On Sept 21st, you requested: "Regarding request 2 below can the reviewers confirm that the request is specific to "AST>3XULN and TBL>2XULN" for the clinical and safety

databases included in DSR 105828 using the same cut-off dates for each as the two previous searches for ALT and TBL (Dec 31st 2011 for the clinical database and March 9 2012 for the global safety database)?"
FDA response: Please propose a more recent cut-off than March 9 2012.
On Sept 21st, you clarified: "Just for clarity all of the narratives included in the BLA are generated internally. This is standard process. They are reviewed and approved by our physicians."
FDA response: Physician reviewed and approved narratives are acceptable.

New Clinical Information Request, Sept 24, 2012:
Reference is made to the patients whose LVEF dropped below 50% and/or had a decrease from baseline of 15% or more on EMILIA. Please provide data on duration or decrease and recovery from LVEF decrease.
In addition, please provide the minutes from the Cardiac Review Committee meetings.
We would like this data no later than COB Friday September 28.

Please confirm receipt of email, and if the new I.R. timeline can be met.
Sincerely,
Lisa

From: Erica Evans [mailto:evans.erica@gene.com]
Sent: Wednesday, September 19, 2012 6:51 PM
To: Skarupa, Lisa
Cc: Erica Evans; Monica Shah; Kacuba, Alice
Subject: Re: BLA 125427 Clinical Pharmacology IR Sept 19 2012

Dear Lisa

We acknowledge the Agency's request for "submission of all the program codes for population PK and PK-PD analyses" with a target date to submit this information by Sept 26 2012.

Yesterday we submitted to the BLA as S0007 the information requested by the FDA reviewers at the September 5, 2012 meeting which included the program used for calculating the percentage of missing scans and the programs used for the exposure response (safety and efficacy) and population PK analyses. In yesterday's submission (S0007) all S--plus codes used in the population PK and exposure response analyses to generate plots, tables and analyses results were included. However, the NONMEM control stream to run the final model is part of the final popPK report included under Module 5.3.3.5.1 of the BLA (Pop PK Report # 12-0489; Appendices 7; 7.10, Page # 157) and was not submitted; The control stream is now attached for your reference-

delete column "Reason" in the population PK final dataset prior to running the final model in NONMEM).

Can you please confirm that the program codes as submittted to the BLA satisfy the Agency's request. If not, can you please clarify which additional program codes for population PK and PK-PD analyses the Agency are seeking.

Kind regards
Erica

On Wed, Sep 19, 2012 at 10:40 AM, Skarupa, Lisa <Lisa.Skarupa@fda.hhs.gov> wrote:
Good afternoon Erica,

Please see the following Clinical Pharmacology Information Request, please respond within 1 week.
Please submit all the program codes for population PK and PK-PD analyses.

Sincerely,
Lisa

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

/s/

LISA M SKARUPA
01/04/2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	May 30, 2012 from 1:00 pm to 2:00 pm
Meeting Location:	FDA White Oak Campus Bldg 22 Room 1415
Application Number:	IND 071072
Product Name:	T-DM1, trastuzumab emtansine
Indication:	Her2 positive metastatic breast cancer
Sponsor/Applicant Name:	Genentech, Inc.
Meeting Chair:	Patricia Cortazar, M.D., Lead Medical Officer, DOP1
Meeting Recorder:	Lisa Skarupa, RN, MSN, Regulatory Project Manager DOP1

FDA ATTENDEES

Office (OHOP):
Anthony Murgo, M.D., Associate Director for Regulatory Science

Clinical (DOP1):
Robert Justice, M.D., M.S., Division Director
Amna Ibrahim, M.D., Deputy Division Director
Patricia Cortazar, M.D., Lead Medical Officer
Gideon Blumenthal, M.D., Medical Officer
Geoffrey Kim, M.D., Medical Officer

Statistician (DB5):
Rajeshwari Sridhara, Ph.D., Division Director
Shenghui Tang, Ph.D., Lead Mathematical Statistician
Lijun Zhang, Ph.D., Mathematical Statistician

CMC (ONDQA/DPAMS/Branch5):
Anne Marie, Russell, Ph.D., Pharmaceutical Assessment Lead

CDRH (OIVD)-companion assays:
Reena Philip, Ph.D., Deputy Division Director, Immunology
Kevin Lorick, Ph.D., RAC, CDRH Reviewer

SPONSOR ATTENDEES

Genentech Inc., Attendees

Clinical

Dietmar P. Berger, MD, PhD., Vice President, Clinical Development Oncology, HER2 Franchise
Ellie Guardino, M.D., Ph.D., PD Medical Director, Clinical Science; Medical Monitor for Study TDM4370g/ BO21977
Steve Olsen, M.D., Ph.D. Senior PD Group Medical Director, Clinical Science; Global Development Team Leader
Nataliya Chernyukhin, M.D. Safety Science Leader
Jane Kilburn T-DM1 Global Regulatory Leader
Sanne Lysbet de Haas, Ph.D., Personalized Healthcare Care (PHC) Leader for T-DM1

Pharmacology

Sandhya Girish, Ph.D., Senior Scientist, Global Preclinical and Clinical Pharmacology Leader

Statistician

Liang Fang, Ph.D., Senior Statistical Scientist and Project Lead Statistician
Meghna Samant, Ph.D., Senior Statistical Scientist and Project Lead Statistician
Fan Zhang, Ph.D., Associate Director, Biostatistics

Regulatory

Erica Evans, Ph.D., Regulatory Program Management
Monica Shaw, Regulatory Program Management
Alissa Goodale, Global Regulatory Franchise Head for HER and Hematological Malignancies
Padraic Ward, T-DM1 Global Life Cycle Leader

1.0 BACKGROUND

Genentech, Inc. plans to submit a Biologics License Application (BLA) in 2012 for trastuzumab emtansine (T-DM1) for a proposed indication of patients with HER2-positive metastatic (b) (4) breast cancer who previously received trastuzumab and a taxane. The BLA will be based on analysis of safety and efficacy of a single pivotal Phase 3 study (EMILIA: Study TDM4370g/BO21977) and supportive Phase 1 and 2 studies (Studies TDM4374g, TDM4258g, TDM4450g/BO21976, TDM3569g, TDM4688g, and TDM4529g/BO25430).

The purpose of this pre-BLA (Type B) meeting is to follow-up on the March 15, 2012 pre-BLA teleconference, to review 'top-line' results from Study TDM4370g/BO21977, and to discuss the data to form the basis of a BLA for trastuzumab emtansine for the proposed indication. The Applicant seeks advice on the content and format of the BLA and resolution of any outstanding questions regarding the analysis and presentation of the data.

2. DISCUSSION

Clinical/ Biostatistics

Question #1: *Does the Agency agree that the efficacy and safety results from the single pivotal study, TDM4370g/BO21977 provide sufficient clinical experience to characterize the benefits and risks of trastuzumab emtansine and to form the basis of a BLA for the identified patient population for full approval?*

FDA Response to Question #1: **Study TDM4370g/BO21977 appears to provide sufficient clinical experience to characterize the benefit-risk profile of T-DM1 and to form the basis of a BLA. The approvability of the application, and the type of approval would be determined during the review of the BLA.**

Genentech's response received via email May 29, 2012: see Genentech's response to Question#2.

Question #2: *According to current estimates, the next planned and final OS analysis is anticipated to occur (b) (4). If the Sponsor performs an additional interim OS analysis would the Agency want to see these data? If yes, does the Agency agree that such an analysis could be integrated into the confirmatory sequential testing plan?*

FDA Response to Question #2:
If you choose to perform an additional interim OS analysis, we would want to see these data. Please clarify when the proposed additional interim OS data will be submitted to the Agency if you perform such an analysis. Considering your planned BLA submission timeline, it may not be feasible to include this additional interim analysis during the BLA review. However, it is acceptable to add an additional interim OS analysis with appropriate alpha adjustment in the sequential testing plan.

Reference ID: 3147284

Genentech's response received via email May 29, 2012:
An additional interim analysis is planned when at least 50% of the targeted 632 deaths are observed. The data cut off for this analysis is expected to occur in Q3 2012 and the minimum follow up is expected to be approximately 10 months. The type 1 error rate will be strictly controlled at the 0.05 level by the continued use of the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary pre-specified in the protocol and the statistical analysis plan (SAP). The alpha spent at this analysis will be based on the pre-specified boundary function and the actual number of deaths included in the analysis.

If the pre-specified boundary is crossed at this second interim analysis, and a statistically significant OS benefit is demonstrated, then the Sponsor considers that it would be ethical to offer the patients in the control arm who are still on study (either on treatment or in survival follow up) the opportunity to receive trastuzumab emtansine treatment at the discretion of the investigator.

All patients will continue to be followed for long term safety and survival until approximately 632 deaths have been reported and the final analysis of OS has been completed.

If the pre-specified boundary for OS is not crossed, the study will continue without crossover.

Genentech's subsequent Questions (2a, 2b, 2c) for FDA were received via email May 29, 2012:

Question #2a: Does the Agency have any comments on the revised statistical plan and crossover of control arm patients to receive trastuzumab emtansine?

Meeting Discussion for Question #2a: **FDA stated that the proposed revised statistical plan and crossover of control arm patients to receive trastuzumab emtansine is acceptable.**

Question #2b: If the results of the second OS interim analysis are statistically significant, Genentech will plan to submit the data as an amendment to the BLA. This amendment will be submitted as soon as possible after the analysis is performed and will include a summary of the results including the Kaplan-Meier curve, hazard ratio (with 95% CI), p-value and median OS estimates (with 95% CI). In addition, the analysis datasets containing the variables needed to perform the OS analysis will also be provided. We anticipate that this submission will occur prior to submission of the 90Day safety report.

Is this plan acceptable to the Agency?

Meeting Discussion for Question #2b: **FDA stated that this is acceptable.**

Question #2c: If a statistically significant OS benefit is demonstrated at the second interim analysis, can the Agency comment on the inclusion of these data in the USPI at the time of initial approval?

Meeting Discussion for Question #2c: **FDA stated that inclusion of a statistically significant OS benefit in the PI at the time of initial approval is probable. However, this will depend on timing of the submission and action.**

Reference ID: 3147284

General

Question #3: *Does the Agency agree that the Sponsor has fully addressed the feedback received at the March 15, 2012 Type C teleconference on the proposed content and format for the BLA, as detailed in Section 15 and Table 16 of this premeeting package? Specifically:*

a. Is the plan for the Integrated Summary of Safety (ISS) and Summary of Clinical Safety (SCS) acceptable?

FDA Response to Question #3a: **Yes.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

b. Is the plan for the Integrated Summary of Efficacy (ISE) and Summary of Clinical Efficacy (SCE) acceptable?

FDA Response to Question #3b: **Yes.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

c. Does the Agency agree with the proposed plan for submission of the Case Report Forms (CRFs)?

FDA Response to Question #3c: **Yes.**

Genentech's response received via email May 29, 2012: Can the Agency confirm that CDRH will have access to the BLA and the CRFs via the cross reference letter provided in DAKO's PMA submissions. Genentech does not plan to submit separate copies of the CRFs to CDRH.

Meeting Discussion for Question #3c: **FDA stated that CDRH is able to view CRFs in the BLA submission.**

d. Regarding the CRFs and based on the information provided in the premeeting package, can the Agency clarify if a meeting with the review staff will be required prior to the submission of the BLA in order for Genentech to provide a demonstration on the organization and structure of the CRFs and their navigation? If a pre-submission meeting is required, can the Agency suggest dates in August 2012 when such a meeting can be scheduled?

FDA Response to Question #3d: **A pre-submission meeting would be preferred. Please discuss potential dates with Lisa Skarupa, RPM after submitting a meeting request.**

Genentech's response received via email May 29, 2012: After the final submission to the BLA on August 24 2012, does the Agency anticipate asking Genentech to provide an overview of the clinical and clinical pharmacology data as part of an applicant orientation meeting? If so, could these meetings be combined, i.e., planned to occur on the same day? If yes, Genentech will propose to request such a meeting to occur the week of August 27, 2012.

Reference ID: 3147284

Meeting Discussion for Question #3d: **FDA stated that they can occur on the same day. FDA requested that they submit a meeting request.**

e. Is the plan for the Safety Update acceptable?

FDA Response to Question #3e: **Yes.**

Genentech's response received via email May 29, 2012: For clarity, in the 90 Day safety update Genentech plans to include CRFs only for patients in study TDM4370g/BO21977 for whom a narrative is submitted. Updated narratives will be provided for study TDM4529g. We do not plan on including narratives for study TDM4450g. Can the Agency confirm this plan is acceptable?

Meeting Discussion for Question #3e: **FDA stated this is acceptable to exclude narratives for study TDM4450g from the 90 Day safety update. As previously agreed to at the March 15, 2012 meeting, if there are any hepatic failure cases in any study the Applicant will provide narratives.**

Question #4: *Is the plan for the in-depth analysis of hepatotoxicity as discussed at the March 15, 2012 teleconference and as presented in Section 15.1 of this pre-meeting package acceptable?*

FDA Response to Question #4: **Yes.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

Question #5: *Can the Agency comment on the acceptability of the format and content of the datasets and programs proposed for submission in the BLA?*

FDA Response to Question #5: **The format and content of the datasets appear to be acceptable.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

Regulatory

Question #6: *Given the totality of the treatment effect, including the robust and consistent IRC assessed PFS HR of 0.65; p<0.0001, interim OS data (HR of 0.621; p<0.0005), IRC-assessed PFS sensitivity analysis, landmark 1 year and 2 year survival rates, and secondary efficacy parameters (including investigator-assessed PFS, IRC assessed ORR, DOR, and QoL) and a tolerable safety profile observed for single agent trastuzumab emtansine compared to the approved standard of care (lapatinib plus capecitabine) in Study TDM4370g/BO21977, does the Agency agree that this represents a sufficient advancement in the*

Reference ID: 3147284

treatment of HER2-positive MBC to qualify the proposed BLA for consideration of Priority Review?

FDA Response to Question #6: **Based on the top-line results that you have provided in the meeting package, it appears that your application qualifies for priority review. A final determination regarding priority review will be conducted at the time of BLA filing.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

Question #7: *Will the single pivotal Phase III study (TDM4370g/BO21977) and supportive Phase I and Phase II studies (TDM4374g, TDM4258g, TDM4450g/BO21976, TDM3569g, TDM4688g and TDM4529g/BO25430) be adequate to support a safety and effectiveness claim for the following proposed indication for trastuzumab emtansine:* (b) (4)

FDA Response to Question #7: **Approvability of this NME will be a based on a multi-disciplinary review of data from the aforementioned studies.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

Question #8: *Based on the results from Study TDM4370g/BO21977, does the Agency foresee any safety concerns that would trigger the requirement for a REMS for the use of trastuzumab emtansine in the proposed indication?*

FDA Response to Question #8: **REMS determination will occur during review of the safety database and an evaluation of the risks as related to the benefits of T-DM1 in the proposed patient population.**

Genentech's response received via email May 29, 2012: The responses were received and no further discussion is required.

Question #9: *Does the Agency foresee that the proposed BLA will be reviewed by the Oncologic Drugs Advisory Committee (ODAC)? If so, can the Agency comment on the timing of an ODAC review?*

FDA Response to Question #9: **A determination of the need for an ODAC discussion will occur during the review of the BLA.**

Genentech's response received via email May 29, 2012: For our planning purposes, can the Agency provide guidance as to the earliest date by which a decision around an ODAC will be communicated to Genentech?

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Meeting Discussion for Question #9: **FDA stated that at this time we do not anticipate that an ODAC meeting will be required. However, the determination of the need for an ODAC discussion will occur at time of filing.**

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

None.

5.0 ATTACHMENTS AND HANDOUTS

None.

Reference ID: 3147284

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

/s/

LISA M SKARUPA
06/18/2012

PATRICIA CORTAZAR
06/19/2012

MEETING MINUTES

MEETING DATE: November 3, 2009 **TIME:** 4PM **LOCATION:** room 1309

Drug Name: Trastuzumab-MCC-DM1 **IND:** 71,072 **Type of meeting:** EOP2

Sponsor: Genentech, Inc. **Meeting Request Submission Date:** 8-27-09
Briefing Document Submission Date: 10-2-09

FDA Invitees, titles and offices:
Robert Justice, M.D., Division Director
Patricia Cortazar, M.D., Acting Deputy Division Director
Edvardas Kaminskas, M.D., Acting Medical Team Leader
Albert Deisseroth, M.D., Clinical Reviewer
David McGuinn, Ph.D., Pharmacology Reviewer
Shenghui Tang, Ph.D., Statistical Team Leader
Somesh Chattopadhyay, Ph.D., Statistical Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Sarah Schrieber, Ph.D., Clinical Pharmacology Reviewer
Genevieve Schechter, M.D., Medical Officer
Jacinta Arrington, M.D., Medical Officer
Paul Zimmerman, R.Ph., Project Manager

Sponsor, titles and offices
Qasim Ahmad, M.D., Clinical Scientist, Roche Clinical Science
Michael Budde, Ph.D., Manager of Statistics, Roche Biostatistics
Erin E. Jones, M.S., Associate Director, Genentech Regulatory Affairs
Jane Kilburn, Global Regulatory, Roche Regulatory Affairs
Barbara Klencke, M.D., Associate Group Medical Director, Genentech Clinical Science
Marion Schrenk, M.D.,Global Lifecycle Leader, Roche Development
Robin Stewertson, Senior Associate, Genentech Regulatory Affairs
Vivian Ng Ph.D., Senior Biostatistician, Genentech Biostatistics
Mikael von Euler, MD PhD is the Head of Her2 Clinical Development at Roche
Sandhya Girish, Ph.D., Pharm Science, Genentech (by phone)

Meeting Objective:
To discuss the proposed Phase 3 Study BO22589 entitled, "A randomized, 3 arm, multicenter, phase III study to evaluate the efficacy and safety of the T-DM1 combined with pertuzumab or T-DM1 combined with pertuzumab-placebo, versus the combination of Herceptin plus taxane, as first-line treatment in HER2-positive progressive or recurrent locally advanced or metastatic breast cancer".

QUESTIONS for DISCUSSION with FDA RESPONSE

Non-clinical

1. Does the Agency agree (b) (4) ?

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-71072	GI-1	GENENTECH INC	TRASTUZUMAB MCC DM1(PRO132365)

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

/s/

PATRICIA CORTAZAR
11/09/2009