CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

NDA/BLA#: 125547 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DOP2 PDUFA Goal Date: 12-2-2015 Stamp Date: 12/2/2014

Proprietary Name: PORTRAZZA

Established/Generic Name: necitumumab

Dosage Form: 800 mg/50 mL (16 mg/mL) solution; for intravenous infusion

Applicant/Sponsor: Eli Lilly and Company

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

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

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

Indication: Treatment of advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin

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.	☐	☐	☐	☐

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

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

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

justification):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

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

Δ Formulation failed:

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

☐ Justification attached.

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

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	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.

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

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

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

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	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 appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

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

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

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

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

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

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

☐ Justification attached.

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

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

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

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

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation 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 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 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.

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	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)

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

/s/

MISSIRATCH BIABLE
01/27/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125547	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: PORTRAZZA Established/Proper Name: necitumumab Dosage Form: Injection		Applicant: Eli Lilly and Company Agent for Applicant (if applicable): N/A
RPM: Mimi Biable		Division: DOP2

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is December 2, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 11-24-2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included 12-2-2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Acceptable letter: 1-30-2015 Review: 1-28-2015
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 1-29-2015 DMEPA: 5-20-2015 DMPP/PLT (DRISK): 8-7-2015 OPDP: 9-14-2015 SEALD: ☒ None CSS: ☒ None Other: 9-14-2015 (OBP Review) 9-2-2015 (DPMH Review) 3-9-2015 (QT IRT Review)
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	1-29-2015 ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 2-11-2015 If PeRC review not necessary, explain: _____	Although Lily had requested a full waiver in the original application and the PeRc had reviewed and granted this request (refer to PeRc meeting minutes uploaded in DARRTS on 2-23-2015), Lilly received an orphan drug designation for this indication on 11-20-2015 therefore is exempt from PREA requirements. A new Pediatric Page was uploaded in DARRTS on 11-24-2015 to reflect this update.
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	PMC email:11-20-2015 PMC email:11-19-2015 CMC PMC tcon 11-17-2015 (uploaded 11-19-2015) CMC IR: 11-16-2015 (panorama) CMC PMC email:11-16-2015 CMC IR: 11-6-2015 (panorama) Quality Micro IR: 11-6-2015 Labeling email:11-4-2015 (uploaded 11-5-2015) CMC IR: 10-23-2015 (panorama) Labeling email:10-20-2015 CMC IR: 10-6-2015 (panorama) Quality Micro IR: 10-2-2015 CMC IR: 10-1-2015 (panorama) Quality Micro PMC: 9-30-2015 Quality Micro IR: 9-30-2015 Labeling email: 9-29-2015 Quality Micro PMC: 9-3-2015 Quality Micro IR: 8-28-2015 LCM Pkg : 8-14-2015 Labeling email: 8-14-2015 CMC IR: 8-14-2015 (panorama) Quality Micro tcon 8-12-2015 (uploaded 11-23-2015) Clin IR email 8-10-2015 Quality Micro IR: 7-28-2015 Clin IR email (2) 6-30-2015 Clin IR email (2) 6-8-2015 Clin IR email 6-5-2015 (uploaded 6-15-2015) Clin IR email 6-2-2015 ClinPharm IR email 5-26-2015 Clin IR email (2) 5-22-2015 Stat IR email 5-19-2015 Midcycle Communication 5-8-2015 (uploaded 5-15-2015) Stat IR email 5-12-2015

	Type C Meetings Minutes 5-1-2015 (uploaded 5-5-2015) Clin IR email 4-27-2015 Clin IR email 4-24-2015 Clin IR email 4-16-2015 Quality Micro IR: 4-14-2015 Mtg Granted Ltr: 4-8-2015 Clin tcon 3-27-2015 (uploaded 4-1-2015) Clin tcon 3-12-2015 (uploaded 3-19-2015) NonClin IR email 2-23-2015 Filing Ltr: 1-30-2015 NonClin IR email 1-23-2015 Ack Ltr 12-8-2014 Pre-sub Ack Ltr 10-30-2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Review Designation Memo 11-23-2015 Wrap-up Meeting 10-13-2015 (uploaded 11-3-2015) Midcycle Meeting: 4-24-2015 (uploaded 5-8-2015) Planning Meeting: 12-2-2014 (uploaded 1-14-2015)
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	11-19-2014
• EOP2 meeting *(indicate date of mtg)*	10-23-2008
• Mid-cycle Communication *(indicate date of mtg)*	5-8-2015 (uploaded on 5-15-2015)
• Late-cycle Meeting *(indicate date of mtg)*	8-24-2015 (uploaded on 9-26-2015)
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	7-9-2015
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	11-24-2015
Division Director Summary Review *(indicate date for each review)*	11-23-2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	10-20-2015
PMR/PMC Development Templates *(indicate total number)*	4 templates (containing a total of 5 PMCs)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review. Signed concurrence on 1-26-2015 (filing review)
• Clinical review(s) *(indicate date for each review)*	8-8-2015 (review), 1-26-2015

	(filing review)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Refer to Page 24 of 129 of the 8-8-2015 Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	Refer to DRISK 8-7-2015 Review (found under labeling reviews)
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	8/14/2015 (letter) 7/29/2015 (review) 7/28/2015 (letter) 6/17/2015 (letter)
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	Signed concurrence on 7-30-2015 review
Statistical Team Leader Review(s) *(indicate date for each review)*	Signed concurrence on 7-30-2015 review & 1-26-2015 filing review
Statistical Review(s) *(indicate date for each review)*	7-30-2015 (review), 1-26-2015 filing review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	Signed concurrence on 8-7-2015 review & 1-23-2015(filing review)
Clinical Pharmacology review(s) *(indicate date for each review)*	8-7-2015 (review), 1-23-2015 (filing review)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	9-10-2015
• Supervisory Review(s) *(indicate date for each review)*	7-24-2015; Signed concurrence on 7-24-2015 review & 1-27-2015 filing review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	7-24-2015 (review), 1-27-2015 filing review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	11-19-2015 (Panorama); Signed concurrence on 11-18-2015 review (Panorama)
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	11-18-2015 review (Panorama), 2-13-2015 filing review(Panorama)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 11-16-2015 DS review (Panorama) and 9-22-2015 DP review(Panorama), 2-13-2015 filing review (Panorama)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See page 8 of 329 of 11-18-2015 Drug Product Primary Quality Assessment review (Panorama)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: 10-22-2015 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

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

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy(BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done See comment included under Pediatrics
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

MISSIRATCH BIABLE
11/24/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5295
Silver Spring, MD 20993

NOV 2 0 2015

Eli Lilly and Company
33 ImClone Drive
Branchburg, NJ 08876

Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs

Re: Designation request # 13-4182
Dated: July 23, 2015
Received: July 23, 2015

Dear Ms. Lynch:

This letter responds to your request for orphan-drug designation of necitumumab for "treatment of squamous non-small cell lung cancer (NSCLC)."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of necitumumab is granted for *treatment of squamous non-small cell lung cancer (NSCLC)*. Please be advised that it is the active moiety or principal molecular structural features of the drug[1] and not the formulation of the drug that is designated.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug's orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26.

If the same drug is approved for the same orphan indication before you obtain marketing approval of your drug, you will have to demonstrate that your drug is clinically superior to the already approved same drug in order to obtain orphan-drug exclusivity. Failure to demonstrate clinical superiority over the already approved same drug will result in your drug not receiving orphan-drug exclusivity. 21 CFR 316.34(c).

[1] The term "drug" in this letter includes drug and biological products.

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Jeffrey Fritsch, RPh at 301-796-8682 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact John D. Milto, MD at 301-796-8687 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

/for Gayatri R. Rao

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

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/s/

MISSIRATCH BIABLE

11/24/2015

Although Lily had requested a full waiver in the original application and the PeRc had reviewed and granted this request (refer to PeRc meeting minutes uploaded in DARRTS on 2-23-2015), Lilly received an orphan drug designation for this indication on 11-20-2015 therefore is exempt from PREA requirements. A new Pediatric Page was uploaded in DARRTS on 11-24-2015 to reflect this update.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: January 7, 2015

FROM: Patricia Keegan, M.D.
Director, Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation Memo for BLA 125547 (necitumumab; Eli Lilly and Company)

TO: BLA 125547

The review status of this file submitted as an Original BLA is designated to be:

☒ Standard (PDUFA V - 12 Months) ☐ Priority (PDUFA V - 8 Months)

In the original BLA submission, Lilly requested priority review designation based on the potential to address an unmet medical need based on their determination that the results of Study I4X-IE-JFCC/IMCL CP11-0806 (SQUIRE), a randomized, multicenter, open-label, trial comparing the safety and efficacy of gemcitabine, cisplatin, and necitumumab with gemcitabine-cisplatin chemotherapy alone in the first-line treatment of patients with stage IV squamous non-small cell lung cancer (NSCLC). The proposed indication is for the "first-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic, squamous, non-small cell lung cancer."

ASSESSMENT OF REQUEST

In evaluating Lilly's request for priority review designation, I considered the results from the clinical development program for necitumumab for the treatment of non-small cell lung cancer (NSCLC), which included two efficacy trials: the SQUIRE trial conducted in patients receiving first-line treatment for squamous NSCLC and the INSPIRE trial conducted in patients receiving first-line treatment non-squamous NSCLC patient population, summarized in this section). I also considered Lilly's justification as to why the results of the INSPIRE trial are not relevant to the SQUIRE trial, and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)
- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications. On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Examples of significant improvement include the following:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

Assessment: This Biologic License Application (BLA) was not submitted under the statutory provisions where priority review designation is mandatory. I concur that Stage IV, squamous, non-small cell lung cancer is a serious condition. However, the results of the two efficacy trials conducted as part of the development program in NSCLC provide conflicting evidence of effectiveness. Specifically, the addition of necitumumab to platinum-based doublet chemotherapy in the SQUIRE demonstrated a clinically modest improvement in overall survival (OS) and in progression-free survival (PFS), however the addition of necitumumab to platinum-based doublet chemotherapy in the INSPIRE trial did not demonstrate an improvement in either OS or PFS, and the trial enrollment was terminated early for potential harm to patients.

The SQUIRE trial was a randomized trial that enrolled 1093 patients receiving first-line treatment for unresectable locally advanced or metastatic squamous non-small cell lung cancer. Lilly states that the trial demonstrated a statistically significant but clinically modest increase in overall survival [hazard ratio (HR) 0.84 (95% confidence intervals 0.74, 0.96); p=0.012 stratified log-rank test], with a difference in median overall survival of 1.6 months with median OS of 11.5 months in the necitumumab plus chemotherapy arm and 9.9 months in the chemotherapy alone arm. There was also a statistically significant but clinically modest increase in progression-free survival [HR 0.85 (95% CI: 0.74, 0.98); p=0.02 stratified log-rank test]. The median PFS was (b) (4) months in the necitumumab-chemotherapy arm and 5.5 months in the chemotherapy alone arm. There was no significant difference in the overall response rate between arms (31% vs. 29%). The risks of necitumumab reported in this trial included an increased risk of rash (78% vs. 12%), weight loss (12% vs. 6%), and venous thromboembolic events (8.2% vs. 5.4%) and increased risks of Grade 3 or higher rash (6.3% vs. 0.6%), venous thromboembolic events (4.3% vs. 2.6%), and vomiting (2.8% vs. 0.9%).

The INSPIRE trial was a randomized trial conducted in patients receiving first-line treatment for unresectable, locally advanced or metastatic, non-squamous, non-small cell lung cancer. The trial was terminated prematurely (after 633 of the planned 947 patients were enrolled) based on the recommendation of the data monitoring committee (DMC) due to an increased rate of serious thromboembolic events (including fatal events) in the necitumumab plus chemotherapy (pemetrexed and cisplatin) arm as compared to the chemotherapy alone arm. The final analysis of this trial was conducted after 474 deaths (rather than the planned final analysis after 732 deaths). In this clinical trial, the addition of necitumumab to chemotherapy did not improve survival [HR 1.01 (0.84, 1.21); p=0.96], with median survival times of 11.3 months in the necitumumab plus chemotherapy arm compared with 11.5 months in the chemotherapy alone arm. There was also no statistically significant difference between arms in terms for PFS [HR = 0.96 [95% CI: 0.80, 1.16; p=0.66], with median PFS times of 5.6 months in both arms. Finally, there was no significant difference in the overall response rate between arms (31% vs. 32%).

Lilly notes that the INSPIRE trial investigated the safety and efficacy of necitumumab in a different patient population (non-squamous NSCLC vs. squamous NSCLC) and in combination with a different chemotherapy backbone (cisplatin/pemetrexed vs. cisplatin/gemcitabine) than in the SQUIRE trial. While it is true that these differences are present, there is insufficient information to suggest that these differences alone account for the differences in efficacy. Specifically, Lilly has not provided evidence that there are unique drug interactions between necitumumab and pemetrexed, which might account for differences in exposure leading to differences in efficacy. Similarly, there was no compelling data to support a conclusion that necitumumab could not be effective for the treatment of non-squamous NSCLC; exploratory data based on the intensity of EGFR expression was inconsistent between the two trials and thus did not support that differences in EGFR expression between the two types of NSCLC (squamous and non-squamous) would explain the differences in outcome.

Given the differences in results between the two trials, there is uncertainty as to whether the addition of necitumumab to a platinum-based doublet regimen results in increased effectiveness as compared to chemotherapy alone. In addition, there was no evidence in reduction in toxicity or of enhanced patient compliance in this supplement. Finally, as noted above, this BLA was not submitted under the statutory provisions where priority review designation is mandatory. Based on my assessment, the criteria for priority designation are not met.

REVIEW DESIGNATION: Standard

{See appended electronic signature page}
Patricia Keegan, M.D.
Director, Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
11/23/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: Wednesday August 12, 2015; 2 – 3 PM EST

Application Number: BLA 125547/0
Product Name: Necitumumab
Sponsor/Applicant Name: Eli Lilly and Co (Lilly)

Proposed Indication: First-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer

Subject: Discuss Lilly's proposal for a strategy for endotoxin testing/share data in the response to FDA's July 28, 2015 quality Micro IR

FDA Participants:
Lakshmi Narasimhan, Ph.D.
Candace Gomez-Broughton, Ph.D.
Patricia Hughes, Ph.D.
Colleen Tomas, Ph.D.
Bo Chi, Ph.D.
Chana Fuchs, Ph.D.
Lee Pai-Scherf, M.D.
Gideon Blumenthal, M.D.
Missiratch (Mimi) Biable, M.S.

Sponsor Participants:
Deborah Lynch, Assoc. Vice President, Global Regulatory Affairs
Michael De Felippis PhD., Senior Research Fellow, Bioproduct Research and Development
Dayue Chen PhD., Senior Research Advisor, Bioproduct Research and Development
Ruth Schulz PhD., Assoc. Vice President, Global Regulatory Affairs – CMC

1.0 BACKGROUND:

This teleconference was held with Lilly in response to FDA's July 28, 2015 quality microbiology information request- specifically question #3 regarding endotoxin sample management and Lilly's request for a teleconference with the microbiology reviewers to share additional data (interim report for recoverability of LPS in Necitumumab (LY3012211) Drug Product - see attached), to review the data presented in the slide deck (also attached), and to discuss Lilly's proposal for a strategy for endotoxin testing.

2.0 DISCUSSION:

Lilly went over the attached documents and discussed necitumumab low endotoxin recovery data with the microbiology reviewers.

3.0 ACTION ITEMS:

Lilly to submit the information presented during the teleconference an amendment to the BLA.

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

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/s/

MISSIRATCH BIABLE
11/23/2015

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: RE: BLA-125547 Labeling PMR/PMC Discussion Comments
Date: Friday, November 20, 2015 5:02:00 PM
Importance: High

Hello Deb,

Thank you for the email regarding PMC#2 . The Quality Microbiology team requests that Lilly adheres to the original timeline as initially proposed and a study report be submitted in one year.
Please note that if the data are unacceptable and new methods need to be developed, you can request an extension.

Please confirm your agreement and submit your response your BLA by **10:00Am, Monday, November 23, 2015** with a courtesy copy to me via email.

Thanks,
Mimi

From: Deborah Lynch [mailto:deborah.lynch@lilly.com]
Sent: Friday, November 20, 2015 3:07 PM
To: Biable, Missiratch (Mimi)
Subject: RE: BLA-125547 Labeling PMR/PMC Discussion Comments
Importance: High

Dear Mimi,

Following our telephone conversation this afternoon, Lilly would like to provide some background information to explain the change in the timing around the second microbiology PMC for Necitumumab.

On August 28 FDA issued an Information Request by e-mail on Product Quality Microbiology topics, in the response Lilly proposed repeating an endotoxin (LPS) recovery study on drug substance (the response was submitted by e-mail on September 4 and to the BLA on September 8 as sequence 0035).

On September 30 the attached PMC was issued, but as the work requested in the PMC had been done and submitted in the BLA, Lilly proposed language that reflected the proposal put forth in the response to the August 28 IR, shown in the attached response file (submitted as sequence 0038 on October 8, 2015). Lilly provided an explanation for the change in the wording in the cover letter to this submission. Lilly proposed a 1-year timeframe to repeat the study, which did not take into account next steps should the study be unsuccessful. With the addition of the requirement to develop a new method in the event that the study is unsuccessful, received on November 19, Lilly is proposing to extend the PMC to account for the time it would take to develop a new method. Lilly still intends to repeat the endotoxin recovery study within 12 months, as stated in the original response to the PMC (sequence 0038).

I hope that this provides clarification around the additional time required to complete the PMC, as currently worded.
Please do not hesitate to contact me should additional information be required.

Thanks,
Deb

Deborah Lynch
Global Regulatory Affairs
Eli Lilly and Company
440 U.S. 22 Bridgewater, NJ 08807
☎: (908) 541-8026 : (b) (6)

From: Deborah Lynch
Sent: Thursday, November 19, 2015 8:05 PM
To: 'Biable, Missiratch (Mimi)'
Subject: RE: BLA-125547 Labeling PMR/PMC Discussion Comments
Importance: High

Dear Mimi,

Please find attached Lilly's response to the revised PMC language received this afternoon. In the light of the changes to PMC #2, Lilly is proposing new dates for the completion of the studies and submission of report(s). Lilly will submit this document to the BLA by 12 noon tomorrow, unless we hear from the Agency that the new proposed dates are not acceptable.

If you have any questions regarding our response, please don't hesitate to call me.

Many thanks for your consideration of this request,
Deb

Deborah Lynch
Global Regulatory Affairs
Eli Lilly and Company
440 U.S. 22 Bridgewater, NJ 08807
☎: (908) 541-8026 : (b) (6)

From: Biable, Missiratch (Mimi) [mailto:Missiratch.Biable@fda.hhs.gov]
Sent: Thursday, November 19, 2015 4:23 PM
To: Deborah Lynch
Subject: BLA-125547 Labeling PMR/PMC Discussion Comments
Importance: High

Hi Deb,

Upon further review, the team has made minor revisions to the proposed language for the CMC PMCs. Please review and submit your agreement to your BLA by **noon, Friday,**

November 20, 2015, with a courtesy copy to me via email.

(b) (4)

Complete endotoxin (LPS) recovery study using three batches of drug substance manufactured during a recent campaign and submit the study report in accordance with 21 CFR 601.12. If the results do not meet acceptance criteria, develop an alternative method to detect endotoxin in the drug substance.

The timetable you submitted on October 8, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 09/16
Final Report Submission: 11/16

Re-evaluate all necitumumab drug substance lot release and stability specifications after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured by (b) (4) Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 18, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 12/20
Final Report Submission: 02/21

Re-evaluate all necitumumab drug product lot release and stability specifications after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications, based on the available drug substance and drug product data.

The timetable you submitted on November 18, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 12/20
Final Report Submission: 02/21

Further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly.

The timetable you submitted on November 18, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	12/17
Final Report Submission:	06/18

Kindly confirm receipt and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

Responses to Questions

Proposed Post-Marketing Commitment

(b) (4)

Lilly Final Post-Marketing Commitment

(b) (4)

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/s/

MISSIRATCH BIABLE
11/20/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 17, 2015

Application Number: BLA 125547
Product Name: Portrazza (necitumumab)
Sponsor/Applicant Name: Eli Lilly and Co. (Lilly)

Subject: To discuss FDA's proposed CMC post-marketing commitments (PMCs) sent to Lilly via email on November 16, 2015 for Portrazza (necitumumab)

FDA Participants
Mimi Biable, M.S.
Chana Fuchs, Ph.D.

Sponsor/Applicant Participants
Ruth Schulz, Ph.D., Assoc. Vice President, Global Regulatory Affairs--CMC
Wendy Lime, Assoc. Vice President and Group Head, Global Regulatory Affairs – CMC
Deborah Lynch, Assoc. Vice President, Global Regulatory Affairs

BACKGROUND:
In follow-up to the three FDA proposed CMC PMCs emailed to Lilly on November 16, 2015 and in response to Lilly's November 17, 2015 electronic communication (email), see attached, in which Lilly proposed alternative wording to the two of the proposed PMCs, FDA held a teleconference with Lilly to further discuss and obtain clarification regarding Lilly's PMC wording.

DISCUSSION:
The discussion was based on the attached email received from Lilly via email on November 17, 2015. Lilly proposed the following:

- For PMC # 2 regarding DP stability, Lilly proposed to change the number of lots to 20 lots instead of the FDA proposed 30 lots (b) (4) [redacted] FDA requested that in their PMC report submission, Lily address different statistical approaches that may be more relevant, in addition to the (b) (4) approach.

- For PMC #3, Lilly proposed to include a protocol and gain agreement from the FDA as part of the PMC. FDA questions whether a pre-defined protocol would

allow Lilly to address the main issue, which is the lack of knowledge of the critical quality attributes associated with ADCC. Lilly agreed, based on FDA's explanation of intent, that a protocol may be too constraining, and agreed to keep the PMC with the original FDA language. FDA agreed that Lilly can still communicate with the review team on any changes to control strategy prior to filing the PMC submission.

ACTION ITEMS:
Lilly agreed to revise the PMCs as follows:
PMC #1 – keep as proposed by FDA
PMC #2 – change the number of lots from 30 to 20.
PMC #3 – keep as proposed by FDA

From: Deborah Lynch
To: Biable, Missiratch (Mimi)
Subject: RE: BLA-125547 Labeling PMR/PMC Discussion Comments
Date: Tuesday, November 17, 2015 11:21:51 AM

Dear Mimi,

Lilly acknowledges receipt of three post-marketing commitments for necitumumab CMC related to the drug substance and drug product specifications, and to the control strategy as it relates to antibody-dependent cell-based cytotoxicity (ADCC). Lilly wishes to propose alternative wording in the final response, and requests the reviewers' agreement that these modifications are appropriate and reflect the Agency's intention:

#2 – Lilly proposes to reassess the drug product specifications after the production of at least 20 batches of drug product. This is because drug product specifications are reassessed when drug substance specifications are updated, and Lilly anticipates that at least 20 batches of drug product will be available when 30 batches of drug substance are available for assessment, as described in #1.

#3 – In order to ensure that the actions that Lilly takes with regard to this commitment fully address the Agency's concerns, Lilly proposes to expand the commitment to include the development of a protocol to further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, with the intention of sharing the protocol with the Agency prior to its execution.

Lilly intends to submit the proposed post-marketing commitments by e-mail before 3 PM this afternoon.

Many thanks for your consideration of this request.
Deb

Deborah Lynch
Global Regulatory Affairs
Eli Lilly and Company
440 U.S. 22 Bridgewater, NJ 08807
☎: (908) 541-8026 : (b) (6)

From: Biable, Missiratch (Mimi) [mailto:Missiratch.Biable@fda.hhs.gov]
Sent: Monday, November 16, 2015 5:23 PM
To: Deborah Lynch
Subject: BLA-125547 Labeling PMR/PMC Discussion Comments
Importance: High

Hello Deb,

Please see attached and confirm receipt of this communication. Please note that we are requesting that you respond to our proposal by tomorrow 3:00 PM, Tuesday, November 17,

2015

Kindly confirm receipt and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 16, 2015

From: Mimi Biable, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: BLA 125547, Necitumumab: Proposed PMC Language

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for "Necitumumab."

Please note that additional post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by 3:00 PM, Tuesday, November 17, 2015.

Product Quality Microbiology

1. To re-evaluate all necitumumab drug substance lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured by (b) (4) Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
   This study will be conducted according to the following schedule:

   Study Completion: XX/XXXX
   Final Report Submission: XX/XXXX

2. To re-evaluate all necitumumab drug product lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug product manufactured by the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
   This study will be conducted according to the following schedule:

   Study Completion: XX/XXXX
   Final Report Submission: XX/XXXX

3. To further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly. This study will be conducted according to the following schedule:

Study Completion:	XX/XXXX
Final Report Submission:	XX/XXXX

Please let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
11/16/2015

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/s/

MISSIRATCH BIABLE
11/19/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547 Labeling PMR/PMC Discussion Comments
Date:	Thursday, November 19, 2015 4:22:00 PM
Importance:	High

Hi Deb,

Upon further review, the team has made minor revisions to the proposed language for the CMC PMCs. Please review and submit your agreement to your BLA by **noon, Friday, November 20, 2015**, with a courtesy copy to me via email.

Conduct endotoxin and sterility test method qualification study using two additional batches of Necitumumab Drug Product manufactured according to the commercial drug substance and drug product manufacturing processes and submit the results in accordance with 21 CFR 601.12.

The timetable you submitted on September 17, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	06/16
Final Report Submission:	09/16

Complete endotoxin (LPS) recovery study using three batches of drug substance manufactured during a recent campaign and submit the study report in accordance with 21 CFR 601.12. If the results do not meet acceptance criteria, develop an alternative method to detect endotoxin in the drug substance.

The timetable you submitted on October 8, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	09/16
Final Report Submission:	11/16

Re-evaluate all necitumumab drug substance lot release and stability specifications after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured by (b) (4) Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 18, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	12/20
Final Report Submission:	02/21

Re-evaluate all necitumumab drug product lot release and stability specifications after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications, based on the available drug substance and drug product data.

The timetable you submitted on November 18, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	12/20
Final Report Submission:	02/21

Further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly.

The timetable you submitted on November 18, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	12/17
Final Report Submission:	06/18

Kindly confirm receipt and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
11/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547

GENERAL ADVICE

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 Imclone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act for necitumumab. We also refer to your email received on November 11, 2015, in which you requested follow up information from the FDA. The following is in response to the referenced email communication:

The information provided in Lilly's responses to date appears to be sufficient for completion of the review. The proposed updated specifications appear acceptable. Please submit to the BLA the updated documents as identified in your email, specifically updated sections 3.2.S.2.2, 3.2.S.2.4, 3.2.S.4.1, 3.2.P.5.1, 3.2.S.5, 3.2.S.7.2, 3.2.P.8.2, and include the updated versions of the reference standard qualification protocols as submitted in your response to the information request dated October 1, 2015.

In addition to the items specified in your referenced email, Lilly had a number of questions in the various responses submitted to section 1.11.1. Most of these should have been addressed as part of the ongoing review communication; however, if any of these were not yet addressed, please identify those for which you need further clarification.

This information will be included in your biologics license application file.
If you have questions call me, at 301-796-4798.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=0014262141
Date: 2015.11.16 22:06:57 -05'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: BLA-125547: Product Quality Microbiology Information Request -- Response Required
Date: Friday, November 06, 2015 2:30:00 PM
Importance: High

Dear Deb,

The Product Quality Microbiology reviewer has the following information request that we wish you to address by **COB, Tuesday, November 10, 2015**.

3.2.S.2.4.2 Microbiological Controls

(b) (4) Bioburden and test results should be reported to reflect the sample volume.
Please report results per volume tested and amend the BLA accordingly.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
11/06/2015

BLA 125547 **INFORMATION REQUEST**

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 Imclone Drive
Branchburg, NJ 08876

Dear Ms. Lynch,

Please refer to your original Biologics License Application received October 22, 2014 submitted under section 351(a) of the Public Health Service Act for necitumumab.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your submission. Please submit your response prior to COB **November 11, 2015.**

> Regarding DP stability data, the 12 month time point on accelerated stability shows a consistent and reproducible difference on between the 3 DP lots manufactured at Lilly and all the DP lots manufactured at (b) (4) Please provide data from any investigation that was done regarding this difference and if any clear cause was identified.
> Note that although the stability data under real-time storage conditions do not show an apparent difference between the Lilly and (b) (4) lots, the accelerated stability data suggests that any extension of expiration dating based on an approved protocol would need to be based on data from the Lilly lots. Please update the BLA as relevant.

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=0014262141
Date: 2015.11.06 15:31:54 -05'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: Necitumumab BLA 125547- Proposed Labeling (Round 4)
Date: Wednesday, November 04, 2015 4:45:00 PM
Attachments: FDA_Edits_of_11_4_2015.docx
Importance: High

Dear Deb,

Thank you for the email. I have communicated to the team your acceptance of FDA's edits to the indication statement and the teleconference, scheduled for this Friday, November 6, 2015 from 3:00-3:30 PM, is canceled.

FDA is in agreement with the two additional edits made by Lilly- included in Lilly's October 27, 2015 amendment (which were update to subsection cross-referencing- under Sections 5.6: Non-Squamous NSCLC - Increased Toxicity and Increased Mortality and revision to AE grading under Section 6.1: Clinical Trials Experience).

Please find attached FDA's fourth round of proposed edit to the Necitumumab PI. Where necessary, please update the Table of Contents, update table and figure numbers as needed and correct formatting where required.

If you don't have additional edits, please submit a clean version incorporating all edits, via email, no later than **3PM Monday, November 9, 2015** and follow with a formal submission to your BLA.

Please confirm receipt and let me know should you have any questions.

Regards,
Mimi

From: Deborah Lynch [mailto:deborah.lynch@lilly.com]
Sent: Monday, November 02, 2015 2:26 PM
To: Biable, Missiratch (Mimi)
Subject: FW: Necitumumab BLA 125547- FDA Request for Teleconference

Hi Mimi,

In follow-up to our telephone call this afternoon, I would like to confirm that Lilly accepts the "Indication Statement" presented by FDA in the October 20, 2015 proposed labeling comments (round 3). I very much appreciate your efforts to organize the teleconference on November 6th; however, in light of Lilly's acceptance of the FDA proposed indication statement I believe there is no longer a need for the teleconference.

Please let me know if the USPI noting acceptance of the indication statement should be formally submitted to the BLA at this time.

Thanks again for your assistance.

Deb

Deborah Lynch
Global Regulatory Affairs
Eli Lilly and Company
440 U.S. 22 Bridgewater, NJ 08807
☎: (908) 541-8026 : (b) (6)

From: Biable, Missiratch (Mimi)
Sent: Wednesday, October 28, 2015 2:52 PM
To: 'Deborah Lynch'
Subject: Necitumumab BLA 125547- FDA Request for Teleconference
Importance: High

Good Afternoon Deb,

I am contacting you to request a teleconference (TCON) to discuss your October 27, 2015 submission, to BLA 125547, containing revised proposed labeling for necitumumab. Please note that our schedules are extremely full/booked and the only opening we have available is Friday, November 6, 2015 from 3:00-3:30 PM.

Kindly respond to confirm your availability for this TCON and please provide a toll-free conference call-in number.

Thank you in advance for a response.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
11/05/2015

BLA REVIEW WRAP-UP MEETING SUMMARY
October 13, 2015

BLA 125547/NME
Portrazza (necitumumab)
Eli Lilly and Company

Proposed Indication: First-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine-cisplatin chemotherapy

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Action Due Date: December 2, 2015

Dates That Outstanding Signed Reviews Are Due:

CMC Primary	8-8-2015
CMC Secondary	8-15-2015
CDTL	10-21-2015
Division Director	11-11-2015
Office Director	12-2-2015

Discuss Remaining Outstanding Pre-Action Items:

1. **Pending issues:** Status of CMC review.

   Discussion: CMC is planning to send an IR regarding the validity of Lilly's small scale models to support full scale (i.e. supporting their control strategy). CMC anticipates finalizing review in 4 weeks' time and will touch base with team in a week for an update.

2. **Labeling:**

   a. Revised carton & container labeling received August 31st, addressing all FDA comments and is acceptable.

   b. PI is still being negotiated. Revised PI from Lilly expected on October 13, 2015. Labeling meeting scheduled for October 20, 2015.

2. **PMCs and PMRs:** No PMR. Agreement reached with Lilly on language & milestones on 2 Quality Micro PMCs. Additional potential CMC PMCs could be forthcoming.

3. **Employee list (yes/no) for Action Package:** To be emailed the week of Oct 26.

5. **Press Release/ASCO Burst:** Press office has been notified.

6. **Action Package Preparation:** nearly complete for review by CPMS and DD.

7. **Approval letter:** Pending, RPM will draft.

8. **Inspections**:

   a. **Clinical Site Inspections:** All inspections complete with no issues with exception of Site 321 (Dr. Tudor Eliade Ciuleanu). Dr. Ciulenau responded to the the Form FDA 483 inspection observation and the written responses and detailed corrective actions provided were found to be adequate by OSI and will not affect overall study outcome.

   b. **Manufacturing Site Inspections:** No Issues.

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/s/

MISSIRATCH BIABLE
11/03/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547 **INFORMATION REQUEST**

Eli Lilly and Company
Attn: Deborah Lynch
AVP, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application 125547 received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for necitumumab.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB October 30, 2015.

1. Acceptance criteria for the purity, (b) (4) were established based on calculating (b) (4) for these attributes. (b) (4) In addition, FDA does not agree with the approach (b) (4) Therefore, FDA does not agree with the proposed acceptance criteria for attributes measured by SE-HPLC, CE-SDS, IEC, (b) (4) for DS and DP at release and on stability because these acceptance criteria are not supported by your manufacturing and clinical experiences. We have the following recommendations DS and DP specifications:

For Drug Substance:

Drug Substance Test	Release Acceptance Criteria	End of Shelf life acceptance Criteria
Size Exclusion	(b) (4)	

HPLC	(b) (4)	
CE-SDS Reduced		
CE-SDS Non-Reduced		
Ion Exchange Chromatography (IEC)	Conforms to Necitumumab Reference Standard	Conforms to Necitumumab Reference Standard
		(b) (4)
(b) (4)	Conforms to Necitumumab reference standard	
		(b) (4)

For Drug Product:

Drug product Test	Release Acceptance Criteria	End of Shelf life acceptance Criteria
Size Exclusion		(b) (4)

HPLC	(b) (4)	
CE-SDS Reduced		
CE-SDS Non-Reduced		
Ion Exchange Chromatography (IEC)	Conforms to Necitumumab Reference Standard	Conforms to Necitumumab Reference Standard (b) (4)

2. Identify the control strategy in place that would control for parameters impacting the ADCC functionality of necitumumab or add the appropriate specifications to ensure consistency in the ADCC functionality of the necitumumab DS and DP lots.
3. We have concerns regarding the validity of the small scale model based on the data presented in the BLA. We not agree that equivalence of the (b) (4) small scale model has been demonstrated. According to data provided in Table Q19b-2 in the response to our IR (0032), notable differences are observed between the outcomes of the small scale model and the lots from the commercial scale runs (b) (4) In addition we note that the acceptance criteria described in Table 3.2.S.2.6.2.1.3.6-1 are set (b) (4) which is not appropriate for the intended purpose. No data have been provided for the (b) (4) small-scale studies. Therefore, your proposed control strategy is not supported by the data submitted. Update the control strategy (b) (4) as identified in Table 3.2.S.2.6.2.1.3.2-4, as well as (b) (4) these parameters are associated with variations in charge as identified in Figure Q9-1 in your responses from 31 Aug 2015.

4. FDA does not agree with Lilly's rationale [redacted] (b) (4) as described in your response to our information requests of 8/31/2015 (Question 25). Update Section 3.2.S.2.2 to included additional information below:

[redacted] (b) (4)

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=0014262141
Date: 2015.10.23 21:03:47 -04'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Biable, Missiratch (Mimi)

From: Biable, Missiratch (Mimi)
Sent: Tuesday, October 20, 2015 5:57 PM
To: 'Deborah Lynch'
Subject: Necitumumab BLA 125547- Proposed Labeling (Round 3)
Attachments: FDA_Edits_of_10_20_2015.docx

Importance: High

Dear Deb,

Please find attached FDA's third round of proposed edits to the Necitumumab package insert.

In addition to these edits, please update the Table of Contents, update table and figure numbers as needed and correct formatting where required.

Please review our proposed edits/comments to the necitumumab labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your counterproposal along with any supporting data to your BLA by **Wednesday, October27, 2015**, with a courtesy copy to me via email.

Please confirm receipt of this communication and let me know should you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
10/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547

INFORMATION REQUEST

Eli Lilly and Company
Attn: Deborah Lynch
AVP, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Vice President Lynch:

Please refer to your Biologics License Application 125547 received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for necitumumab.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **October 12, 2015.**

You (Lilly) have stated in your 31 Aug 2015 IR response that all Drug Substance (DS) and Drug Product (DP) compendial and non compendial analytical testing will be performed at:

Site	Responsibilities
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 USA Establishment Identification Number: 1819470	Drug product manufacture. Release testing and stability testing including all compendial methods and non-compendial methods for drug product except cell based potency. Secondary packaging/labeling of drug product
ImClone Systems LLC 33 ImClone Drive Branchburg, NJ 08876 USA Establishment Identification Number: 3002889358	Release testing and stability testing including all compendial methods and non-compendial methods for drug product except container closure integrity, sterility, and volume in container.

But in your BLA you state that testing for non-compendial assays will be validated/and transferred to the following facilities:

Table 3.2.P.5.3-4 Test Laboratory Certification Summary for Non-Compendial Analytical Procedures for Necitumumab Drug Product

Analytical Procedure	ImClone Quality Control Laboratories	Lilly Global Quality Laboratories (GQL)	Lilly Indianapolis Parenteral (IPAR) Quality Control Laboratories
Protein Concentration (b) (4)	(b) (4)		
Size Exclusion High Performance Liquid Chromatography (SE-HPLC)			
Ion Exchange Chromatography (IEC)			
Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS) Non-Reduced			
Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS) Reduced			
Polysorbate 80			
Cell Based Potency Assay			

What is the relationship between GQL, IPAR and "ImClone quality control laboratories" and the two facilities you submitted on 31 Aug 2015? If methods validated at one facility will be implemented at a separate, geographically distinct location submit transfer reports for all methods that will be performed at the alternate location(s). If the transfer reports have been submitted, identify the location of the reports within the BLA.

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=0014262141
Date: 2015.10.06 12:53:15 -04'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: RE: BLA-125547: Product Quality Microbiology Information Request -- Response Required
Date: Friday, October 02, 2015 1:47:00 PM
Importance: High

Dear Deb,

The Product Quality Microbiology reviewer confirms that the information request (IR) sent to Lilly on Wednesday, September 30, 2015 is a follow up to the August 14, 2015 IR.
Please note the reviewer is requesting for the shipping validation study reports.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

From: Deborah Lynch [mailto:deborah.lynch@lilly.com]
Sent: Thursday, October 01, 2015 4:54 PM
To: Biable, Missiratch (Mimi)
Subject: RE: BLA-125547: Product Quality Microbiology Information Request -- Response Required

Hi Mimi,

I would also like to ask that if the response submitted for the August 14, 2015 Information Request addresses question 2 of the September 30, 2015 Information Request , our response will reference this email correspondence and refer to the August 14th response,

If, however, this is not the case, can you kindly provide further clarification on any additional information needed to address the reviewers question.

Thanks,
Deb

From: Deborah Lynch
Sent: Thursday, October 01, 2015 3:55 PM
To: 'Biable, Missiratch (Mimi)'

Subject: RE: BLA-125547: Product Quality Microbiology Information Request -- Response Required

Dear Mimi,

The Lilly CMC team has a question regarding Question 2, below, on the request for drug substance shipping study reports. The Information Request dated August 14, 2015, included the following question:

23. Provide shipping validation reports for the shipping of DS from ImClone, NJ to the DP manufacturing site. Include full descriptions of the packaging, temperature monitoring systems, data for ability to ship in both cold and hot seasons.

Lilly responded to this question in our submission dated August 31, 2015.

Would it be possible to confirm that the question raised in your e-mail yesterday is a follow-up to the response provided on August 31?

Appreciate your efforts in obtaining clarification so our response best addresses the reviewers question.

Thanks,
Deb

From: Biable, Missiratch (Mimi) [mailto:Missiratch.Biable@fda.hhs.gov]
Sent: Wednesday, September 30, 2015 4:26 PM
To: Deborah Lynch
Subject: BLA-125547: Product Quality Microbiology Information Request -- Response Required
Importance: High

Dear Deb,

The Product Quality Microbiology reviewer has the following information request that we wish you to address by **COB, Thursday, October 8, 2015**.

Quality Microbiology – Drug Substance

1. [redacted] (b) (4) Provide justification for this limit [redacted] (b) (4) in accordance with process capability.
2. Please provide the reports for the drug substance shipping validation studies. Include dates of the studies as well as the lot numbers for the drug substance used in the studies.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
10/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547

INFORMATION REQUEST

Eli Lilly and Company
Attn: Deborah Lynch
AVP, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Vice President Lynch:

Please refer to your Biologics License Application 125547 received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for necitumumab.

We are reviewing your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB **October 12, 2015.**

1. Regarding the requalification of the current PRS and WRS:

   a) In Table 3.2.S.5.4.1-1, the acceptance criteria for potency measured by the Biacore binding and cell-based assays indicate (b) (4) Revise the acceptance criteria for potency determined by the Biacore binding and cell- based potency assays to clearly define (b) (4) If the (b) (4) described in section 3.2.S.5.4.1 will be included as part of the acceptance criteria, a detailed summary of the approach should be provided, including the quantitative criteria that must be met to allow the continued use of the PRS for its intended purpose.

   b) We noted "Da = Dalton; w/v = weight volume" in the footnote of Table 3.2.S.5.4.1-1; however no related contents are found in the table. Revise the table and include the missing information.

   c) (b) (4)

Provide detailed information including a list of the physicochemical assays and the associated acceptance criteria.

d) Provide a copy of the current PRS and WRS requalification protocols.

2. Regarding future replacement of working reference standards, it does not appear, based on the information found in 3.2.S.5, Reference Standard or Materials, that a defined strategy, including tests and acceptance criteria, for qualification of future primary reference standards is included in the BLA. Information and data supporting qualification of subsequent primary reference standards must be submitted as a prior approval supplement after the BLA is approved. Alternatively, a protocol for qualification of future primary reference standards can be submitted as a prior approval supplement after the BLA is approved. To gain concurrence on the strategy for qualification of future working reference standards, submit protocols for manufacturing and qualification of future WRS and requalification of future WRS to the BLA.

3. In regard to the DoE studies [redacted] (b) (4) you provided high level summary data from the preliminary and confirmatory DoE studies for all evaluated Unit Operations. The information provided is insufficient to allow for an evaluation of the studies.

   a) [redacted] (b) (4) Provide justification [redacted] (b) (4)

   b) Provide justification [redacted] (b) (4)

   c) [redacted] (b) (4) Provide the control strategy [redacted] (b) (4)

   d) Provide additional information for the preliminary and confirmatory DoE studies [redacted] (b) (4) including the experimental design (parameter settings for each run), the CQAs assessed, a summary of the results for CQAs assessed from each run performed, and a brief description of statistical analyses.

4. Provide the identity of the control [redacted] (b) (4) used in generating data represented in Figure 3.2.S.3.1.7.2.1-2 and indicate [redacted] (b) (4)

5. In your response to our information requests of 8/31/2015 (Question 20a), you provided highly summative data in Table Q20a-1 and Table Q20a-2, which are not sufficient to allow for an evaluation of the studies. Provide more detailed information, including the results for the CQAs assessed in the studies and an explanation of the results from the statistical analyses.
6. We noted that the acceptance criterion for protein concentration is (b) (4) mg/L in Table 3.2.S.2.5.6.2-1 (b) (4) (b) (4) Since the protein concentration (b) (4) is defined as (b) (4), explain how protein concentrations in (b) (4) samples can be (b) (4) (b) (4) If this is an error, update the table with correct value.

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andrew Shiber -A, 0.9.2342.19200300.100.1.1=0014362141
Date: 2015.10.01 16:33:05 -04'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: BLA-125547: Product Quality Microbiology Information Request -- Response Required
Date: Wednesday, September 30, 2015 4:25:00 PM
Importance: High

Dear Deb,

The Product Quality Microbiology reviewer has the following information request that we wish you to address by **COB, Thursday, October 8, 2015**.

Quality Microbiology – Drug Substance

1. (b) (4) (b) (4) Provide justification for this limit in accordance with process capability.
2. Please provide the reports for the drug substance shipping validation studies. Include dates of the studies as well as the lot numbers for the drug substance used in the studies.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
09/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 30, 2015

From: Mimi Biable, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: BLA 125547, Necitumumab: Proposed PMC Language

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for "Necitumumab."

Please note that additional post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on Thursday, October 8, 2015.

Product Quality Microbiology

1. [redacted] (b) (4)

   Study Completion: XX/XXXX
   Final Report Submission: XX/XXXX

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf

- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf

- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.

- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

Please let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0154

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MISSIRATCH BIABLE
09/30/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	Necitumumab BLA 125547- Proposed Labeling
Date:	Tuesday, September 29, 2015 10:36:00 AM
Attachments:	FDA Edits of 9.29.2015.docx
Importance:	High

Dear Deb,

Please find attached FDA's second round of proposed edits to the Necitumumab PI.

In addition to these edits, please update the Table of Contents, update table and figure numbers as needed and correct formatting where required.

Please review our proposed edits and comments to the necitumumab labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your counterproposal along with any supporting data to your BLA by **Tuesday, October 6, 2015**, with a courtesy copy to me via email.

Please confirm receipt of this communication and let me know should you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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MISSIRATCH BIABLE
09/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 3, 2015

From: Mimi Biable, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: BLA 125547, Necitumumab: Proposed PMC Language

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for "Necitumumab."

Please note that additional post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on Friday, September 18, 2015.

Product Quality Microbiology

1. [redacted] (b) (4)

Study Completion:	XX/XXXX
Final Report Submission:	XX/XXXX

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf

- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf

- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.

- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

Please let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
09/03/2015

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: BLA-125547: Product Quality Microbiology Information Request -- Response Required
Date: Friday, August 28, 2015 4:57:00 PM
Importance: High

Dear Deb,

The Product Quality Microbiology reviewer has the following information request that we wish you to address by **COB, Friday, September 4, 2015**.

3.2.S.4.2 Analytical Procedures

Please submit the following documents:

1. QCM-AS-0018 Bioburden Testing using (b) (4)
2. QCM-GN-0009 Bioburden Method Suitability
3. VPQ 0377-Validation of Kinetic-QCL Chromogenic Assay
4. QCM-EN-0011-LAL Inhibition/Enhancement Using Kinetic-QCL Chromogenic Assay

3.2.S.4.3.1 Endotoxin Hold Time Study for Necitumumab Drug Substance
The endotoxin hold time studies done with bulk drug substance (BDS) show (b) (4)

Please establish an endotoxin sample hold time of not more than (NMT) (b) (4) hours. Please amend the BLA accordingly.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C. (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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MISSIRATCH BIABLE
08/28/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	Necitumumab BLA 125547- Proposed Labeling
Date:	Friday, August 14, 2015 11:15:00 AM
Attachments:	FDA_Edits_of_8_14_2015.docx
Importance:	High

Dear Deb,

Please find attached FDA's first round of proposed edits to the Necitumumab PI. In addition to these edits, please update the Table of Contents, update table and figure numbers as needed and correct formatting where required.

We also have the following comments on your carton and container labeling:

General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with United States Pharmacopeia General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

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

Carton Labeling

3. Add the route of administration "For Intravenous Infusion Only" below the strength statement on the side and top panels. Additionally, consider deleting "Route of Administration: Intravenous Infusion" from the side panel.

4. Decrease the prominence of "Rx only" by remove the bolding. Consider relocating "Rx only" to the top right corner of the label.

5. Consider decreasing the size of the logo to provide more white space on the principal display panel to improve the readability of the critical information.

6. Add the units of measure to the temperature range in the storage statement so that it appears as "2°C to 8°C (36°F to 46°F)".

7. Combine the storage and protection from light statements. For example:

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

8. Revise the list of ingredients to read:

> Contents: Each mL contains 16 mg necitumumab, citric acid anhydrous (0.256 mg), glycine (9.984 mg), mannitol (9.109 mg), polysorbate 80 (0.1 mg), sodium chloride (2.338 mg), sodium citrate dihydrate (2.55 mg), and water for injection.

Vial Container Label

9. See comments 4, 6, and 7.

Please review our proposed edits and comments to the necitumumab labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your counterproposal along with any supporting data to your BLA by **Friday, August 28, 2015**, with a courtesy copy to me via email.

Please confirm receipt of this communication and let me know should you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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MISSIRATCH BIABLE
08/14/2015

BLA 125547 INFORMATION REQUEST

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 Imclone Drive
Branchburg, NJ 08876

Dear Ms. Lynch,

Please refer to your Biologics License Application (BLA) dated December 2, 2014, received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for necitumumab.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comment and requests for information. We request a prompt written response in order to continue our evaluation of your submission. Please submit your response prior to COB August 31, 2015 .

1. Provide any additional available stability data with updated timepoints for all lots of drug substance (DS) and drug product (DP) on stability studies.

2. Update form 356h and sections 3.2.S.2.1 and 3.2.P.3.1 to include the specific tests to be executed at each testing site.

3. Revise the relevant sections (356h, 3.2.S.2.1, 3.2.A.1) to specify the suite to be licensed for necitumumab DS manufacturing. During FDA inspection of the DS manufacturing facility it became apparent that (b) (4) was used to manufacture necitumumab clinical and process validation batches. No manufacturing history or data to support the manufacturing of necitumumab (b) (4) was identified. Therefore, (b) (4) can be used for commercial manufacturing of necitumumab DS.

4. Submit the drug substance and drug product sampling plans used for lot release and stability testing.

5. Identify the lots of DS and DP used in each of the clinical trials supporting safety or efficacy of necitumumab.

6. Section 3.2.P.2.4.3 identifies that extractable and leachable studies were performed for the stopper but does not include extractable and leachable information for the glass vial. (b) (4)

(b) (4) Submit results from extractable and leachable studies for the Type I glass tubing vial used as the container closure system for necitumumab DP.

7. We note that leachable studies are currently ongoing for the DS and DP container closure systems. Provide the results of the completed leachable studies in the annual report of manufacturing changes.

8. The BLA specifies that an identity test for necitumumab is performed (b) (4) to confirm the identity of the DS (b) (4) in Section 3.2.P.3.3.2. Clarify which identity test(s) is performed at this step.

9. (b) (4) Explain how your control strategy would control (b) (4) in your product.

10. We could not find the following protocols in the BLA. Provide these protocols or identify where they may be found if these were included in the submission. Note that detailed protocols are required to be approved with the BLA in order to allow for concurrent validation and the proposed (b) (4) activities. Protocols should include (b) (4) product quality testing (b) (4) (b) (4) (b) (4) The results from the (b) (4) studies should be submitted to the BLA in the annual report of manufacturing changes.

11. [redacted] (b) (4) Identify [redacted] (b) (4) and specify what limits will be used [redacted] (b) (4)

12. Provide the data [redacted] (b) (4)

13. [redacted] (b) (4)
Please provide the information to support your identified control limits.

14. The acceptance criterion [redacted] (b) (4) is set [redacted] (b) (4)
    a. Provide the rationale, with supporting data, [redacted] (b) (4).
    b. Provide data as identified in question14a, above [redacted] (b) (4).
    c. Provide data to support the control limits [redacted] (b) (4)
    d. Provide data [redacted] (b) (4) Explain how your controls address a situation [redacted] (b) (4)

15. [redacted] (b) (4)
    a. [redacted] (b) (4)

[redacted] (b) (4)
Provide the results for current WCB from the same study.

b. You identify that the acceptance criteria [redacted] (b) (4) Submit this information, including any justification regarding the approach used. We note that the acceptance criteria [redacted] (b) (4)

a. Description of the full scale qualification [redacted] (b) (4) specifies that performance [redacted] (b) (4) will be confirmed [redacted] (b) (4) We do not agree [redacted] (b) (4) therefore, we do not agree [redacted] (b) (4) Revise Section 3.2.S.2.3.2.6 to specify the number of lots of DS that will be assessed [redacted] (b) (4)

16. In section 3.2.S.2.3, page 17, [redacted] (b) (4) is listed in Table 3.2.S.2.3.2.4-1. Please clarify the source [redacted] (b) (4)

17. Explain the [redacted] (b) (4) observed for lot 508429 at [redacted] (b) (4) (Figures 3.2.S.2.6.3.3.5.2-3 and 3.2.S.2.6.3.3.5.2-5)

18. We note that the stability test period for the MCB is [redacted] (b) (4) Submit available MCB and WCB stability data and trending performed to date. Provide a rationale with supporting data [redacted] (b) (4)

19. Regarding the qualification [redacted] (b) (4)

a. Provide detailed information [redacted] (b) (4).

b. [redacted] (b) (4)
Based on CQAs provided in Table 3.2.S.2.6.2.1.3.2-1 are highly summative data and not sufficiently comprehensive for details and quality attribute assessment. Provide more detailed information, including the data and the statistical methods used for the analyses.

20. You stated [redacted] However, you did not provide adequate data to allow an evaluation of these studies.
    a. Provide the detailed information of the data and statistical method by which [redacted] are determined.
    b. Provide information for how the [redacted] were established.
    c. The control limit [redacted] is set [redacted] Provide method for the determination [redacted].

21. We note that "research materials" was included in the comparability study described in section 3.2.S.2.6.3. Provide the information for these "research materials".

22. The FcRn binding activity was provided [redacted] Provide the absolute values of K_d , k_{on}, and k_{off} obtained from the Biacore assay.

23. Provide shipping validation reports for the shipping of DS from ImClone, NJ to the DP manufacturing site. Include full descriptions of the packaging, temperature monitoring systems, data for ability to ship in both cold and hot seasons.

24. The certificate of analysis [redacted] sourced from Lilly provided in Section 3.2.S.2.3 does not include information [redacted] Provide documentation of [redacted] testing.

25. Description of the manufacturing process is lacking in detail regarding the process description and control. Update section 3.2.S.2.2. with additional information. For example, the following types of information should be include (note that this is not a comprehensive list and only examples of the information to be included):
[redacted]

(b) (4)

26. You indicate (b) (4) It is not clear (b) (4) which information was already included in the BLA. Please verify (b) (4)

27. In regarding to the multivariate DoE studies (b) (4) you did not provide sufficient information in the BLA submission to allow for an evaluation of the studies. Provided following information in the response:
    a. For the preliminary DoE study, provide the method used for setting the parameter testing ranges, original data, and a description of the statistical method; specify the assays used for purity (b) (4)
    b. For the confirmatory DoE study, provide the actual data and detailed information for the statistical analytical method, including representative plots and results from the ANOVA.
    c. You stated that the control ratios (CR) were calculated for all CQAs under worst-case scenarios. Provide detail information for how the worst case was determined and how the control ratio is calculated.
    d. Provide detailed information for how the PARs to the critical process parameters were established.
    e. (b) (4)

[redacted] (b) (4) Provide data to support that [redacted] (b) (4) on the CQAs of the product.

28. You identify that. [redacted] (b) (4)

This does not address the issue [redacted] (b) (4)

Identify any corrective actions done to resolve this issue [redacted] (b) (4)

29. Regarding the quality attribute assessment (Table 3.2.S.2.6.1.1-1):
    a. [redacted] (b) (4) Provide the rational or justification with supporting data for your scoring method.
    b. Provide additional clarification for how to determine [redacted] (b) (4)

30. [redacted] (b) (4) Please provide further explanation on your assessment and considerations that resulted in these numbers.

31. The submission was not clear on your actions when in process specifications and in process controls (critical vs. non-critical) are not met. Please expand on these points.

32. The BLA includes a number of commitments for future activities. Provide a comprehensive list of commitments for future activities that are included in the BLA, as well as Lilly's plans for updating the BLA for each of these.

33. Provide a comprehensive list of all the protocols included in the submission that are intended to be approved with the BLA. Some examples of protocols include the protocols for [redacted] (b) (4) validation studies that are identified in this IR document, [redacted] (b) (4) validation protocols, and the new

WCB protocol. These and the other protocols that are in the BLA should be included in this list.

If you have any questions, please contact Missiratch (Mimi) Biable, Senior Regulatory Health Project Manager, at (301) 796-0154

Sincerely,

Chana Fuchs -S

Digitally signed by Chana Fuchs -S
DN: c=US, a=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chana Fuchs -S, 0.9.2342.19300300.100.1.1=2000601803
Date: 2015.08.14 17:16:49 -04'00'

Chana Fuchs, Ph.D.
Team Leader
DBRR IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547: Clinical Information Request -- Response Required
Date:	Monday, August 10, 2015 4:44:00 PM
Importance:	High

Dear Deb,

The Clinical reviewer has the following information request (IR) that we wish you to address before **COB, Wednesday, August 12, 2015**.

Concerning Lilly's Necitumumab Advisory Committee backgrounder Figures APP.1.6. and APP.1.7 and slides CS-45 and SA233 of Lilly's ODAC oral presentation (Association Between Baseline Risk Factors and thromboembolic events), please provide:

1. Analysis of association between prior history of VTE or ATE and risk of VTE or ATE during study by treatment arm for both SQUIRE and INSPIRE trials.

2. Provide in tabular format, listing of patients (ID, demographics) with prior history of VTE or ATE (date, preferred term of prior event), treatment received (arm, cycle, date) and VTE or ATE while on study (date, preferred term).

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
08/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/S-0

INFORMATION REQUEST

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) dated December 2, 2014, received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for "Necitumumab."

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA:

1. (b) (4)

   a. (b) (4)

2. Validation of Analytical procedures

   a. One lot manufactured at (b) (4) (C1200159) and two lots (C262169 and C266776) manufactured at Lilly during commercial development were used for method verification of bioburden, sterility and rabbit pyrogen testing. It is not clear whether these lots used for the method qualification studies were representative of the commercial manufacturing lots. Please clarify and if these lots are not representative of the commercial lots, submit information and results from method qualification studies (for the tests mentioned above) performed using 3 commercial drug product lots.

3. Regarding endotoxin hold time study for necitumumab drug product:

   a. Please clarify if the endotoxin hold time study was performed [redacted] (b) (4)

   b. The endotoxin hold time studies have demonstrated [redacted] (b) (4) You have stated in your amendment dated April 21, 2015, in response to our April 16, 2015 information request, that [redacted] (b) (4) will be proposed [redacted] (b) (4) Please submit your proposal [redacted] (b) (4)

We request a response by August 3, 2015, in order to continue our evaluation of your BLA.

4. In your April 21, 2015 amendment, you stated that a microbiological study report that supports the 24 hour infusion solution storage time of necitumumab at 2 to 8°C will be provided by July 30, 2015. Please provide an update on the status of the report.

If you have any questions, please contact Missiratch (Mimi) Biable, Senior Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Patricia Hughes, Ph.D.
Acting Branch Chief
Division of Microbiology Assessment
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

PATRICIA F HUGHES TROOST
07/28/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Clinical Information Request -- Response Required
Date:	Tuesday, June 30, 2015 3:33:00 PM
Importance:	High

Dear Deb,

The Clinical reviewer has the following information request (IR) that we wish you to address before **COB, Tuesday, July 7, 2015**.

Concerning SQUIRE study, for the events of skin reactions, hypomagnesemia and venous thromboembolic events, provide in tabular format the following analyses:

1. Time to onset
2. Time to worse grade
3. Time to resolution and outcome
4. Management, if any
5. Action taken with study drugs (necitumumab and chemo)

For the events of hypomagnesemia, please provide separate analyses based on reported AE and laboratory finding.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
06/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 30, 2015

From: Mimi Biable, RPM, DOP2/OHOP/CDER/FDA

Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for: BLA 125547/Necitumumab

---

We are requesting your assistance in populating the attached tables for your New Molecular Entity, Necitumumab, that is currently under review in the Division, this information will be posted publically, if approved, at the FDA drug snapshot website: http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

We are asking this information to allow for greater transparency by providing information to the public about participation in clinical trials for newly-approved drugs and biologics.

The website will include information on the study design, the results of efficacy and safety studies, and whether there were any differences in efficacy and side effects among sex, race, and age subgroups. It is not intended to replace or replicate the package insert, which are intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focus on subgroup data and analyses
- Links to PI for the product and to the FDA reviews at Drugs@FDA
- Information will be published approximately 30 days after drug/biologic approval

Therefore, we are requesting that you provide your data and complete the attached tables as well as provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data, if these are not already in the BLA 125547.

We are requesting you submit this information no later than July 28, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C.(US)
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	**Comparator/ Control** (n=) n (%)	**Treatment Group(s)** (n=)		**Total** (n=) n (%)
		Treatment arm #1 (n=) n (%)	**Treatment arm #2** (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparator/control (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)	**Comparator/control** (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication[2]			
All other than controlled trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			

[1] *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

[2] to be used in product's labeling

[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials
(If efficacy population = safety population, refer to Table 2.1 or 2.2)

Demographic Parameters	**Comparator/ Control** (n=) n (%)	**Treatment Group(s)** (n=)		**Total** (n=) n (%)
		Treatment arm #1 (n=) n (%)	**Treatment arm #2** (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population (Events ≥ 2% of drug-treated subjects and more frequent than placebo)[1]

	Male (N=)		**Female** (N=)	
MedDRA System Organ Class Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

	Age ≥17-<65 years (N=)		**Age ≥65 years** (N=)	
MedDRA Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population
Source: list datasets or other sources of information

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/s/

MISSIRATCH BIABLE
06/30/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Clinical Information Request -- Response Required
Date:	Monday, June 08, 2015 2:01:00 PM
Importance:	High

Dear Deb,

The Clinical reviewer has the following information request (IR) that we wish you to address by **COB, Tuesday, June 9, 2015**.

Concerning subjects with deaths attributed to a TE event in both SQUIRE and INSPIRE trials, please provide the ID of the patients (6 patients in the SQUIRE trial and 15 patients in the INSPIRE trial) identified by Lilly as grade 5 events due to a TE. We have noticed discrepancies between AEs leading to dead that are noted in the CRFs, datasets and case narratives, the clinical reviewer is having difficulties reconciling the attribution of causes of death.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
06/08/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Clinical Information Request -- Response Required
Date:	Monday, June 08, 2015 9:21:00 AM
Attachments:	INSPIRE.Deathwithin30days.IR.doc
Importance:	High

Dear Deb,

The Clinical reviewer has the following information request (IR) that we wish you to address before **COB, Friday, June 12, 2015**.

In reference to supporting study INSPIRE, Cause of Death during Study and within 30 days of Study Drug:

1. Please address the reviewer's questions in the attached table.

2. For all patients with causes of dead assessed as "Sudden Death" or "Death NOS" please provide in tabular format, the results of Mg++, Ca++ and K++ prior to death and corresponding management, if any.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

INSPIRE - Deaths within 30 days of last dose of study drug

N+ PC arm	Age/Sex	Days on study	Cause of death per CRF	Comments and IR to Lilly
156-5011	70M	31	PD	Patient died suddenly at home. Cause of death should be Sudden Death or Death NOS per narrative unless there is additional information to state otherwise. Please comment
156-5024	71M	103	PD	Patient had grade 4 hypomagnesemia and hypocalcemia in the last Chemistry result. Provide information concerning management of the electrolyte disturbance Provide justification for assessment of disease progression as cause of dead.
160-5011	60F	80	AE	Hospitalized with hypocalcemia, agitation Last Mg C2 d8 – Mg 0.26 mmol/L Lab Range: 0.77 - 1 Last dose Oct 26 full dose – Ca, Mg not checked - Provide in tab format Mg and Ca levels and management for this patient thru the study Provide information support for the diagnosis of Pulmonary Emboli
165-5008	65F	19	Unknown Died at home, unknown	Agree - Cause of death unknown
220-5004	73M	14	PD DEATH CAUSE UNKNOWN	Reviewer does not agree with the cause of dead attributed to PD (please provide justification). Narrative – Cause of death is stated as Unknown D1 5/11 last (b) (6), last (b) (6) Cycle 2 – no chemistry results in CRF. Hospitalized with diarrhea grade 2, weakness grade 4, died while in hospital. Provide laboratory results at during hospitalization and prior to death. CRF – disease progression (please provide documentation of progression)
222-	58M	5	PD	Patient died only 4 days after initiation

5003				of treatment. Provide circumstances of death Narrative states the cause of dead was "Sudden death due to disease progression" Cause of death should be "Sudden death" – please comment
226-5004	54M	60	PD	Progressive hypomagnesemia grade 4 per CRF and narrative. Provide information about management of hypomagnesemia. AE brain mets, progressive brain mets contributing to death.
275-5014	58F	11	DEATH NOS	Agree
320-5001	50M	10	CARDIORESPIRATORY FAILURE	Ccause of death should be Sudden Death or Death NOS per narrative. Please confirm. No relevant history Hepatitis C compensated, hx pulmonary Tb Labs 6/28 – unremarkable
324-5002	55F	7	PD	Sudden death at home 6 days after initial dose. Cause of death should be Sudden Death or Death NOS per narrative. Please comment. HTN Labs unremarkable
707-5005	74M	22	PD	No significant medical history C1d8 last dose 8/20 (b) (6) – died Died at home. PI stated PD, Sudden death at home (b) (6) after initial dose. Cause of death should be Sudden Death or Death NOS per narrative. Please comment.
PC ARM	**AGE/SEX**	**DAYS ON STUDY**	**CAUSE OF DEATH**	**Comments to Lilly**
160-5012	63F	42	Suspected Pulmonary embolism	Sudden death at home while walking. Cause of death should be Sudden Death or Death NOS per narrative. Please comment.
161-5001	78F	110	DEATH DUE TO	Sudden death at home Cause of death should be Sudden Death

			SUSPECTED PE	or Death NOS per narrative. Please comment.
384-5001	64F	114	PULMONARY EMBOLISATION	Sudden onset chest and back pain. Died the same day (at home or hospital?). Clinical dx PE was not confirmed. Cause of death should be Sudden Death or Death NOS per narrative unless there is additional information to state otherwise. Please comment.
406-5002	71M	2	PD	Reviewer disagree with PD– sudden death at home (b) (6) after 1st rx (b) (6) Sudden Death or Death NOS per narrative unless there is additional information to state otherwise. Please comment.
406-5013	51M	11	PULMONARY EMBOLI	Died at home Cause of death should be Sudden Death or Death NOS per narrative unless there is additional information to state otherwise. Please comment
707-5003	64M	75	PD	Cause of death should be Sudden Death or Death NOS per narrative unless there is additional information to state otherwise. Please comment

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/s/

MISSIRATCH BIABLE

06/08/2015

The RPM sent a clarifying email to the sponsor on June 8, 2015 at 10:16 AM pointing out the typo in item #2- should read K+ (correct) and not ++.

From: Pierce, Melanie
To: "deborah.Lynch@lilly.com"
Subject: Information request BLA 125547
Date: Friday, June 05, 2015 9:28:00 AM

Hello Ms. Lynch,

On behalf of Mimi Biable, I have the following information request for BLA 125547.

> Concerning the subgroup of subjects with 0% EGFR expression by IHC (24 in GC+N arm and 23 in GC arm), please provide in tabular format and line listing the incidence of all grade >/ 3 AEs and AEs of special interest.

Please respond by COB, Tuesday, June 9, 2015.

Thank you,

Melanie

Melanie B. Pierce
Chief, Project Management Staff (Acting)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Melanie.Pierce@fda.hhs.gov
Phone: 301-796-1273

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/s/

MELANIE B PIERCE
06/15/2015

From:	Biable, Missiratch (Mimi)
To:	"deborah.lynch@lilly.com"
Subject:	BLA-125547/0: Clinical Information Request -- Response Required
Date:	Tuesday, June 02, 2015 5:16:00 PM
Attachments:	SummaryInfo.TEs.doc
Importance:	High

Dear Deb,

The Clinical team has the following information request that we wish you to address before **COB, Friday, June 5, 2015**.

Concerning supporting study INSPIRE, please provide the ID # for the 16 subjects in the Neci+Pemetrexate/Cisplatin and the 5 subjects in the Pem/Cisplatin arm who died with defined and potential TE SAEs by Jan 15, 2011, leading to study closure by DSMB (please see attached table for additional information).

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

CP11-0805 and CP11-0806, summary information on thromboembolic SAEs, status 31Aug2010 vs 03Dec2010 vs 03Dec2010 revised vs 15Jan2011

		31Aug2010			03Dec2010			03Dec2010 revised[1]			15Jan2011		
		A[2]	B[2]	Δ% A-B	A[2]	B[2]	Δ% A-B	A[2]	B[2]	Δ% A-B	A[2]	B[2]	Δ% A-B
CP11-0805	**No. of patients randomized (total)**	319			518			518			595		
	No. (%)[4] of pat. with defined[5] and potential[6] TE SAEs												
	all	18 (11,3)	6 (3,8)	7,5	26 (10,0)	12 (4,6)	5,4	26 (10,0)	12 (4,6)	5,4	31 (10,4)[7]	12 (4,0)	6,4
	of them fatal	9 (5,6)	1 (0,6)	5,0	14 (5,4)	5 (1,9)	3,5	14 (5,4)	5 (1,9)	3,5	16 (5,4)[7]	5 (1,7)	3,7
	No. (%) of pat. with defined TE SAEs												
	• arterial	8 (5,0)	3 (1,9)	3,1	8 (3,1)	5 (1,9)	1,2	8 (3,1)	5 (1,9)	1,2	10 (3,4)[7]	5 (1,7)	1,7
	of them fatal	3 (1,9)	1 (0,6)	1,3	3 (1,2)	2 (0,8)	0,4	3 (1,2)	2 (0,8)	0,4	4 (1,3)[7]	2 (0,7)	0,6
	• venous	5 (3,1)	3 (1,9)	1,2	11 (4,2)	7 (2,7)	1,5	8 (3,1)	5 (1,9)	1,2	11 (3,7)	5 (1,7)	2,0
	of them fatal	1 (0,6)	0 (0,0)	0,6	4 (1,5)	3 (1,2)	0,3	1 (0,4)	1 (0,4)	0,0	2 (0,7)	1 (0,3)	0,4
	No. (%) of pat. with potential TE SAEs												
	• potential	5 (3,1)	0 (0,0)	3,1	7 (2,7)	0 (0,0)	2,7	10 (3,9)	2 (0,8)	3,1	10 (3,4)	2 (0,7)	2,7
	of them fatal	5 (3,1)	0 (0,0)	3,1	7 (2,7)	0 (0,0)	2,7	10 (3,9)	2 (0,8)	3,1	10 (3,4)	2 (0,7)	2,7
		A[3]	B[3]	Δ% A-B	A[3]	B[3]	Δ% A-B	A[3]	B[3]	Δ% A-B	A[3]	B[3]	Δ% A-B
CP11-0806	**No. of patients randomized (total)**	189			323			323			403		
	No. (%) of pat. with defined and potential TE SAEs												
	all	5 (5,3)	5 (5,3)	0,0	11 (6,8)	11 (6,8)	0,0	11 (6,8)	11 (6,8)	0,0	15 (7,4)[7]	13 (6,5)	0,9
	of them fatal	2 (2,1)	3 (3,2)	-1,1	4 (2,5)	4 (2,5)	0,0	4 (2,5)	4 (2,5)	0,0	6 (3,0)[7]	4 (2,0)	1,0
	No. (%) of pat. with defined TE SAEs												
	• arterial	1 (1,1)	2 (2,1)	-1,0	2 (1,2)	3 (1,9)	-0,7	2 (1,2)	3 (1,9)	-0,7	3 (1,5)	4 (2,0)	-0,5
	of them fatal	0 (0,0)	1 (1,1)	-1,0	0 (0,0)	1 (0,6)	-0,6	0 (0,0)	1 (0,6)	-0,6	0 (0,0)	1 (0,5)	-0,5
	• venous	2 (2,1)	1 (1,1)	1,0	5 (3,1)	5 (3,1)	0,0	5 (3,1)	5 (3,1)	0,0	6 (3,0)	6 (3,0)	0,0
	of them fatal	0 (0,0)	0 (0,0)	0,0	0 (0,0)	0 (0,0)	0,0	0 (0,0)	0 (0,0)	0,0	0 (0,0)	0 (0,0)	0,0
	No. (%) of pat. with potential TE SAEs												
	• potential	2 (2,1)	2 (2,1)	0,0	4 (2,5)	3 (1,9)	0,6	4 (2,5)	3 (1,9)	0,6	6 (3,0)[7]	3 (1,5)	1,5
	of them fatal	2 (2,1)	2 (2,1)	0,0	4 (2,5)	3 (1,9)	0.6	4 (2,5)	3 (1,9)	0.6	6 (3,0)[7]	3 (1,5)	1.5

[1] revised: reassignment of cases as per recommendation of the IRAC of 21Dec2010

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/s/

MISSIRATCH BIABLE
06/02/2015

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: BLA-125547/0: Clinical Pharmacology Information Request -- Response Required
Date: Tuesday, May 26, 2015 12:44:00 PM
Importance: High

Dear Deb,

The Clinical Pharmacology team has the information request (IR) that we wish you to address before **COB, Wednesday, Jun 3, 2015**.

This IR is regarding your immunogenicity data and evaluation of clinical impact of ADAs.

1. Immunogenicity data reporting: your proposed labeling states [redacted] (b) (4) However, your immunogenicity data report shows [redacted] (b) (4) incidence of treatment-emergent anti-necitumumab antibodies [33/814 (4.1%)]. Please clarify this discrepancy.

2. Impact of ADA on Safety of Necitumumab: in your BLA submission, in Module 2.5 Clinical Overview subsection 2.5.3.1.5. *Immunogenicity of Necitumumab*, you state "The development of ADAs, treatment-emergent ADAs, and neutralizing antibodies showed no correlation with safety outcomes. There was no relationship between IK, IRRS, or treatment-emergent adverse events (TEAEs). Overall, there was no association between development of ADA and any clinical evidence of IRRs in any of the patients." Please point out the location of these analyses in your BLA submission or provide report of these analyses.

3. Impact of ADA on PK of Necitumumab: in your BLA 2.5 submission, in Module 2.5 Clinical Overview subsection 2.5.3.1.5. *Immunogenicity of Necitumumab*, you state "The low immunogenic profile of necitumumab precludes a definitive analysis of the effect of development of ADAs and treatment-emergent ADAs on the PK of necitumumab." However, your plots of necitumumab exposure (or clearance) versus ADA status (positive or negative) show all ADA positive patients except one had low necitumumab exposure and higher clearance as compared to ADA negative patients. Please provide the magnitude of the difference in exposure and clearance and propose labeling language describe the impact of ADAs on necitumumab exposure.

Please provide line listing of patient ID and corresponding ADA status (binding and neutralizing antibodies), PK data, efficacy outcome (OS), IRR and major TEAEs in Trial JFCC (SQUIRE) for FDA review and further analyses.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/26/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Clinical Pharmacology Information Request -- Response Required
Date:	Friday, May 22, 2015 9:34:00 AM
Importance:	High

Dear Deb,

The Clinical Pharmacology team has the following information request that we wish you to address before **COB, Friday, May 29, 2015**.

This information request is in reference to your May 14, 2015 amendment containing a report entitled "Regulatory Response: Additional Exposure-Response Analysis," in response to the FDA's April 24, 2015 information request.

> Please submit the data and code that were used to generate Figure 3.4 (Necitumumab exposure-response curve for overall survival based on final model with original (left panel) versus updated patient population (right panel).

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/22/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Clinical Pharmacology Information Request -- Response Required
Date:	Friday, May 22, 2015 1:38:00 PM
Importance:	High

Dear Deb,

The Clinical Pharmacology team has another information request (IR) that we wish you to address before **COB, Friday, May 29, 2015**.

This IR is in reference to your May 14, 2015 amendment containing a report entitled "Regulatory Response: Additional Exposure-Response Analysis," in response to the FDA's April 24, 2015 IR.

> Please submit the data and code that were used to generate Figure APP.4.1 (Visual predictive check for overall survival model).

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/22/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Stat Information Request -- Response Required
Date:	Tuesday, May 19, 2015 3:43:00 PM
Importance:	High

Dear Deb,

The statistical reviewer has the following information request that we wish you to address by **Friday, May 29, 2015**.

Regarding your pivotal study SQUIRE (CP11-0806, I4X-IEJFCC), please provide a table summarizing the compliance rates (with the number of patients eligible to provide assessment) for LCSS and EQ-5D at each assessment period. Per the study protocol, LCSS and EQ-5D assessments were to be performed once at baseline (within 14 days of randomization), once during each cycle of study chemotherapy, and once every 6 weeks thereafter until disease progression.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/S-0

MID-CYCLE COMMUNICATION

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

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

We also refer to the teleconference between representatives of your firm and the FDA on May 8, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Missiratch (Mimi) Biable, M.S., R.A.C. (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: May 8, 2015

Application Number: BLA 125547/0
Product Name: Necitumumab
Indication: First-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) in combination with gemcitabine-cisplatin chemotherapy
Applicant Name: Eli Lilly and Company (Lilly)

Meeting Chair: Gideon Blumenthal
Meeting Recorder: Missiratch (Mimi) Biable

FDA ATTENDEES
Patricia Keegan, M.D., Director DOP2
Mimi Biable, M.S., Regulatory Health Project Manager
Lee Pai-Scherf, M.D., Medical Officer
Gideon Blumenthal, M.D., Medical Officer (TL and CDTL)
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Yaning Wang, Ph.D., Pharmacometrics (TL)
Sarah Dorff, Ph.D., Genomics
Rosane Charlab Orbach, Ph.D., Genomics (TL)
Lijun Zhang, Ph.D., Statistics
Rajeshwari Sridhara, Ph.D., Statistics (Division Director)
Whitney Helms, Ph.D., Non-Clinical (TL)
Ying-Xin Fan – Drug substance Reviewer
Yan Wang – Drug product Reviewer
Ralph Bernstein – assay validation (including immunogenicity) Product Reviewer
Chana Fuchs, Ph.D., Product (TL)
Lakshmi Narasimhan, Ph.D., Quality Micro DP
Otto Townsend, OSE/DMEPA
Wana Manitpisitkul, Safety Evaluator, OSE/OPE/DPV-II
Mona Patel, OSE/DRISK
Azada Hafiz, OMPT/ OSP/OPSA/PEIS

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese

APPLICANT ATTENDEES
Eli Lilly and Company
Timothy Cook, Vice President, Global Product Lead, Necitumumab

Paul Cornwell, PhD, Sr. Research Scientist, Non-Clinical Lead - Necitumumab
Jonathan Denne, PhD, Senior Director, Statistics
Richard Gaynor, MD, Sr. Vice President, Oncology Product Development
Gerrit Grau, MD, Sr. Medical Advisor, Global Patient Safety
Stephen Knowles, MD, Senior Director, Global Patient Safety
Raffael Kurek, MD, Medical Fellow, Global Medical Lead - Necitumumab
Deborah Lynch, Necitumumab Regulatory Lead, Global Regulatory Affairs
Shivani Nanda, Necitumumab Lead Statistician
Ruth Schulz, PhD, Associate Vice President, Global Regulatory Affairs-CMC
Katherine Sugarman, MD, Senior Director, Global Regulatory Affairs
Johan Wallin, PhD, Sr. Research Scientist, Clinical Pharmacology Lead

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

FDA conveyed the following issues to Lilly:

Clinical
As previously communicated to Lilly during the face to face/Type C meeting held on May 1, 2015, the main clinical issue is the benefit - risk assessment for necitumumab for the proposed indication.

FDA noted that the small magnitude of effect on overall survival (OS) observed in the SQUIRE trial when added to platinum doublet chemotherapy, the robustness of the effect on survival given the absence of an improvement in survival in the INSPIRE study in patients with non-squamous, NSCLC as well as the small to no effect on secondary endpoints within SQUIRE (PFS and ORR); the inability of the biomarker (EGFR overexpression by IHC) to predict clinical benefit; and increased risk of serious adverse drug reactions with the addition of necitumumab, including sudden deaths and thromboembolic events, hypomagnesemia and associated electrolyte imbalance, skin rash, infusion reaction, and eye disorders remain as the major concerns.

Nonclinical
FDA noted that adding a pregnancy warning to the necitumumab labeling is recommended to comply with new PLLR format.

Clinical Pharmacology
FDA asked why an infusion time of (b) (4) minutes for necitumumab administration is proposed in the package insert rather than the commonly used 60 minutes.

Lilly stated that the proposed (b) (4) minutes infusion time was based on (b) (4) Further, Lilly stated that (b) (4) 60 minutes is reasonable and will be taken into consideration given that it is clinically insignificant as the half-life of necitumumab is long.

3.0 INFORMATION REQUESTS

There is a pending Clinical Pharmacology information request, that was sent to Lilly on April 24, 2015 and the response date is May 15, 2015.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and the Division currently does not foresee the need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

FDA communicated to Lilly that this application will be taken to ODAC and will be presented on July 9, 2015.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Proposed labeling and any PMR/PMC request are due to Lilly by August 14, 2015.

The Late-Cycle Meeting between you and the review team is currently scheduled for August 24, 2015. We intend to send the briefing package to you approximately 10-12 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/

MISSIRATCH BIABLE
05/15/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Stat Information Request -- Response Required
Date:	Tuesday, May 12, 2015 2:58:00 PM
Importance:	High

Dear Deb,

The statistical reviewer has the following information request that we wish you to address by **Friday, May 22, 2015**.

Regarding your pivotal study SQUIRE (CP11-0806, I4X-IEJFCC), please provide the SAS programs (without macros) with adequate documentation to reproduce the results in:

1. CSR Table JFCC.11.2 for "Number of Metastatic Organ Systems" and

2. CSR Table JFCC.11.6 "Post-study systemic anticancer therapy."

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 24, 2015

From: Mimi Biable, M.S., RPM, DOP2/OHOP/CDER

Subject: Midcycle Meeting Minutes: Portrazza (necitumumab), BLA125547/0

Supplemental Application: BLA 125547/S-0

Product: Portrazza (necitumumab)

Submission Date: December 2, 2014

Received Date: December 2, 2014

PDUFA Date: December 2, 2015

Sponsor: Eli Lilly and Company (Lilly)

Attendees included: Patricia Keegan, Gideon Blumenthal, Lee Pai-Scherf, Monica Hughes, Mimi Biable, Lijun Zhang, Safaa Burns, Hongshan Li, Hong Zhao, Yaning Wang, Sarah Dorff, Margot Brower, Whitney Helms, Ying-Xin Fan, Yan Wang, Ralph Bernstein, Chana Fuchs, Candace Gomez-Broughton, Lakshmi Narasimhan, Latonia Ford, Otto Townsend, Mona Patel

Proposed Indication: First-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) in combination with gemcitabine-cisplatin chemotherapy

This midcycle meeting, for BLA 125547/S-0, was a face-to-face internal FDA meeting.

Discussion Items:

- Discussed the applicable studies/information submitted
  i. Clinical and Statistical - Efficacy & Safety
  ii. Clinical Pharmacology - PopPK analysis of data from 807 patients from 5 clinical trials including SQUIRE.
  iii. Pharmacology/Toxicology- MOA, Toxicology, Reproduction Toxicology, and Impurity Issues
  iv. OSI - Status of Clinical Site Inspections
  v. Quality and Quality Microbiology- Status of facility inspections

- Discussed the status of review of the data

- Discussed findings to date

Summary of Mid-cycle Discussion:

- Summary of discussion of applicable studies/information submitted

  i. SQUIRE Study (Pivotal Study 14X-IE-JFCC/IMCL CP11-0806):

  - Evaluated patients with stage IV squamous NSCLC with progression after platinum-based chemotherapy
  - Study was randomized 1:1 (**Arm A**: necitumumab 800 mg IV on Days 1 and 8 of each 3-week cycle, gemcitabine 1250 mg/m^2 IV on Days 1 and 8 of each 3-week cycle for a maximum of 6 cycles, cisplatin 75 mg/m^2 IV on Day 1 of each 3-week cycle for a maximum of 6 cycles; **Arm**: B gemcitabine 1250 mg/m^2 IV on Days 1 and 8 of each 3-week cycle for a maximum of 6 cycles, cisplatin 75 mg/m^2 IV on Day 1 of each 3-week cycle for a maximum of 6 cycles)
  - Randomization in this study was stratified by: Eastern Cooperative Oncology Group (ECOG) PS (0-1 vs. 2)status and geographic region
  - The majority of patients in SQUIRE discontinued study due to disease progression. Proportion of patients discontinuing treatment due to disease progression was 371 (68%) in the necitumumab plus gemcitabine-cisplatin chemotherapy arm vs 348 (64 %) in the gemcitabine-cisplatin chemotherapy only arm.
  - Primary endpoint: Overall Survival (OS). Secondary endpoints: Progression-Free Survival (PFS), Objective response rate (ORR), safety, pharmacokinetics (PK), Immunogenicity, EGFr expression.
  - Planned: Minimum of 844 OS events to demonstrate an OS with a HR of 0.80 (stratified log rank test, 2-sided α=0.05)
  - Enrolled: 1093 patients (of which only 36 were in USA), treated: 1079 patients of which 538 were randomized to receive necitumumab plus gemcitabine-cisplatin chemotherapy vs 531 patients randomized to receive gemcitabine-cisplatin chemotherapy alone

  ii. INSPIRE Study (Pivotal Study 14X-IE-JFCB/IMCL CP11-0805):

  - Evaluated patients with stage IV non-squamous NSCLC
  - Randomized, open-label, add-on trial of cisplatin 75 mg/m^2 Day 1 plus pemetrexed 500 mg/m^2 Day 1 every three weeks or cisplatin and pemetrexed (same schedule) in combination with necitumumab 800 mg Days 1 and 8 every three weeks
  - Primary endpoint: OS. Secondary endpoints: PFS, ORR, time-to-treatment failure, immunogenicity, and PK.
  - Sample size: 947 but enrolled only 633 patients due to study termination per recommendation from DSMB.

- Summary of discussion on the status of the review of the data/ findings to date:

  i. Review ongoing

  Clinical and Stats: The statistical review of the pivotal study SQUIRE efficacy data confirmed the results of primary endpoint (OS) and key secondary endpoints (PFS and ORR). Results from multiple sensitivity analyses demonstrated the robustness of treatment effect on OS by varying patient populations, sources of stratification factor data, or imputation approaches for patients lost to follow-up or withdrawing consent. In

addition, subgroup analyses showed that the treatment effect on OS is consistent across various subpopulations (age, gender, region, race, ECOG PS, and smoking history).

Preliminary review of safety data identified an imbalance in the number of sudden death/death of unknown cause in the treatment arm compared to control arm in the pivotal study SQUIRE. Untreated or suboptimally treated hypomagnesemia with associated electrolyte imbalance were identified in several patients and were likely to have directly caused or contributed to the deaths. One subject in the control arm with a history of recent atrial arrhythmia and septal infarct should not have been enrolled in the study. The incidence of thromboembolic events, both venous and arterial were found to be increased in the necitumumab arm. Our ongoing review of SQUIRE data has not found an increased number of fatalities in the necitumumab arm that can be directly attributed to these thromboembolic events. Hypomagnesemia and associated electrolyte imbalance, skin rash, infusion reaction, unspecified eye disorders occurred at a much higher incidence in the necitumumab arm. Detailed review of these and other events regarding time of onset, management and outcome of these and other events observed in the SQUIRE and INSPIRE trials as well as the 120-day safety update data submitted on April 14, 2015 will be the subject of continuing review in the coming months. Our findings on the imbalance in sudden deaths and possible contributing cause of death were communicated to the Applicant with a request for response (response received on April 30, 2015).

Pharm/Tox: Review ongoing and no major issues identified thus far. Pregnancy warning will be recommended to the necitumumab labeling to comply with new PLLR format.

Clinical Pharmacology: The PopPK analysis of data from 807 patients from 5 clinical trials including SQUIRE indicates that:

- The PKs of necitumumab are well described by an approximation of the target-mediated drug disposition model (TMDD).
- The Pop parameter estimates for total clearance (CLtot) and steady state volume of distribution (Vss) are 14 mL/h (CV=39%) and 7.0 L (CV=31%), respectively following the 800 mg given on Days 1 and 8 of every 3-week cycle. This corresponds to an elimination half-life of approximately 14 days. The predicted time to reach steady state was approximately 100 days.
- Gemcitabine and cisplatin did not affect the PK of necitumumab and vice versa.
- Age, gender, race, hepatic or Clcr has no effect on PK to warrant any dosage adjustment.
- In the 814 patients with both baseline and post-treatment samples, treatment-emergent ADAs was 4.1%, and neutralizing antibodies was 1.4%. The presence of ADA has no association with an infusion-related reaction (IRR). The numbers of patients with ADAs and treatment-emergent ADAs were insufficient to draw statistically supported conclusions regarding any potential impact on PKs of necitumumab.

Clinical Pharmacology/OSE: Proposed infusion time for necitumumab administration is (b) (4) minutes rather than at commonly used 60 minutes (b) (4) 60 min is reasonable and will be clinically insignificant as the half-life of necitumumab is long.

ii. Risk:

- REMS: At this point, the team does not anticipate that a REMS will be needed.
- PMC/PMRs: None anticipated.

CMC and Quality Microbiology: Review ongoing and no major issues identified thus far.

Status of OSI Inspections: DOP2 consult requested for 4 clinical sites to be inspected for study I4X-IE-JFCC (CP11-0806) conduct but due to the ban on all travel to Russia and Ukraine, only 3 clinical sites will be inspected. See table below.

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
Sponsor: Eli Lilly	Pending (Likely mid-May 2015)	ORA planning stage	N/A	N/A
CI: Ciuleanu, Tudor Eliade (ROU)	April 27th – May 1st, 2015	ORA planning stage	N/A	Site 321
CI: Crequit, Perrine (FRA)	April 20th-24th, 2015	Ongoing	No issues identified. Should close out NAI.	Site 133
CI: Dediu, Mircea (ROU)	April 20th-24th, 2015	Ongoing	No information to date.	Site 324

- **Upcoming Internal Team Meetings:**

1. Midcycle communication (telecon) with Lilly — May 8, 2015
2. Advisory Committee Meeting — July 9, 2015
   [AC practice sessions: June 16, 22, 29, 2015 (6/29- during Monday Rounds)]
3. Internal for Late Cycle Meeting (LCM) — August 6, 2015
   [LCM package due August 16, 2015]
4. LCM — August 24, 2015
5. Labeling and PMR/PMC meeting, if needed — TBD (after AC)
   [Labeling & PMRs/PMCs to Lilly: August 14, 2015]
6. Wrap-Up meeting — October 13, 2015

Review Due Dates:

Primary Review	8-8-2015
Secondary Review	8-15-2015
CDTL Review	10-21-2015
Division Director Review	11-10-2015
Office Director Review	12-2-2015

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/s/

MISSIRATCH BIABLE
05/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/S-0

MEETING MINUTES

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for "Necitumumab."

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2015. The purpose of the meeting was to discuss the benefit and risk assessment of BLA 125547/S-0; present additional data from the 120-day safety update; and discuss new safety analyses from SQUIRE (CP11-0806, I4X-IE-JFCC), "A Phase 3 Study of Necitumumab plus Gemcitabine and Cisplatin versus Chemotherapy Alone in the First-Line Treatment of NSCLC."

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-0154.

Sincerely,

{See appended electronic signature page}
Missiratch (Mimi) Biable, M.S., R.A.C. (U.S.)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: Friday, May 1, 2015, 3:00 PM - 4:00 PM
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: BLA 125547/S-0
Product Name: Necitumumab
Indication: Advanced or metastatic squamous non-small cell lung cancer
Sponsor/Applicant Name: Eli Lilly and Company (Lilly)

Meeting Chair: Patricia Keegan
Meeting Recorder: Mimi Biable

FDA ATTENDEES

Richard Pazdur, M.D., Director, OHOP
Patricia Keegan, M.D., Director, DOP2
Gideon Blumenthal, M.D., Clinical Team Lead, DOP2
Lee Pai-Scherf, M.D., Medical Officer, DOP2
Mimi Biable, M.S., Senior Regulatory Health Project Manager, DOP2
Shenghui Tang, Ph.D., Biostatistics Team Leader, OB/Biometrics V
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, DCPV
Hongshan Li, Ph.D., Pharmacometrics, Reviewer, DCPV
Margaret E Brower, Ph.D., Non-Clinical Reviewer, DHOT
Whitney Helms, Ph.D., Non-Clinical, Team Leader, DHOT

SPONSOR ATTENDEES

Eli Lilly and Company

Timothy Cook, Vice President, Necitumumab Global Product Team Lead
Jonathan Denne, Ph.D., Senior Director, Statistics
Richard Gaynor, M.D., Sr. Vice President, Oncology Product Development
Stephen Knowles, M.D., Senior Director, Global Patient Safety
Raffael Kurek, M.D., Medical Fellow, Global Medical Lead – Necitumumab
Deborah Lynch - Necitumumab Regulatory Lead, Global Regulatory Affairs
Robert Metcalf, Ph.D., Vice President, Global Regulatory Affairs and Quality
Katherine Sugarman, M.D., Senior Director, Global Regulatory Affairs

Clinical Advisor

Everett Vokes, M.D., Physician-in-Chief, University of Chicago Medicine and Biological Sciences

BACKGROUND

On April 1, 2015, Eli Lilly and Company (Lilly) submitted a type A meeting request to discuss the benefit and risk assessment of BLA 125547/S-0; present additional data from the 120-day safety update; and to discuss new safety analyses from the SQUIRE trial (CP11-0806, I4X-IE-JFCC). This meeting was requested as follow-up to the March 12, 2015, teleconference in which FDA expressed significant concerns regarding the benefit and risk profile of necitumumab for the proposed indication, and to the March 27, 2015, teleconference in which Lilly requested a face-to-face discussion with FDA to discuss the necitumumab data and a path forward. This meeting request was granted as a type C meeting based on the statement of purpose, objectives, and proposed agenda. The meeting package was submitted on April 15, 2015.

Based on information contained in the meeting package, Lilly maintained that the benefit and risk assessment for necitumumab is favorable for the proposed indication in squamous NSCLC. Lilly stated that the data represent advancement in the treatment of first-line squamous NSCLC and provide a therapeutic option to meet an important unmet medical need. Further, Lilly stated that evaluation of the safety date from SQUIRE and the additional studies demonstrate an acceptable and manageable safety profile for necitumumab. Lilly concluded that necitumumab's profile is consistent with other approved EGFR monoclonal antibodies and that necitumumab's profile allows for appropriate labeling to ensure safe and effective use.

SPONSOR QUESTIONS AND FDA RESPONSES

1. **SPONSOR QUESTION 1:** Can FDA please comment on the conclusions and next steps?

   Discussion during the meeting:
   Lilly acknowledged FDA's concerns about the necitumumab benefit-risk profile given the increased risk of sudden death and of venous (VTE) and arterial thromboembolic events (ATE) in the necitumumab-treated patients, which FDA has noted in prior discussions.

   Lilly presented the attached slide deck, containing an executive summary of the efficacy and safety data from SQUIRE and proposed next steps for the necitumumab application to address FDA's concerns. Specifically, Lilly proposes to address safety concerns through product labeling and proposed new language for inclusion in the Warnings and Precautions section regarding the increase risks of thromboembolic events, of hypomagnesemia and related electrolyte imbalances, and of sudden deaths.

   FDA reiterated that the concerns about the benefit-risk profile of necitumumab remain, considering the small magnitude of effect on overall survival (OS) observed in the SQUIRE trial when added to platinum doublet chemotherapy, questions regarding the robustness of the effect on survival given the absence of an improvement in survival in the study conducted in patients with non-squamous, NSCLC that is not explained by

differences in EGFR overexpression, and the increased risk of serious adverse drug reactions with the addition of necitumumab, including sudden deaths and thromboembolic events.

FDA informed Lilly that a final determination has not been made on whether this application required discussion at the June 2015 Oncologic Drugs Advisory Committee (ODAC). FDA will provide definitive advice regarding whether this application will be presented at the ODAC in the coming weeks.

PREA REQUIREMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

ISSUES REQUIRING FURTHER DISCUSSION

N/A

ACTION ITEMS

Action Item/Description	Owner	Due Date
Determine if BLA 125547/S-0 will be presented at ODAC	FDA	Week of May 11, 2015.

ATTACHMENTS AND HANDOUTS

- Lilly's presentation

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/s/

MISSIRATCH BIABLE
05/05/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Urgent Clinical Information Request -- Response Required
Date:	Monday, April 27, 2015 5:16:00 PM
Attachments:	Death.NOS.Suddendeaths.doc
Importance:	High

Dear Deb,

The Clinical reviewer has the following urgent information request that we wish you to address before **COB, Thursday, April 30, 2015**.

Based on the review of the information provided in the SQUIRE safety dataset, Clinical Study Report table JFCC.14.183, patients narratives and CRFs we have identified a total of 15 patients (12 in the GC + Necitumumab arm and 3 in the GC alone arm) who died while on study or within 30 days after the date of last dose with sudden death at home or unknown causes (see attached table).

We have the following information request:

1. Subject ID 159-6005 experienced grade 3 hypomagnesemia during the course of study (Mg++ at baseline 0.77 mmol decreased to 0.34 (grade 3) but did not receive magnesium replacement. Please provide documentation of treatment, if any.

2. Subject ID 160-6008 received oral magnesium replacement for grade 2 hypomagnesemia with no resolution during the course of study. Clarify if the patients received IV replacement (provide documentation).

3. Subject ID 273-6044 had grade 2 hypomagnesemia on Feb 22, 2012 and last seen on March 30, 2012. Please clarify if replacement was prescribed and a follow-up Mg level.

4. Subject ID 371-6005 experienced Grade 3 hypomagnesemia, hypokalemia and hypocalcemia AE on March 20, 2012. Action taken per CFR was none. Please confirm that no action was taken.

5. Subject ID 272-6004 serum magnesium level was 0.5 mg/dL (grade 4) on July 21, 2011. Please confirm that no action was taken.

6. Subject ID 643-6003 ECG at the time of enrollment on (b) (6) reports "atrial fibrillation with rapid ventricular response, left axis deviation, right ventricular conduction delay, septal infarct". Clarify why this patient was enrolled on study. Provide a follow-up ECG, if available.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Senior Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

GC + Necitumumab

	ID	Age	Day of last Rx (days on study)	Listed primary Cause of Death	Comment	Co-morbilities	
1	159-6005	61m	**13d** (85)	Unknown	Found death at home	COPD, HTN, ECG abnormal (LPHB)	Mg++ baseline 0.77, ↓ to 0.34 (grade 3) no treatment
2	160-6008	63wm	**19d** (111)	Unknown	Found death at home	COPD, alcohol, ulcer, Parkinson	Mg++ 0.51 (grade 2) despite oral replacement
3	224-6003	57wm	**8d** (245)	Unknown	Died at home	COPD, arteriosclero	↑ K+(6.0) 8 days prior
4	271-6016	64mw	**14d** (21)	Death NOS	Died at home.	COPD, HTN, DM	
5	273-6023	62wm	**11d** (59)	Unknown	Only registry office report of death	CAD	
6	273-6043	54wm	**28d** (148)	Unknown	Only registry office report of death	None relevant	
7	273-6044	80wm	**24d** (90)	Unknown	Only registry office report of death	HTN, chronic atrial fib., thrombosis	Grade 2 ↓ Mg++ (0.47)
8	277-6001	55wm	**9d** (16)	Death (NOS)	Sudden death at home	CAD, hx MI	
9	371-6005	62wm	**28d** (81)	Cardiac arrest	Died at home	COPD, HTN	Labs last visit ((b) (4) days prior to death): Mg 0.39 (grade 3), K 3.1 Ca 1.97 Action taken –None. CSR page 436/2759
10	406-6005	61wm	**8d** (31)	Unknown	Died at home	COPD	
11	542-6002	74asianm	**9d** (9)	Unknown	Sudden death at home	COPD	
12	653-6001	63wm	**3d** (10)	Sudden death	C-R arrest at home, no response to resuscitation	CAD, HTN, hx HD	

GC alone

	ID	Age	Day of last Rx (days on study)	Listed primary Cause of Death	Comment	Co-morbilities	
1	272-6004	62wm	**11d** (74)	Unknown	Sudden death at home	varices	Mg++ 0.5 mg/dL (1.3 – 2.7) 10 days prior to dead (b) (6)
2	324-6007	46wm	**6d** (6)	Death NOS	Sudden death at home	Hx meningitis, DM	
3	643-6003	56b m	**3d** (3)	Unknown	Family found patient dead	Atrial fibrillation/ arrhythmia prior to enrollment	New onset atrial fib (grade 3) 3 weeks prior to enrollment Last ECG (b) (6) – atrial fibrillation with rapid ventricular response, left axis deviation ,

							right ventricular conduction delay, septal infarct

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/s/

MISSIRATCH BIABLE
04/27/2015

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: BLA-125547/0: Clinical Pharmacology Information Request -- Response Required
Date: Friday, April 24, 2015 3:55:00 PM
Importance: High

Dear Deb,

This email is in reference to the exposure-response analyses included in BLA125547 for necitumumab.

The Clinical Pharmacology team has the following information request that we wish you to address by **COB, Friday, May 15, 2015**:

1. In Study JFCC, 62 patients on necitumumab treatment arm were excluded from the exposure-response analysis. Predict the Css (steady-state mean concentration) for each of these 62 patients based on their dosing history and the final population pharmacokinetics model and submit the data and code for Css prediction.

2. Include these 62 patients in the exposure-response datasets and update all exposure-response analyses. Submit the datasets and the results for the updated exposure-response analyses.

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
04/24/2015

From:	Biable, Missiratch (Mimi)
To:	"Deborah Lynch"
Subject:	BLA-125547/0: Clinical Information Request -- Response Required
Date:	Thursday, April 16, 2015 11:55:00 AM
Importance:	High

Dear Deb,

The Clinical reviewer has the following information request that we wish you to address before **COB, Tuesday, April 21, 2015**.

After review of the meeting package for the May 1, 2015 face to face meeting, received on Wednesday, April 15, 2015, please provide the following additional information:

1. A side-by-side comparison of EGFR protein expression (total % positive and by H-score) findings for SQUIRE and INSPIRE population

2. A side-by-side comparison of the baseline risk factors for VTE and ATE between SQUIRE and INSPIRE population

3. A side-by-side comparison of the incidence and severity (by NCI-CTCAE grade and severity) of VTE and ATE between SQUIRE and INSPIRE

Please provide your response via email to me and follow that with a formal submission to your BLA.

Confirm receipt of this communication and let me know if you have any questions.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
04/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/S-0

INFORMATION REQUEST

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) dated December 2, 2014, received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for "Necitumumab."

We are reviewing the chemistry, manufacturing and controls section of your application and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA:

Labeling

1. The proposed labeling claims that reconstituted drug product may be stored for up to 24 hours at 2-8°C. Please submit microbiological studies in support of the 24 hour post-reconstitution storage time at 2-8°C. Describe the test methods and results that employ a minimum countable inoculum ((b) (4) CFU) to simulate potential microbial contamination that may occur during reconstitution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-reconstitution storage period is not more than (b) (4) hours at 2-8°C.

Container closure integrity test

2. Please clarify if negative controls are included in the dye ingress test and if they are exposed to the test conditions.

3. You have provided the CCI dye ingress test results for batches manufactured at both (b) (4) and Lilly sites. Please clarify if the challenge conditions, positive control preparation, sensitivity of the method (LOD) are the same for both sites.

Necitumumab drug product manufacturing process and process controls

4. Please specify (b) (4) during the commercial manufacturing process.

5. Please revise the Table 3.2.P.3.4.1, (b) (4)

6. A sample volume (b) (4) is used for the endotoxin testing of the formulation (b) (4) and formulated bulk drug product. Please provide justification.

Process Validation

7. The acceptance criteria and results for the (b) (4) test are listed (b) (4) in the Section 3.2.P.3.5. Please provide the actual values for the acceptance criteria and results for the (b) (4) test. Also, clarify if the testing was performed with drug product (b) (4)

8. It is not clear from the submission (b) (4) Please indicate (b) (4), 3.2.P.3.5.2.2.2.1, 3.2.P.3.5.2.2.2.2, and 3.2.P.3.5.2.2.2.3. In addition, clarify (b) (4)

9. You have provided the recent requalification summary results (b) (4) Please provide qualification reports, including summary (b) (4)

10. (b) (4)

11. Please provide information and summary data (b) (4)

12. Please provide validation information and summary data (b) (4) under worst case conditions. In your response,

a. Describe [redacted]

b. Include [redacted]

c. Include a comparison of the validation and production operating parameters [redacted]

13. For the media fill lots C038065, C038067, C038068, and C288794, please provide

a. The media fill durations

b. The list of organisms and conditions used for media fill growth promotion verification and the results from growth promotion tests.

c. A comparison of necitumumab production parameters to that of media fills performed with the necitumumab container closure system.

14. The viability study demonstrated [redacted]. Please consider [redacted]

15. Please clarify [redacted]

16. Provide the [redacted] study for the Necitumumab Drug Product Final Container Finished Vials.

Analytical procedures

17. Provide the details of bioburden testing and method qualification summary data from 3 formulated bulk drug product lots.

18. Your Endotoxin Hold Time Study [redacted] Please clarify if the hold time of the DP endotoxin samples was limited to < [redacted] hours [redacted]

19. Please provide the lot numbers of the Necitumumab drug product used for the sterility test method verification study.

Container Closure system

20. Please provide endotoxin acceptance criteria for the [redacted] stoppers.

Stability

21. Provide implement CCI testing at (b) (4) month time point in the stability protocol.

Endotoxin Specification

22. Please clarify if the endotoxin contribution from the 0.9% saline was considered when setting the release endotoxin specification of the drug product.

We request a response by April 20, 2015, in order to continue our evaluation of your BLA.

If you have any questions, please contact Mimi Biable, Senior Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Patricia Hughes, Ph.D.
Acting Branch Chief
Division of Microbiology Assessment
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

PATRICIA F HUGHES TROOST
04/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/S-0

MEETING REQUEST GRANTED

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

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

We also refer to your April 1, 2015, correspondence requesting a type A meeting to discuss your plans for this BLA and present additional data from the pivotal phase 3 study, SQUIRE as well as data from your ongoing phase 2 studies. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: May 1, 2015
Time: 3:00 PM- 4:00 PM EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Invited CDER Participants: Lee Pai-Scherf, M.D.
Gideon Blumenthal, M.D.
Patricia Keegan, M.D.
Richard Pazdur, M.D.
Missiratch (Mimi) Biable, M.S.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Please e-mail me any updates to your attendees at Missiratch.biable@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government

Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Mimi Biable, 6-0154.

Please refer to the following link for visiting the White Oak Campus:
http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/ucm241748.htm

Submit background information for the meeting (one electronic copy to the application and 5 desk copies to me). If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by April 15, 2015, we may cancel or reschedule the meeting.

Submit the 5 desk copies to the following address:

Mimi Biable
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2191
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-0154.

Sincerely,

{See appended electronic signature page}
Missiratch (Mimi) Biable, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Eli Lilly and Company
MEETING START DATE AND TIME	May 1, 2015, 3:00 pm
MEETING ENDING DATE AND TIME	May 1, 2015, 4:00 pm
PURPOSE OF MEETING	Type C Guidance
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22 Room 1311
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Missiratch Biable Regulatory Health Project Manager WO22 Room 2191 301-796-0154
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MISSIRATCH BIABLE
04/08/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 27, 2015

Application Number: BLA 125547/0
Product Name: Necitumumab
Sponsor/Applicant Name: Eli Lilly and Co (Lilly)

Proposed Indication: First-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer

Subject: Follow-up discussion with Lilly regarding the status of the Necitumumab BLA

FDA Participants:
Division of Oncology Products 2
Lee Pai-Scherf, M.D.
Gideon Blumenthal, M.D.
Patricia Keegan, M.D.
Richard Pazdur, M.D.
Dianne Spillman
Monica Hughes, M.S.
Missiratch (Mimi) Biable, M.S.

Sponsor Participants:
Richard Gaynor, M.D. – Sr. Vice President, Oncology Product Development
Robert Metcalf, Ph.D. – Vice President, Global Regulatory Affairs and Quality
Timothy Cook – Vice President, Thoracic Products and Necitumumab Global Product Team Lead
Katherine Sugarman, M.D. – Senior Director, Global Regulatory Affairs

1.0 BACKGROUND:

In follow up to the March 12, 2015 teleconference, FDA held a teleconference with Lilly to discuss the status of the necitumumab biologic license application (BLA), submitted on December 2, 2014 for the use of necitumumab for the first-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer.

2.0 DISCUSSION:

Lilly stated that after careful consideration following the March 12, 2015 teleconference, Lilly would like to request a face-to-face discussion with FDA to go over the application data and find a path forward for this application. FDA reminded Lilly that the review clock is still ongoing. Lilly agreed to provide a summary data prior to the meeting to facilitate the discussion.

3.0 ACTION ITEMS:

FDA will schedule a meeting with Lilly in the coming weeks.

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/s/

MISSIRATCH BIABLE
04/01/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 12, 2015

Application Number: BLA 125547/0
Product Name: Necitumumab
Sponsor/Applicant Name: Eli Lilly and Co (Lilly)

Proposed Indication: First-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer

Subject: Discuss the status of the Necitumumab BLA given recent approvals in squamous NSCLC

FDA Participants:
Division of Oncology Products 2
Lee Pai-Scherf, M.D.
Gideon Blumenthal, M.D.
Joseph Gootenberg, M.D.
Richard Pazdur, M.D.
Missiratch (Mimi) Biable, M.S.

Sponsor Participants:
Richard Gaynor, M.D. – Sr. Vice President, Oncology Product Development
Robert Metcalf, Ph.D. – Vice President, Global Regulatory Affairs and Quality
Timothy Cook – Vice President, Thoracic Products and Necitumumab Global Product Team Lead
Katherine Sugarman, M.D. – Senior Director, Global Regulatory Affairs

1.0 BACKGROUND:

Lilly submitted a biologic license application (BLA) on December 2, 2014 for the use of necitumumab for the first-line treatment, in combination with gemcitabine-cisplatin chemotherapy, of patients with locally advanced or metastatic squamous non-small cell lung cancer.

2.0 DISCUSSION:

On March 12, 2015 FDA held a teleconference with Lilly to discuss the status of the Necitumumab BLA given recent approvals in squamous NSCLC. FDA discussed the recent approval of nivolumab in second line squamous NSCLC, in which nivolumab, in a head-to-head trial against docetaxel, demonstrated a large magnitude of prolongation in overall survival. FDA stated that given the magnitude of survival benefit in the second line setting, this will impact the standard of care for squamous lung cancer.

As previously discussed at the necitumumab applicant orientation meeting, FDA remains concerned about the benefit-risk profile of necitumumab, considering the relatively small magnitude of OS benefit observed in the SQUIRE trial when added to platinum doublet chemotherapy, and the negative study in adenocarcinoma NSCLC, as well as the serious adverse event profile, including venous and arterial thromboembolic events.

FDA stated that this BLA will be discussed at ODAC. FDA's concerns about the necitumumab benefit-risk profile and risk of venous and arterial thromboembolic events will be discussed, particularly in light of the changing standard of care with an approved immunotherapy in squamous NSCLC.

3.0 ACTION ITEMS:

Lilly will take this information under consideration and will notify FDA should they decide not to continue to pursue this application.

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/s/

MISSIRATCH BIABLE
03/19/2015

PeRC Meeting Minutes
February 11, 2015

PeRC Members Attending:
Lynne Yao
Rosemary Addy (Non-Responsive reviews only)
George Greeley
Ruthanna Davi
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Peter Starke
Daiva Shetty
Andrew Mulberg
Greg Reaman
Andrew Mosholder (Non-Responsive reviews only)
Hari Cheryl Sachs
Julia Pinto
Olivia Ziolkowski
Gilbert Burckhart
Kevin Krudys
Barbara Buch
Rachel Witten
Dianne Murphy
Maura O'Leary (Non-Responsive reviews only)
Kim Dettlebach Non-Responsive
Sonal Vaid Non-Responsive
Nisha Jain Non-Responsive
Adrienne Hornatko-Munoz (Non-Responsive reviews only)

Agenda

9:00	NDA	Non-Responsive		
9:20	NDA			
9:40	IND			
10:00	IND			
10:20	IND			
10:30	IND			
10:50	NDA			
	NDA			
	IND			
	BLA	*125547*	*Portrazza (necitumumab) Full Waiver*	*For the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).*
	BLA	Non-Responsive		
	IND			
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Non-Responsive

Portrazza (necitumumab)

- Proposed Indication: For the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).

- PeRC Recommendations:
  - The PeRC agreed with the plan for full waiver.

Non-Responsive

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/s/

GEORGE E GREELEY
02/23/2015

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: Necitumumab/BLA 125547- Nonclinical Information Request-- Response Required
Date: Monday, February 23, 2015 6:11:00 PM
Importance: High

Dear Deb,

The Nonclinical reviewer has the following information request regarding the antibody evaluation that was conducted for Study (b) (4) 023.07 (26-week toxicity study in monkeys).

In your submission, you documented that a separate antibody evaluation was conducted on samples collected prior to terminal and recovery necropsy. These data were not submitted with the study report. Please provide this information

Please confirm receipt and let me know should you have any questions.

Thank you,

Missiratch (Mimi) Biable, M.S., R.A.C (US)

Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
02/23/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125547

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Eli Lilly and Company
33 ImClone Drive
Branchburg, New Jersey 08876

ATTENTION: Deborah Lynch
AVP, Regulatory Affairs

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) dated and received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for Necitumumab, 800 mg/50 mL (16 mg/mL).

We also refer to your correspondence, dated and received December 2, 2014, requesting review of your proposed proprietary name, Portrazza.

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

If any of the proposed product characteristics as stated in your December 2, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Missiratch Biable, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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/

TODD D BRIDGES
01/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/S-0

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologics License Application (BLA) dated December 2, 2014, received December 2, 2014, submitted under section 351(a) of the Public Health Service Act for "Necitumumab."

We also refer to your amendment dated January 20 and 28, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is December 2, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 14, 2015. In addition, the planned date for our internal mid-cycle review meeting is April 24, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

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

We request that you submit the following information by February 6, 2015:

Clinical

1. Concerning Patient Narratives and Case Report Forms (CRFs), for each study, provide a Table of Significant and Notable Patients (ToSNP) consisting of a listing of all patients who experienced notable events with links to narratives and CRFs for those patients. Categorize the narratives and CRFs as:

    a. Death while on study or within 30 days after the date of last dose.

    b. Patients who died while experiencing an ongoing treatment related adverse event at the time of death, regardless of the date of the last study dose.

    c. Discontinuation due to adverse events (AEs)

    d. Suspected unexpected serious AEs

    e. Thromboembolic serious adverse events (SAEs) and SAEs of potential thromboembolic origin (i.e. fatal and nonfatal cases where thromboembolism was not proven but could be suspected based on the data available [including cases of unexplained death]) from the Lilly safety database, defined by the Global Patient Safety physician as per case review applying medical judgment and using standardized MedDRA queries for embolic/thrombotic events as a supportive tool

2. In the pivotal study 14X-IE-JFCC/IMCL CP11-0806 (SQUIRE), only 35 out of 1093 patients were from a U.S. investigational site. Provide your rationale for assuming the foreign data will be applicable to the U.S. population/practice of medicine.

If the items listed above have been previously submitted, identify the section and page where the information can be found.

Quality Microbiology

3. Please provide the most recent drug substance manufacturing schedule for inspection planning purposes by February 6, 2015.

PRESCRIBING INFORMATION

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

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

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

4. White space should be present before each major heading in HL. There is no white space between the HL Heading and HL Limitation Statement. There is no white space between the product title and Initial U.S. Approval.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 19, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Ms. Missiratch (Mimi) Biable, Senior Regulatory Health Project Manager, at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
01/30/2015

From: Biable, Missiratch (Mimi)
To: "Deborah Lynch"
Subject: Necitumumab/BLA 125547- Nonclinical Information Request-- Response Required
Date: Friday, January 23, 2015 9:12:00 AM
Importance: High

Dear Deb,

The formatting and spacing in Study (b) (4) 023.07 needs to be corrected. There are odd spaces in the text and tables and a problem making the tables unreadable. Submit a corrected version of this report by January 30th, 2015. In the resubmission describe any other changes made to the final report.

Please confirm receipt and let me know should you have any questions.

Thank you,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
01/23/2015

Initial Planning Meeting Minutes
January 12, 2015

BLA 125547/0

Product:	Necitumumab
Proposed Proprietary Name:	Portrazza
Submission Date:	December 2, 2014
Received Date:	December 2, 2014
Sponsor:	Eli Lilly and Co. (Lilly)

Proposed Indication: Necitumumab in combination with gemcitabine-cisplatin chemotherapy for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.

eCTD submission: SDN 001 (Non-Clinical); SDN 002 (Clinical) and SDN 003 (CMC and proprietary name request): EDR Location: \\CDSESUB1\evsprod\BLA125547\125547.enx

Current Review Team for BLA 125547:
Patricia Keegan, M.D., Director, DOP2 — ATTENDED
Lee Pai-Scherf, M.D., Clinical — ATTENDED
Gideon Blumenthal, M.D, Clinical (TL and CDTL) — ATTENDED
Monica Hughes, M.S., CPMS, DOP2
Mimi Biable, M.S., Regulatory Health Project Manager— ATTENDED
Jennie Chang, Pharm. D. Acting Associate Director for Labeling
Lijun Zhang, Ph.D., Statistical Reviewer— ATTENDED
Shenghui Tang, Ph.D., Statistics (TL)
Safaa Burns, Ph.D., Clinical Pharmacology — ATTENDED
Hong Zhao, Ph.D., Clinical Pharmacology (TL) — ATTENDED
Margaret E Brower, Ph.D., Non-Clinical — ATTENDED
Whitney Helms, Ph.D., Non-Clinical (TL) — ATTENDED
Teicher Agosto, ONDQA, Regulatory Business Process Manager (RBPM)
Audrey Jia, Ph.D., CMC — ATTENDED
Chana Fuchs, Ph.D., CMC (TL) — ATTENDED
Jibril Abdus-Samad, OBP
Candace Gomez-Broughton, Ph.D., Quality Micro DS — ATTENDED
Lakshmi Narasimhan, Ph.D., Quality Micro DP — ATTENDED
Patricia Hughes, Ph.D., Quality Micro (TL) — ATTENDED
Frances Fahnbulleh, OSE RPM— ATTENDED
Otto Townshend, OSE/DMEPA— ATTENDED
Alice Chi-Ming Tu, OSE/DMEPA (TL)
Mona Patel, OSE/DRISK — ATTENDED
Naomi Redd, OSE/DRISK (TL) — ATTENDED
Lauren Iacono-Connor, OSI
Susan Thompson, OSI
Nazia Fatima, OPDP — ATTENDED

Additional Attendees:
John Metcalfe, Brach Chief, OPS
Latonia Ford, *OSE RPM*

Agenda Items:

*A standard reminder that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss .

1. Review Status:

a. Priority Review requested--- however we will be granting a standard review
b. User Fee Paid
c. Categorical Exclusion from environmental assessment requested
d. Requested full waiver of pediatric studies
e. Proprietary Name Review request received 12-2-2014 –review ongoing in DMEPA
f. Risk Management Plan included in this NME application

2. Dates for Milestones and for When Letters Must Issue:

Milestone (PDUFA V-- Standard review)	**Due**
Acknowledgment Letter	12-16-2014 *Issued 12-8-2014*
Filing Action Letter	1-31-2015
Deficiencies Identified Letter (74 Day Letter)	2-14-2015
Send proposed labeling/PMR/PMC/REMS to applicant	8-14-2015
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 8-8-2015 8-15-2015 10-21-2015 11-11-2015 12-2-2015
FINAL Action Letter Due	12-2-2015

3. Consults/Collaborative Reviewers:

OPDP	Nazia Fatima, OPDP (Marybeth Toscano covering future meetings)
OSE	Frances Fahnbulleh - OSE RPM

	Mona Patel- DRISK Otto Townsend - DMEPA
Quality Micro/OMPQ	Candace Gomez-Broughton- DS Lakshmi Narasimhan - DP
QT-IRT	Consult sent 1-9-2015
OSI	Lauren Iacono-Connor assigned
Pediatric Page/PeRC	PeRC review date scheduled - 2-11-2015
SGE's or Patient Representatives	Are SGE's Needed? See discussion note under item 4 (ODAC)

Are there any additional consults needed? None

Discussion: No additional consult at this time. RPM to follow up with OSI to see if Lilly submitted the dataset in the preferred format for site inspection assignments. Clinical site identification/selection meeting to be scheduled.

4. ODAC Needed?

Discussion: this application will be taken to ODAC given the one positive and one negative trial results. Patient Reps for ODAC will be needed. RPM to follow-up with Dianne Spillman (OHOP IO) regarding the ODAC date, currently tentatively on the calendar for June 17, 2015.

5. Upcoming Internal Team Meetings:

Applicant Orientation Presentation: Friday, January 23, 2015

Filing Meeting scheduled for: Friday, January 23, 2015

Team Meetings and frequency of team meetings:
Discussion: Monthly team meeting to be scheduled by RPM

Mid-Cycle Meeting scheduled for**:** April 24, 2015

[Midcycle communication (telecon) to sponsor:
Scheduled for: May 8, 2015

Labeling meetings:
Discussion: Will hold off on labeling meetings until after ODAC

PMR/PMC meeting, if needed: TBD

Internal meeting for Late Cycle Meeting: TBD

Late Cycle Meeting: TBD

Wrap-up Meeting: TBD

6. Other Issues/Concerns:

Discussion: OPQ reorg including how CMC IRs will be communicated to the sponsor was briefly discussed.

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/s/

MISSIRATCH BIABLE
01/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/0

BLA ACKNOWLEDGMENT

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product:	Necitumumab
Date of Application:	December 2, 2014
Date of Receipt:	December 2, 2014
Our Reference Number:	BLA 125547/0

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 31, 2015, in accordance with 21 CFR601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0154.

Sincerely,

{See appended electronic signature page}
Missiratch (Mimi) Biable, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MISSIRATCH BIABLE
12/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102512

MEETING PRELIMINARY COMMENTS

Eli Lilly and Co.
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Necitumumab."

We also refer to your August 15, 2014, correspondence, received August 15, 2014, requesting a meeting to discuss the results of exploratory analyses investigating the role of EGFR protein expression in the study results from SQUIRE (CP11-0806, I4X-IE-JFCC), a Phase 3 study of necitumumab plus gemcitabine and cisplatin versus chemotherapy alone in the first-line treatment of NSCLC.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type C
Meeting Category:	Other; Clinical
Meeting Date:	November 24, 2014
Application Number:	IND 102512
Product Name:	Necitumumab
Indication:	Treatment of non-small cell lung cancer (NSCLC)
Sponsor/Applicant Name:	Eli Lilly and Co. (Lilly)

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 24, 2014, between Lilly and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On August 15, 2014, Lilly submitted a meeting request (SDN 538) to discuss the results of the exploratory analyses investigating the role of EGFR protein expression obtained in the Phase 3 SQUIRE trial (CP11-0806, I4X-IE-JFCC). The meeting package was submitted on October 22, 2014 as SDN 543.

The SQUIRE trial investigated the use of necitumumab plus gemcitabine and cisplatin (GC + N) versus chemotherapy (GC) alone in the first-line treatment of 1093 randomized patients with Stage IV squamous non-small cell lung cancer (NSCLC). The study met its primary endpoint by

demonstrating a statistically significant improvement in overall survival (OS) in the necitumumab arms versus the control arm. The median OS was 11.5 months in the GC + N arm versus 9.9 months in the GC arm. A pre-BLA meeting was held on June 23, 2014, and the first module of the rolling BLA was submitted on October 22, 2014, with the final module to be submitted in December 2014.

EGFR protein expression was evaluated in the SQUIRE study using the Dako EGFR pharmDx Kit which is marketed as an aid in identifying colorectal cancer patients eligible for treatment with cetuximab or panitumumab. Samples evaluable for EGFR protein expression were available from a total of 982 patients (89.8%) which included 486 patients in the GC+N arm and 496 patients in the GC arm.

As part of the pre-specified statistical analysis plan, the primary analysis of the EGF IHC data dichotomized H-scores into 2 mutually exclusive subgroups: H score $\geq$ 200 and H-score < 200 (on a scale of 1-300). The cutpoint value of 200 was chosen based on data, where a subgroup of NSCLC patients with EGFR H-score $\geq$200 were shown to have an OS hazard ratio indicating greater cetuximab benefit relative to the HR within the group of patients with H-score < 200.

There were no relevant differences in terms of baseline demographics and disease characteristics between arms or between the subset of patients included in the analysis and the intent-to-treat population. Efficacy outcomes in the EGFR IHC population closely mirrored those in the ITT population. The large majority of patients (95.2%) had tumor samples expressing EGFR; only 4.8% had tumors with undetectable EGFR protein. The H-score was evenly distributed in both arms. An analysis of OS and progression-free survival (PFS) by EGFR subgroup (H-score $\geq$ 200 vs. H-score < 200) showed inconsistent results with no treatment by cutpoint interaction; H-score with a cut-off of 200 was thus not predictive of efficacy outcomes in this study.

Patients whose tumors lacked detectable EGFR expression by IHC (24 in the GC + N arm; 23 in the GC arm), did not appear to benefit in terms of OS or PFS from the addition of necitumumab to gemcitabine and cisplatin compared to gemcitabine and cisplatin alone. Results of the key efficacy endpoints by percent of EGFR expression by IHC (0% vs. > 0% positive) are summarized in the following table provided by Lilly.

**Table 4.5. Summary of Efficacy Parameters by Percent Positive (>0 vs. 0)
TR Population
SQUIRE**

	Percent Positive >0		Percent Positive =0[d]	
	GC+N N = 462	GC N = 473	GC+N N = 24	GC N = 23
Overall Survival				
p-value[a]	0.004		0.072	
HR (95% CI)[b]	0.81 (0.70, 0.93)		1.86 (0.94, 3.65)	
Median – months	11.73	9.99	6.47	17.35
Interaction p-value[a]	0.018			
Progression-free Survival				
p-value[a]	0.015		0.611	
HR (95% CI)[c]	0.83 (0.72, 0.97)		1.19 (0.61, 2.30)	
Median– months	5.72	5.49	4.24	5.59
Interaction p-value[a]	0.305			

Abbreviations: CI = confidence interval; Cis = cisplatin; EGFR = epidermal growth factor receptor; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; Gem = gemcitabine; HR = hazard ratio; N = number of patients; Neci = necitumumab; TR = translational research.

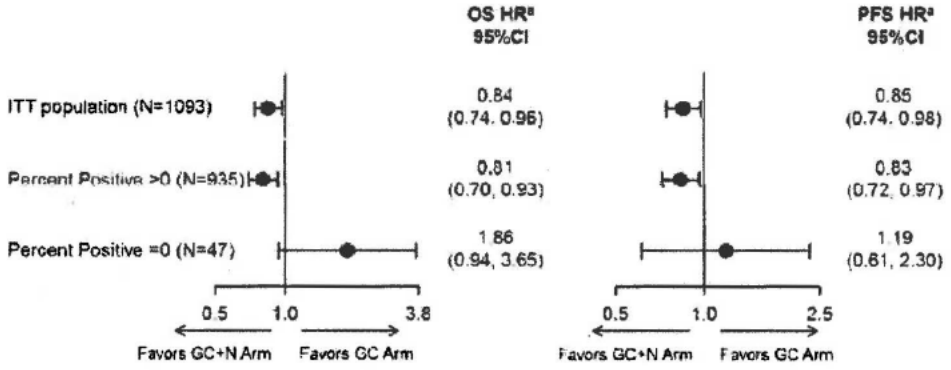
a p-Value obtained from Likelihood Ratio chi-square test of significance.

b Hazards ratio for death from any cause comparing Gem/Cis + Neci to Gem/Cis within protein expression subgroup. Hazards ratio greater than 1 indicates increasing hazards with Gem/Cis + Neci compared to Gem/Cis within protein expression subgroup.

c Hazards ratio for death from any cause or progressive disease comparing Gem/Cis + Neci to Gem/Cis within protein expression subgroup. Hazards ratio greater than 1 indicates increasing hazards with Gem/Cis + Neci compared to Gem/Cis within protein expression subgroup.

d Zero percent positive is equivalent to H-score=0 for EGFR staining.

Figure 4.7. Forest plots of OS and PFS by Percent Positive (> 0 vs. 0) (TR population), SQUIRE



Based on the above findings, Lilly would like to discuss (b) (4)

QUESTIONS AND FDA RESPONSES

1. (b) (4)

Does FDA agree (b) (4) *?*

FDA Response:
No. (b) (4)

2. Does FDA have any comments (b) (4) *?*

FDA Response:
(b) (4)

3. Can FDA please comment on the proposed (b) (4)
(b) (4)

[redacted] (b) (4)

FDA Response:
Please refer to FDA's responses to Questions 1 and 2.

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/s/

SHARON K SICKAFUSE
11/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547/0

BLA PRESUBMISSION ACKNOWLEDGEMENT

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

We have received your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product:	Necitumumab
Date of Submission:	October 22, 2014
Date of Receipt:	October 22, 2014
Our Reference Number:	BLA 125547/0

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-0154.

Sincerely,

{See appended electronic signature page}
Missiratch (Mimi) Biable, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MISSIRATCH BIABLE
10/30/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 102512

ImClone Systems, Incorporated
Attention: Cheryl Anderson
Senior Vice President, Regulatory Affairs
33 ImClone Drive
Somerville, NJ 08876

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Human Monoclonal Antibody IgG1 (IMC-11F8, ImClone) to Epidermal Growth Factor Receptor (EGFR)."

We also refer to the meeting held on October 23, 2008, between representatives of your firm and this agency. A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Meeting Type:	Teleconference
Meeting Category:	Pre-IND/EOP2
Meeting Date and Time:	October 5, 2008; 1:00PM-2:00PM EST
Meeting Location:	White Oak Bldg 22, room 2201
Application Number:	102512
Product Name:	Human Monoclonal Antibody IgG1 (IMC-11F8, ImClone) to Epidermal Growth Factor Receptor (EGFR)
Received Briefing Package	August 19, 2008
Sponsor Name:	ImClone Systems Incorporated
Meeting Requestor:	Cheryl Anderson
Meeting Chair:	Patricia Keegan, Acting Medical Team Leader
Meeting Recorder:	Raymond Chiang

FDA Attendees
Office of Oncology Drug Products
Division of Biologic Oncology Products

Richard Pazdur	Office Director
Patricia Keegan	Division Director
Genevieve Schechter	Medical Officer
Michael Orr	Pharmacology/Toxicology Reviewer
Anne M. Pilaro	Pharmacology/Toxicology Supervisor
Raymond Chiang	Regulatory Project Manager

Office of Pharmaceutical Sciences
Office of Biotechnology Products
Division of Monoclonal Antibodies

Chana Fuchs	CMC Team Leader
Michele Dougherty	CMC Reviewer

Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Hong Zhao	Clinical Pharmacology Team Leader
Jun Yang	Clinical Pharmacology Reviewer

Office of Translational Sciences
Office of Biostatistics
Division of Biometrics V

Mark Rothmann	Statistical Team Leader
Yuan Li Shen	Statistian Reviewer

Office of Translational Sciences
Office of Clinical Pharmacology

Michael Pacanowski	Pharmacologist

Office of In Vitro Diagnostics
Office of Surveillance and Biometrics

Robert Becker	Chief Medical Officer
Dai Li	Medical Officer
Gene Pennello	Math Statistician
Donna Roscoe	Scientific Reviewer
Reena Phillip	Scientific Reviewer

Sponsor Attendees:
ImClone Systems Incorporated:

Cheryl Anderson	Senior VP, Regulatory Affairs
E. Rowinsky, M.D.	Executive VP and Chief Medical Officer
H. Youssoufian, M.D.	Senior VP, Clinical Research
L. Witte, Ph.D.	Senior VP, Clinical Research
E. Yamashita	VP, Regulatory CMC and Operations
T. Katz	AVP, Biostatistics
F. Fox	AVP, Clinical Pharmacology
Y. Yan, DVM, Ph.D.	AVP, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

On May 20, 2008, ImClone submitted a meeting request which FDA determined was more appropriated classified as a Pre-IND/End of Phase 1 (EOP1) meeting due to the fact that the Phase 2 clinical trial was presently ongoing; this was communicated to ImClone in written correspondence dated June 11, 2008. ImClone requested withdrawal of their May 20, 2008 meeting request with plans to resubmit the meeting request after completion of modifications to the planned Phase 3 protocol.

On August 18, ImClone resubmitted a Type B (Pre-IND/EOP2) meeting request to discuss the clinical development plan for Human Monoclonal Antibody IgG1 (IMC-11F8, Imclone) to Epidermal Growth Factor (EGFR).

IMC-11F8, a recombinant bacteriophage library-derived human monoclonal antibody of the immunoglobulin G subclass 1 (IgG1), blocks the ligand binding side of epidermal growth factor receptor (EGFR).

ImClone has conducted both Phase 1 and Phase 2 studies with IMC-11F8 in Europe. A Phase 1 dose-escalation study to determine the pharmacokinetic profile, screen for the development of antibodies against IMC-11F8, and determine the antitumor activity of IMC-11F8 as monotherapy in patients with solid tumors who have failed standard therapy or for whom no standard therapy is available was completed. A Phase 2 clinical trial of IMC-11F8 in combination with 5-fluorouracil, leucovorin, and oxaliplatin in the treatment of metastatic colorectal cancer has complete enrollment

ImClone proposes to initiate (b) (4)

Meeting Purpose: To reach agreement on the clinical and nonclinical development plans to support approval of IMC-11F8 (b) (4)

2.0 DISCUSSION

Clinical:

2.1 Does the Agency agree that the overall clinical study design of this randomized global Phase 3 study is likely to be adequate to generate information that could support approval for the designated claim?

FDA Response: No, FDA does not agree that the overall clinical study design (b) (4) would support the approval of IMC-11F8 (b) (4)

(b) (4)

[redacted]

FDA suggested an alternate trial design comparing 11F8 and the modified FOLFOX6 regimen to bevacizumab and the modified FOLFOX6 regimen with a goal of demonstrating superiority in overall survival (primary endpoint) and PFS (secondary endpoint).. ImClone had no additional comments

Please provide comment on:

a. the patient population to be enrolled

FDA Response: The patient population inclusion and exclusion criteria are

acceptable

Discussion during meeting: *ImClone understood and had no additional comments*

b. the primary endpoint (b) (4)

FDA Response: The proposed primary endpoint (b) (4) is not acceptable.

Discussion during meeting: *Please see "discussion during meeting" under question #1.*

c. the Independent Radiologic Review Committee charter designed to ensure objective identification of progression events.

FDA Response: The IRRC charter is acceptable. Please be advised that the scanned eCRF for radiological review was not readable. The flow diagrams in Figures 1 and 2 were difficult to read.

Discussion during meeting: *ImClone had no additional comments.*

d. the proposed modified FOLFOX6 (5-FU/FA and Oxaliplatin) regimen (b) (4) (b) (4)

FDA Response: The proposed modified FOLFOX6 is acceptable (b) (4) (b) (4)

(b) (4)

Discussion during meeting: *Please see "discussion during meeting" under question #1.*

e. the acceptability of the Independent Data Monitoring Committee (IDMC) charter to protect patients and to secure the integrity of the results of the planned Phase 3 study

FDA Response: Please discuss the following statements in Section 2 of the IDMC charter:

[redacted] (b) (4)

Also in Section 2.4 the following statement appears: [redacted] (b) (4)

Please discuss [redacted] (b) (4) Please distinguish between the responsibilities of the Steering Committee and the IDMC in terms of "the safety of all patients". Please provide examples of situations in which the Steering Committee would decide not to follow the advice of the IDMC.

Please discuss how voting will be handled during the closed session of the IDMC. Does the vote have to be unanimous? How will a split vote be handled since the IDMC is comprised of [redacted] (b) (4) members?

Discussion during meeting: *ImClone had no additional comments*

2.2 Does the Agency agree with out statistical analysis plan for the proposed Phase 3 [redacted] (b) (4) study?

Please comment on

a. the trial hypothesis for the primary endpoint

FDA Response: Please see comment from 1.b. [redacted] (b) (4)

Discussion during meeting: *ImClone understood and had no additional comments.*

b. the calculated sample size

FDA Response: Please revise the sample size calculation section of the protocol and statistical analysis plan [redacted] (b) (4)

Discussion during meeting: *ImClone understood and had no additional comments.*

c. the acceptability of the plan [redacted] (b) (4) , especially in light of ImClone's plans to conduct a single pivotal study to support approval

FDA Response: The overall type I error rate should be controlled at 0.01 level for regulatory approval based on a single trial. Please also see the last comment regarding the secondary endpoints in the Additional Statistical Comments section.

Discussion during meeting: *ImClone understood and had no additional comments.*

Clinical Pharmacology:

2.3 A comparison of the derived PK parameters from noncompartmental PK analysis of unaudited data from the Phase 1 CP11-0401 study (monotherapy) and Phase 2 IMCL CP11-0602 study (mFOLFOX6 and IMC-11F8 in combination) demonstrated nearly identical IMC-11F8 pharmacokinetics. This suggests pharmacokinetic interaction between mFOLFOX6 and IMC-11F8 is unlikely. In addition, ImClone Systems plans to perform additional PK analyses in the Phase 3 trial. Does the Agency agree [redacted] (b) (4)

Does the Agency agree [redacted] (b) (4)

FDA Response: No. ImClone should also evaluate [redacted] (b) (4) This assessment can be incorporated in the proposed phase 3 trial. Please submit the DDI evaluation plan for FDA review.

Discussion during meeting: *ImClone proposed [redacted] (b) (4) FDA requested that ImClone submit the [redacted] (b) (4) proposal for review and comment.* [redacted] (b) (4)

(b) (4)

2.4 Does the Agency agree that the collection of immunogenicity data as described in the briefing document would provide adequate information to support approval for the subject claim?

FDA Response: Yes, the proposed immunogenicity sampling plan appears to be acceptable. However, if there is evidence of binding anti-product antibodies in individual patients, an assessment of the neutralizing capacity of the anti-IMC-11F8 antibodies should be conducted in such patients.

Discussion during meeting: *ImClone understood and had no additional comments.*

2.5 Although they are fundamentally different in the molecular structures and they have totally different derivations, the currently available data suggest that the pharmacological and pharmacodynamic properties of IMC-11F8 are similiar to those of marketed EGFR targeted monoclonal antibody therapeutic agents. Therefore, the potential risk of IMC-11F8 to cause alteration of the QT/QTc interval is low. (b) (4) **ImClone Systems does not plan to conduct a QTc study for IMC-11F8 to support a BLA. Does the Agency agree with this approach?**

FDA Response: No. IMC-11F8 is a new molecular entity. During the development of IMC-11F8, ImClone should assess the impact of IMC-11F8 treatment on the QT/QTc interval through routine ECG monitoring in the clinical studies to capture important cardiovascular effects in accordance with the principles discussed in the ICH-E14 guidance document (http://www.fda.gov/cder/guidance/6922fnl.htm). Please include a description of the QT/QTc assessment plan for FDA review.

Discussion during meeting: *ImClone understood and had no additional comments.*

NonClinical:

2.6 Based on its molecular structure and mechanisms of action, the genotoxic and carcinogenic potential of IMC-11F8 is less of concern. ImClone Systems does not plan to conduct genotoxicity and carcinogenicity studies for IMC-11F8 to support filing of BLA. Does the Agency agree with this approach?

FDA Response: Yes. This is a reasonable approach.

Discussion during meeting: *ImClone understood and had no additional comments.*

2.7 Based on the available information regarding potential reproductive and developmental effects of anti-EGFR and the monkey is the only relevant species for reproductive toxicity potential assessment, the Sponsor does not plan to conduct reproductive toxicity studies with IMC-11F8 to support the filing of BLA. Does the Agency agree with this approach?

FDA Response: FDA agrees that this approach is acceptable, under the following conditions. In lieu of conducting reproductive and developmental toxicology studies with IMC-11F8, Imclone must provide data that demonstrate that the pharmacokinetic, pharmacodynamic and toxicologic profiles of IMC-11F8 are similar to cetuximab, such that upon marketing approval, the information presently contained in Sections 8.1 (Pregnancy) and 8.3 (Nursing Mothers) of the Erbitux label will also be applicable for labeling of IMC-11F8.

The Investigator Brochure and informed consent should indicate that animal reproduction studies have not been conducted with IMC-11F8 and should include pertinent nonclinical information regarding reproductive alterations induced by other monoclonal antibodies capable of blocking ligand binding to the EGFR. The information should be clearly organized to illustrate the potential reproductive toxicity risks for patients receiving this class of biotherapeutic agents. The Investigator's Brochure and consent form should also state that if a patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

Discussion during meeting: *ImClone understood and had no additional comments.*

2.8 Does the Division agree that the nonclinical program described in the briefing document is adequate to support the BLA filing for the proposed indication?

FDA Response: The nonclinical program described in the briefing document is a reasonable approach. However, the adequacy of the findings in the nonclinical studies submitted to support the original BLA filing will be determined following review of the nonclinical information provided by ImClone at that time.

Discussion during meeting: *ImClone understood and had no additional comments.*

(b) (4)

[redacted]

(b) (4)

Additional Clinical Comments:

2.10

(b) (4)

2.11

(b) (4)

[redacted]

2.15 Please discuss whether a model informed consent document will be provided to each investigator. If not, please discuss how ImClone will be assured that the informed consent written by the investigator will meet all of the requirements of informed consent and will be acceptable to regulatory authorities?

Discussion during meeting: *ImClone understood and had no additional comments.*

Additional Statistical Comments:

2.16 (b) (4)

2.17

2.18

CMC Comments:

2.19 The CMC section identifies three drug substance manufacturing processes and three drug product presentations which include a change in formulation (b) (4) Please provide a table identifying which

manufacturing process and DP presentation was used for each of the non-clinical studies and clinical trials described. For presentations used in previous clinical and non-clinical studies supporting the proposed IND, comparability data should also be provided.

Discussion during meeting: *ImClone understood and had no additional comments.*

3.0 ACTION ITEMS FOR FDA:

3.1 *FDA internal discussion regarding response to question #9.*

(b) (4)

[redacted]

Linked Applications	Sponsor Name	Drug Name
IND 102512	IMCLONE SYSTEMS INC	Human Monoclonal Antibody IgG1 (IMC-11F8, ImClone) to Epidermal Growth Factor (EGFR)

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/s/

RAYMOND S CHIANG
12/05/2008

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547

LATE-CYCLE MEETING MINUTES

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 24, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Missiratch (Mimi) Biable, Regulatory Project Manager at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
Cross Discipline Team Leader (CDTL)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: August 24, 2015
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: BLA 125547
Product Name: Necitumumab
Applicant Name: Eli Lilly and Company (Lilly)

Meeting Chair: Gideon Blumenthal
Meeting Recorder: Mimi Biable

FDA ATTENDEES
Richard Pazdur, M.D., Director/OHOP
Patricia Keegan, M.D., Director, DOP2
Mimi Biable, M.S., Senior Regulatory Project Manager
Lee Pai-Scherf, M.D., Medical Officer
Gideon Blumenthal, M.D., Medical Officer (TL and CDTL)
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Lijun Zhang, Ph.D., Statistics
Sarah Dorff, Ph.D., Genomics and Targeted Therapy
Rosane Charlab Orbach, Ph.D. Genomics and Targeted Therapy (TL)
Ying-Xin Fan, Ph.D., Quality reviewer - Drug Substance
Yan Wang, Ph.D., Quality reviewer - Drug Product
Chana Fuchs, Ph.D., Quality Assessment Lead (TL)
LT Jibril Abdus-Samad, Pharm.D., Quality Labeling Reviewer
Candace Gomez-Broughton, Ph.D., Quality Micro- Drug Substance
Lakshmi Narasimhan, Ph.D., Quality Micro- Drug Product
Patricia Hughes, Ph.D., Quality Micro- Acting Branch Chief
CDR Latonia Ford, M.B.A., B.S.N., R.N., OSE RPM
LCDR Mona Patel, Pharm.D., OSE/DRISK
Carolyn McCloskey M.D., MPH, OSE/DEPI Reviewer
LCDR Steven Bird, Ph.D., Pharm.D., OSE/DEPI (TL)
Shaily Arora, Pharm.D., OSE/DPV Reviewer
Tracy Salaam, Pharm.D., OSE/DPV (TL)
Peter Waldron, Peter E. Waldron M.D., OSE/DPV2 Reviewer
Lauren Iacono-Connor, Ph.D., OSI Reviewer
Nazia Fatima, Pharm.D, M.BA., OPDP Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese

APPLICANT ATTENDEES
Timothy Cook, Vice President, Global Product Lead, Necitumumab
Jonathan Denne, PhD, Senior Director, Statistics
Richard Gaynor, MD, Sr. Vice President, Oncology Product Development
Stephen Knowles, MD, Senior Director, Global Patient Safety
Raffael Kurek, MD, Medical Fellow, Global Medical Lead - Necitumumab
Deborah Lynch, Necitumumab Regulatory Lead, Global Regulatory Affairs
Robert Metcalf, PhD, Vice President, Global Regulatory Affairs and Quality
Ruth Schulz, PhD, Associate Vice President, Global Regulatory Affairs-CMC
Javad Shahidi, MD, Medical Director-Necitumumab
Katherine Sugarman, MD, Senior Director, Global Regulatory Affairs

1.0 BACKGROUND

BLA 125547 was submitted on December 2, 2014 for Necitumumab.

Proposed indication: First-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine-cisplatin chemotherapy

PDUFA goal date: December 2, 2015

FDA issued a Background Package in preparation for this meeting on August 14, 2015.

2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

   Product Quality Microbiology: (b) (4)

   A request from July 28, 2015 for drug product endotoxin release testing strategy has not yet been submitted. A T-con with Lilly was held on August 12, 2015 to discuss the data from the additional endotoxin recovery studies and the proposal for drug product endotoxin release testing.

Discussion:
FDA acknowledged the teleconference held with Lilly on August 12, 2015 to discuss the endotoxin recovery for Necitumumab Drug Product and Lilly's submission of August 19, 2015. FDA asked for clarification of Lilly's August 19, 2015 submission on the lot numbers found in Table 4, page 9 vs the final page of the report that provided linkage between "Lilly" lot numbers and "Imclone" lot numbers (report titled "edno-recover-01901"). Lilly provided clarification and FDA acknowledged understanding.

3. Outstanding Information Requests as of August 24, 2015:

   A CMC information request was sent to Lilly on August 14, 2015

   Discussion:
   Lilly will provide the requested information by August 31, 2015.

4. REMS or Other Risk Management Actions

   No issues related to risk management have been identified to date and no REMS is planned**.**

   Discussion:
   No discussion.

5. Postmarketing Requirements/Postmarketing Commitments

   Potential CMC and Product Quality Microbiology Post-Marketing Commitments are currently under discussion.

   Discussion:
   FDA plans to send PMC(s) by the end of the week for micro issues.
   FDA may provide additional PMC's after receipt and review of the CMC information request sent to Lilly on August 14, 2015.

6. Major Labeling Issues

   Substantively complete labeling was sent to Lilly on August 14, 2015. Lilly should identify any major labeling concerns for discussion.

   Discussion:
   Lilly acknowledged FDA's labeling comments sent on August 14, 2015. Lilly stated that they are working on proposed edits to the necitumumab package insert (PI) and carton and container labeling and will respond formally by the requested date, August 28, 2015. Lilly provided a general update on the revisions they are proposing to make on the PI:

   - Ensure safety data reflects the full treatment period and not just during treatment with chemotherapy.

- Clarify indication to include patients with metastatic squamous non-small cell lung cancer (b) (4)
- Revise section 8.5 (Geriatric Use) of the PI to add hazard ratio.
- Revise Limitation of Use, Adverse Reactions, Clinical Studies sections of the package insert to clarify population studied.

7. Review Plans

   CMC is currently assessing specifications, stability, commitments, protocols proposed. Items from the IR sent to Lilly on August 14, 2015, are also still pending completion of review.

   Discussion:
   FDA will assess Lilly's response to the CMC information request regarding the specifications and stability protocols once received.

8. Wrap-up and Action Items

   Discussion:
   None.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

GIDEON M BLUMENTHAL
09/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125547

LATE CYCLE MEETING
BACKGROUND PACKAGE

Eli Lilly and Company
Attention: Deborah Lynch
Associate Vice President, Regulatory Affairs
33 ImClone Drive
Branchburg, NJ 08876

Dear Ms. Lynch:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for "Necitumumab."

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 24, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call me at (301) 796-0154.

Sincerely,

{See appended electronic signature page}

Missiratch Biable, M.S., R.A.C. (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: August 24, 2015
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: BLA 125547
Product Name: Necitumumab
Indication: First-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine-cisplatin chemotherapy

Sponsor/Applicant Name: Eli Lilly and Company (Lilly)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Product Quality Microbiology

(b) (4)

A request from July 28, 2015 for drug product endotoxin release testing strategy has not yet been submitted. A T-con with Lilly was held on August 12, 2015 to discuss the data from the additional endotoxin recovery studies and the proposal for drug product endotoxin release testing.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting was held on July 9, 2015.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests – 10 minutes

   Chemistry, Manufacturing and Control (CMC):

   a. A CMC information request is forthcoming and will be sent to Lilly prior the late cycle meeting.

   b. **Product Quality Microbiology**: A complete response to FDA's information request dated July 28, 2015, was discussed at the T-con scheduled for August 12, 2015. During the T-con, the data from the additional endotoxin recovery studies and the proposal for endotoxin sample management and drug product release testing will be discussed.

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

   - Potential CMC and Product Quality Microbiology Post-Marketing Commitments are currently under discussion.

4. Major labeling issues – 10 minutes

   Substantively complete labeling was sent to Lilly on August 14, 2015. Lilly should identify any major labeling concerns for discussion.

5. Review Plans – 5 minutes

   - CMC is currently assessing specifications, stability, commitments, protocols proposed. Items from the IR to be sent to sponsor, prior to the late cycle meeting, are also still pending completion of review.

   - Labeling Discussions Ongoing

   - Press Release and ASCO Burst Planned

6. Other – 2 minutes

   - OSI Inspections Update: FDA conducted 4 BIMO inspections at 3 clinical sites and at Lilly. Preliminarily there were no major issues found during this inspection that would preclude approval. Your response to the OSI requests made prior to the application submission, were extremely helpful in preparing and conducting these clinical inspections.

   - CMC Manufacturing Inspections Update: DS and DP sites were inspected.

7. Wrap-up and Action Items – 10 minutes

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/s/

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08/14/2015