

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125477Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

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

NDA/BLA#: 125477/0 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DOP2 PDUFA Goal Date: 4-23-2014 Stamp Date: 8/23/2013

Proprietary Name: Cyramza

Established/Generic Name: ramuricumab

Dosage Form: 100 mg/10 mL; 500 mg/50mL

Applicant/Sponsor: Eli Lilly and Company

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

- (1) N/A  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

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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 gastric cancer or gastro-esophageal junction adenocarcinoma

**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.

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

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

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

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

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

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

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

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

**This page was completed by:**

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

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

**(Revised: 6/2008)**

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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.**  
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/s/  
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SHARON K SICKAFUSE  
09/10/2013

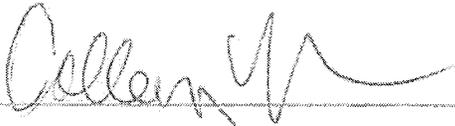
DEBARMENT CERTIFICATION

BLA Application No. 125477/0

Drug Name: Ramucirumab

Pursuant to the provisions of 21 U.S.C. 335a(k) (1), Eli Lilly and Company, through Colleen Mockbee hereby certifies that it did not and will not use in any capacity the services or any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection the this application.

ELI LILLY AND COMPANY

By:  \_\_\_\_\_

Colleen Mockbee, Senior Director, Global Regulatory Affairs - US

Date: 30 April 2013

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125477	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cyramza Established/Proper Name: ramucirumab Dosage Form: injection, for intravenous infusion		Applicant: Eli Lilly and Co. Agent for Applicant (if applicable):
RPM: Sharon Sickafuse		Division: DOP2
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>April 23, 2014</u></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None	

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

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

<p>❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC       </p> <p>         NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)          Subpart I <input type="checkbox"/> Approval based on animal studies       </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request       </p> <p>         BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)          Subpart H <input type="checkbox"/> Approval based on animal studies       </p> <p>         REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input checked="" type="checkbox"/> REMS not required       </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input checked="" type="checkbox"/> Yes, dates 2-6-2014
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO burst

<sup>3</sup> 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.

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

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

❖ Copy of this Action Package Checklist <sup>4</sup>	included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Approval 4-21-2014
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	10-30-2013
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	8-23-2013
<ul style="list-style-type: none"> <li>❖ Proprietary Name           <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	Acceptable letter: 10-25-2013 Review: 10-25-2013
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 10-16-2013 <input checked="" type="checkbox"/> DMEPA 1-21-2014 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 2-27-2014 <input checked="" type="checkbox"/> ODPD (DDMAC) 3-4-2014 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DHOT 4-7-2014; DMA 1-23-2014
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	10-16-2013
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP           <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)           <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>product has orphan drug designation</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<p>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i></p>	<p><input checked="" type="checkbox"/> Verified, statement is acceptable</p>
<p>❖ Outgoing communications <i>(letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons)</i></p>	<p>Revised PI email 3-28-2014  Revised PI email 2-25-2014  PMR/PMC request email 2-21-2014  LCM summary 2-19-2014  LCM pkg 1-29-2014  DMEPA letter 1-28-2014  Clinical IR email 1-24-2014  CMC IR email 1-23-2014  Qual Micro IR email 1-23-2014  CMC IR letter 1-21-2014  Teleconference 1-17-2014  (DARRTS 2-14-2014)  CMC IR letter 1-16-2014  CMC IR letter 1-10-2014  CMC IR letter 1-9-2014  Clin pharm IR email 1-8-2014  CMC IR letter 12-31-2013  MidCycle communication 12-24-2013  CMC IR letter 12-17-2013  CMC IR email 12-10-2013  Qual Micro IR email 12-3-2013  CMC AD email 11-27-2013  Qual Micro IR letter 11-26-2013  Stat IR email 11-14-2013  Qual Micro IR letter 11-8-2013  CMC IR letter 10-31-2013  Filing &amp; DI letter 10-22-2013  Telecon 10-10-2013  IR email 9-24-2013  IR email 9-11-2013  Ack letter 9-6-2013  IR email 8-19-2013  IR email 7-22-2013  Presubmission Ack letter 3-29-2013</p>
<p>❖ Internal memoranda, telecons, etc.</p>	<p>Wrap-up Meeting 3-17-2014  Mid-Cycle Meeting 12-2-2013  Planning Meeting 9-18-2013</p>
<p>❖ Minutes of Meetings</p>	
<ul style="list-style-type: none"> <li>• Regulatory Briefing <i>(indicate date of mtg)</i></li> </ul>	<p><input checked="" type="checkbox"/> No mtg</p>
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i></li> </ul>	<p><input checked="" type="checkbox"/> N/A or no mtg</p>
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i></li> </ul>	<p><input type="checkbox"/> No mtg  Clinical 1-27-2013  CMC 1-23-2013  Clin pharm 2-21-2013</p>
<ul style="list-style-type: none"> <li>• EOP2 meeting <i>(indicate date of mtg)</i></li> </ul>	<p><input type="checkbox"/> No mtg 5-28-2008</p>
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i></li> </ul>	

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-21-2014
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-11-2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4-21-2014 (revised), 3-14-2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 3-20-2014, 3-19-2014, 3-14-2014 (3). Total of 5 templates.
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	Signed concurrence on 1-17-2014 review & 9-20-2013 filing review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	1-17-2014 (review), 9-20-2013 (filing review)
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	1-17-2014 clinical review, page 34
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 1-16-2014
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None signed concurrence on 1-23-2014 review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None signed concurrence on 1-23-2014 review & 10-7-2013 filing review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1-23-2014 (review),

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

	10-7-2013(filing review)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None signed concurrence on 1-23-2014 review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None signed concurrence on 3-14-2014 addendum, 1-23-2014 review & 9-30-2013 filing review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3-14-2014 (addendum), 1-23-2014 (review), 9-30-2013 (filing review), 8-19-2013 (QT review)
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4-7-2014, 2-21-2014, signed concurrence on 1-23-2014 review & 10-8-2013 filing review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1-23-2014 (review), 10-8-2013 (filing review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None signed concurrence on 1-27-2014 review, 1-23-2014 review & 9-30-2013 filing review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1-27-2014, signed concurrence on 1-23-2014 review & 9-30-2013 filing review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1-23-2014 (review), 9-30-2013 (filing review)
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 3-4-2014 (categorical exclusion review), 2-12-2014 (addendum to 1-23-2014 DP review), 1-23-2014 (DP review), 1-10-2014 (DS review), 11-26-2013 (waiver of pre-approval inspection), 10-3-2013 (filing review)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	3-4-2014 quality micro review
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: 4-1-2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> 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.

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/s/  
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SHARON K SICKAFUSE  
04/22/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, March 28, 2014 11:37 AM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** Ramucirumab PI

**Importance:** High

Hi Deb,

My team is available on Thursday, April 3<sup>rd</sup> at 3pm in case we need to discuss anything.



Ram PI FDA  
changes marked...

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/s/  
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SHARON K SICKAFUSE  
03/28/2014

**BLA REVIEW WRAP-UP MEETING SUMMARY**  
**March 17, 2014**

**BLA 125477/0**  
**Cyramza (ramucirumab)**

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**Proposed Indication:** Treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single agent after prior fluoropyrimidine- or platinum-containing therapy

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**Action Due Date: April 23, 2014**

**Dates That Outstanding Signed Reviews Are Due:**

<b>Division Director</b>	4-11-2014
<b>Office Director</b>	4-23-2014

**Discuss Remaining Outstanding Pre-Action Items:**

1. **Labeling:**
  - a. Revised carton & container labeling received March 12<sup>th</sup>. Revised labeling has addressed all FDA comments and is acceptable.
  - b. Labeling meetings are scheduled for March 25<sup>th</sup> & April 3<sup>rd</sup> to discuss Lilly's counterproposal of March 3<sup>rd</sup>.
2. **Compliance Check:** Needs to be sent by BMAB.
3. **PMCs and PMRs:** Agreement reached with Lilly on language for 4 CMC PMCs. Lilly submitted revised language and milestones for 2 PMRs and revised milestones for 4 PMCs on March 12<sup>th</sup>. These are acceptable to the team.
4. **Employee list (yes/no) for Action Package:** To be sent out on email week of March 30<sup>th</sup>.
5. **Press Release/ASCO Burst:** Press office has been notified.
6. **Action Package Preparation:** nearly complete for review by CPMS and DD. Is due to CPMS by April 2<sup>nd</sup>.
7. **Approval letter:** will circulate to the team this week.

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SHARON K SICKAFUSE  
03/17/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, February 25, 2014 4:03 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 - revised PI

Hi Deb,

Attached are our proposed revisions. I think the most efficient way to deal with this is for Lilly to accept the changes that they agree with so that what comes back to me only has your counterproposals marked.



PI\_FDA changes  
marked 2-25-20...

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/s/  
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SHARON K SICKAFUSE  
02/25/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, February 21, 2014 12:12 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 - FDA request for PMRs

Hi Deb,

We have the following request for PMRs:

1. Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for the accurate detection of binding antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. Submit the validation report as a Prior Approval Supplement by Month/Year (Lilly to provide date).
2. Conduct an assessment of anti-drug antibody (ADA) response to ramucirumab with a validated assay (required in PMR 1) capable of sensitively detecting ADA responses in the presence of ramucirumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients. The final report will be submitted by Month/Year (Lilly to provide date.)

The validation report for PMR #1 can either come from the current assay for a new assay.

Please submit an amendment to the BLA with the 2 PMRs & milestones as well as the 4 PMCs discussed during the February 11<sup>th</sup> Late Cycle Meeting and milestones.

The team has decided not to request a new assay for neutralizing antibodies.

Thanks

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/s/  
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SHARON K SICKAFUSE  
02/21/2014



BLA 125477/0

## INFORMATION REQUEST

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the carton and container labeling and the following request for revisions:

Regarding the carton labeling:

1. Delete (b) (4) from the top right-side of the principal display panel.
2. Revise the statement, (b) (4) to read, "Single-Dose Vial". Additionally, relocate this statement from the top of the principal display panel to the lower portion to appear directly before the statement, "Discard unused portion".
3. Relocate the route of administration, "For Intravenous Infusion", to appear below the strength statement.
4. Delete the word (b) (4) from the dosage form statement. Thus, the dosage form should appear as "Injection".
5. Revise the strength presentation such that the numerals and letters share the identical font size and commensurate prominence. For example, **100 mg/10 mL** should read **100 mg/10 mL**.
6. Increase the prominence of the concentration, (10 mg/mL), while maintaining the strength per total volume (**100 mg/10 mL** and **500 mg/50 mL**) as the primary and prominent expression of strength on the label.

7. Add a statement to the principal display panel to alert practitioners to refrigerate Cyramza.
8. Revise the statement, [REDACTED] <sup>(b) (4)</sup> on the side panel to read, “Must Dilute Prior to Use”. Additionally, relocate this statement from the side panel to the principal display panel. Thus, the principal display panel should appear in the following order:

Cyramza  
Ramucirumab  
Injection  
  
XX mg/XX mL  
(xx mg/mL)  
  
For Intravenous Infusion Only  
Must Dilute Prior to Use  
Single-Dose Vial – Discard Unused Portion  
Store in Refrigerator

9. To create space for the other prominent information, relocate the statement, “No US Standard of potency”, to the side panel and decrease the size of the Lilly logo.
10. Revise the statement “[REDACTED]” <sup>(b) (4)</sup> to read “Lot” as this is customary on U.S. drug labels.

Regarding the container label:

11. Please refer to comments #1-6, #9, and #10 above.
12. Revise the statement, [REDACTED] <sup>(b) (4)</sup> on the side panel to read, “Must Dilute Prior to Use”. Additionally, relocate this statement from the side panel to the principal display panel. Thus, the principal display panel should appear in the following order:

Cyramza  
Ramucirumab  
Injection  
  
XX mg/XX mL  
(xx mg/mL)  
  
For Intravenous Infusion Only  
Must Dilute Prior to Use  
Single-Dose Vial – Discard Unused Portion

If you have any questions, please contact 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

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/s/  
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SHARON K SICKAFUSE  
01/28/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, January 24, 2014 2:03 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 clinical IR

**Importance:** High

Hi Deb,

My clinical team has the following IR:

Please submit the MedWatch reports for all cases of reversible posterior leukoencephalopathy syndrome reported in any trial in the ramucirumab development program. These reports were submitted to the IND but we also need them submitted to the BLA.

Thank you

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/s/  
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SHARON K SICKAFUSE  
01/24/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, January 23, 2014 4:11 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 - quality microbiology IR

Hi Deb,

My quality micro team as the following IR:

1. Please clarify if the surface sample data includes samples collected from personnel during the (b) (4) simulation. If not, please provide personnel monitoring data. Also provide a summary of any environmental monitoring excursions.
2. If available, please submit results from the shipping validation study.

Please submit your response by Thursday, January 30<sup>th</sup>. Thanks

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/s/  
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SHARON K SICKAFUSE  
01/23/2014

## Hennessey, Lyndsay

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**From:** Hennessey, Lyndsay  
**Sent:** Thursday, January 23, 2014 1:00 PM  
**To:** deborah.norby@imclone.com  
**Cc:** Sickafuse, Sharon; Hennessey, Lyndsay  
**Subject:** BLA 125477/0 CMC Information Request Clarification Comment

Dear Ms. Norby,

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

Please also refer to the January 21, 2014 email correspondence from Sharon Sickafuse, Senior Regulatory Project Manager, containing a CMC Information Request for BLA 125477. We have started reviewing your response to this request and have the following comment:

Regarding the January 22, 2104 response to question one of the January 21, 2014 information request, it is not clear from the response at what point drug product samples are collected for physico-chemical identity testing relative to the confirmation of identity after the packaging and labeling activities that is based on (b) (4)

In addition, no information is provided regarding how (b) (4)

We do not agree that (b) (4) can be considered sufficiently distinct physical attributes to be used to confirm physical identity of ramucirumab drug product presentations. Samples for the physico-chemical identity testing need to be collected after the vials have been sufficiently labeled with a unique identifier, since 21 CFR 610.14 states that "the contents of a final container of each filling of each lot shall be tested for identity after all labeling operation shall have been completed." It appears that a sample(s) of the ramucirumab drug product vials should be collected for physico-chemical identity testing after the container labels have been applied.

If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact me at 240-402-3746 or Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Kindly acknowledge receipt.

Thank you,

**Lyndsay Hennessey**  
Regulatory Health Project Manager  
FDA/CDER/OPS/OBP-IO  
10903 New Hampshire Ave.  
WO Building 21 Room 1523  
Silver Spring, Maryland 20993-0002  
[Lyndsay.Hennessey@fda.hhs.gov](mailto:Lyndsay.Hennessey@fda.hhs.gov)  
240-402-3746

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/s/  
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LYNDSAY J HENNESSEY  
01/23/2014



BLA 125477/0

## INFORMATION REQUEST

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application. Please submit your responses by January 22, 2014, via electronic mail as well as to the BLA according to the deadline specified in the request.

1. The code of federal regulations (21 CFR 610.14) requires that identity testing be performed on each filled lot after all labeling operations have been completed. The manufacturing step from which the samples used for identity testing of ramucirumab are obtained was not clearly identified in Section 3.2.P.3.3 or Section 3.2.P.5.1. Clarify your current process and amend the process, if necessary, to conform to the regulation. Update the relevant section(s) of the BLA accordingly by February 7, 2014.
2. Regarding the carton and container labels:
  - a. Indicate how the container label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60.
  - b. Per USP 36/NF 31, <1091> Labeling of Inactive Ingredients, revise the carton and container labels to list the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). Commit to revise the carton and container labels as requested, and provide the revised labels by February 7, 2014.

3. [Redacted] (b) (4)

Provide the revised acceptance criteria, and commit to submit the revised protocols to the BLA by February 7, 2014.

4. [Redacted] (b) (4)

Commit to revising the protocols, and submit the revised protocols to the BLA by February 7, 2014.

5. [Redacted] (b) (4)

Provide the results of the completed [Redacted] (b) (4) studies in the annual report of manufacturing changes.

If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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SARAH B KENNETT  
01/21/2014

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** January 17, 2014

**Application Number:** BLA 125477/0

**Product Name:** Cyramza (ramucirumab)

**Sponsor/Applicant Name:** Eli Lilly and Company (Lilly)

**Subject:** Discuss CMC information request sent to Lilly on January 16, 2014

## **FDA Participants**

Division of Oncology Products 2

Missiratch (Mimi) Biable

Office of Biotechnology Products

Division of Monoclonal Antibodies

Michele Dougherty, Ph.D.

Sarah Kennett, Ph.D.

## **Sponsor/Applicant Participants**

Michael Barry, VP CMC Development

Michael Kahsai, VP Quality Control

Qinwei Zhou, VP Bioanalytical Sciences

Wendy Lime – Assoc VP GRA- CMC

Anne Marie O’Connell, Assoc VP GRA-CMC

## **BACKGROUND:**

FDA sent a CMC information request (IR) to Lilly on January 16, 2014 (see attached) and a teleconference was held on January 17, 2014, to discuss items #1, 2, and 3 from the January 16, 2014 IR.

1. The release data provided for drug substance (DS) and drug product (DP) lots manufactured by the C1 DS manufacturing process and for DS and DP lots used in clinical studies do not support the proposed acceptance criteria for select release and stability specifications. We do not agree with the proposed acceptance criteria for the specifications indicated below and have the following recommendations. Submit a revised Drug Substance Specification, Drug Product Specification and post-approval stability protocols.

Drug Substance Test	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria

(b) (4)

(b) (4)		

Drug Product Test	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria
(b) (4)		

Discussion:

The sponsor agreed to revise the acceptance criteria (b) (4) for drug substance lot release and stability and drug product lot release and stability specifications per the Agency request.

The sponsor did not agree with the Agency recommendations (b) (4) and proposed that the drug substance (b) (4). The Agency agreed to the proposal. The sponsor proposed that the end of shelf life criterion for drug product (b) (4). The Agency agreed to the proposal (b) (4).

The sponsor agreed to revise the acceptance criteria for (b) (4) for drug substance lot release and stability and drug product lot release and stability specifications per the Agency request.

The sponsor did not agree with the Agency recommendations for drug substance and drug product release and shelf life acceptance criteria for (b) (4). The sponsor explained that (b) (4).

(b) (4)

The Agency indicated that a post-marketing commitment would be requested to re-evaluate release and shelf-life specifications once a minimum number of lots had been manufactured. The sponsor proposed the following alternate acceptance criteria:

(b) (4)

The Agency agreed to the revised acceptance criteria based on the method experience, supportive stability data, and data from the previous (b) (4) assay format (b) (4)

2. Regarding the proposed primary reference standard (RS) lot, PRS0865, the data provided to support setting the potency of PRS0865 at (b) (4) are not sufficient (b) (4)

The RS used for release of commercial material should be representative of the pivotal clinical study material and suitable to ensure that commercial material potency is reflective of that used in the pivotal clinical studies and that the release and stability acceptance criteria set based on the pivotal study material are meaningful. (b) (4)

We note in the January 9, 2014, response to Question 18a of the December 31, 2013, information request that (b) (4)

(b) (4)

Given this information, we do not agree that the proposed primary RS is sufficiently representative of the pivotal clinical

trial material and the C0 manufacturing process to be acceptable as a primary RS (b) (4)

[Redacted]

Discussion:

The sponsor clarified (b) (4)

The sponsor proposed to set the relative potency of the secondary RS at (b) (4)  
The Agency agreed to the approach, (b) (4)

[Redacted]

(b) (4) The sponsor requested clarification regarding how to submit a reference standard qualification protocol (b) (4)

. The Agency indicated that a protocol should be submitted as a prior approval supplement. Once approved, qualification performed per the approved protocol could be submitted under a reduced reporting category.

3.

[Redacted]

**3.0 ACTION ITEMS:**

The sponsor agreed to submit a revised drug substance specification, drug product specification, drug substance post-approval stability protocol, and drug product post-approval stability protocol to the BLA.

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MISSIRATCH BIABLE

02/14/2014



BLA 125477/0

**INFORMATION REQUEST**

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

Dear Ms. Norby:

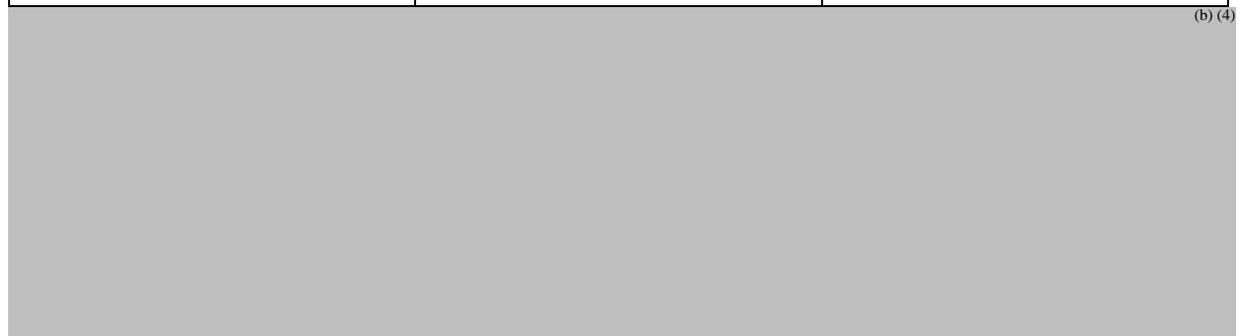
Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application:

- The release data provided for drug substance (DS) and drug product (DP) lots manufactured by the C1 DS manufacturing process and for DS and DP lots used in clinical studies do not support the proposed acceptance criteria for select release and stability specifications. We do not agree with the proposed acceptance criteria for the specifications indicated below and have the following recommendations. Submit a revised Drug Substance Specification, Drug Product Specification and post-approval stability protocols.

Drug Substance Test	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria

(b) (4)



(b) (4)

Drug Product Test	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria
(b) (4)		

2. Regarding the proposed primary reference standard (RS) lot, PRS0865, the data provided to support setting the potency of PRS0865 at (b) (4) are not sufficient. (b) (4)

The RS used for release of commercial material should be representative of the pivotal clinical study material and suitable to ensure that commercial material potency is reflective of that used in the pivotal clinical studies and that the release and stability acceptance criteria set based on the pivotal study material are meaningful. (b) (4)

We note in the January 9, 2014, response to Question 18a of the December 31, 2013, information request that (b) (4)

Given this information, we do not agree that the proposed primary RS is sufficiently representative of the pivotal clinical trial material and the C0 manufacturing process to be acceptable as a primary RS. (b) (4)

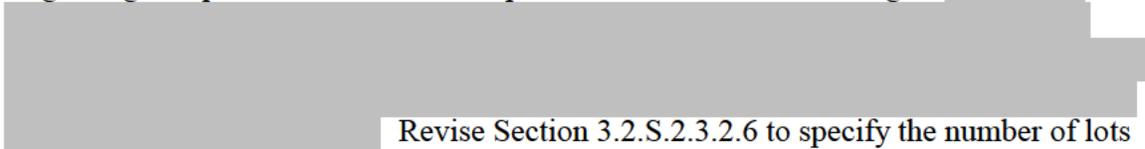
3.



4. We note that the Eli Lilly and Company site responsibilities include release testing and stability testing for drug product. Submit method transfer report summaries for all release and stability methods that were validated at the ImClone Systems, Branchburg, NJ site and will be performed at the Eli Lilly and Company site.

5. We note that the November 4, 2013, response to the October 22, 2013, Filing and Deficiencies Identified letter (Question 6) indicates that (b) (4) testing results for the working cell bank (WCB) and (b) (4) were expected in December 2013. Submit the results of this testing.

6. Regarding the qualification of future replacement WCBs we do not agree (b) (4)



Revise Section 3.2.S.2.3.2.6 to specify the number of lots of DS that will be assessed to support qualification of future replacement cell banks. Once agreement on the protocol for manufacture of ramucirumab WCBs is reached, implementation of a replacement WCB can be submitted in the Annual Report of Manufacturing Changes (ARMC). We note that additional data to support implementation of WCB lot 80009 should be reported via the ARMC

We request a response by January 20, 2014, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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SARAH B KENNETT  
01/16/2014



BLA 125477/0

## INFORMATION REQUEST

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application:

1. We note that supportive stability data for drug substance (DS) drug product (DP) are provided in tabular format only. Submit qualitative data (b) (4) for all DS and DP lots that are representative of clinical product utilized in Phase 3 clinical studies from studies at recommended, stressed, and accelerated storage conditions, where available. Data should include the initial and final time points, plus the recommended storage condition 18 month stability time point for DS and the 12 month stability time point for DP. If data are available from (b) (4) analysis for supportive stability lots, provide all available stability data in tabular format and chromatograms for the stability time points as requested above for any lot where data are available.
2. We note that tolerance intervals for (b) (4) were constructed to demonstrate comparability of DP manufactured at Eli Lilly and Company to DP manufactured at (b) (4). It is not clear what historical DP data were used to construct the tolerance intervals. Provide the summary data, including lot numbers, that were used to calculate the tolerance interval to support DP comparability.

3. Regarding the DS manufacturing process concurrent validation protocols:

a.

b.

(b) (4)

4. Regarding the DP container closure:

a. We note that an assessment of potential (b) (4) was performed with the Type I glass tubing vial and the result of the assessment concluded that (b) (4) is considered to be of low risk for ramucirumab as formulated. Provide a detailed summary of the assessment and a summary of any data available to support the conclusions.

b. Provide a comparison of the dimensions of the 50 ml Type I glass tubing vial and the 10 ml Type I glass tubing vial that are the commercial container closure system. Include a comparison of the headspace associated with each vial size.

We request a response by January 19, 2014, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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SARAH B KENNETT  
01/10/2014



BLA 125477/0

**INFORMATION REQUEST**

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application:

**Drug Substance (DS):**

1. The DS data provided in the Manufacturing Process Development and Process Validation sections (3.2.S.2.6 and 3.2.S.2.5) and responses to subsequent requests for information are not sufficient to support the limited process parameters and controls presented in the Description of Manufacturing Process and Process Controls and Controls of Critical Steps and Intermediates sections (3.2.S.2.2 and 3.2.S.2.4). While we acknowledge that the current controls presented in 3.2.S.2.2 and 3.2.S.2.4 are those that you deemed critical for assuring critical quality attributes of ramucirumab, sufficient data and process understanding are not provided

(b) (4)

(b) (4)

**Drug Product (DP):**

5. Regarding the DP Description of Manufacturing Process and Process Controls for Eli Lilly and Company and the Control of Critical Steps and Intermediates for Eli Lilly, additional process parameters should be included to ensure sufficient control of the DP manufacturing process. Inclusion of information in the pharmaceutical development section (3.2.P.2) only is not sufficient. Revise the description of the DP manufacturing process and control of critical steps and intermediates sections (3.2.P.3.3 and 3.2.P.3.4) to include the following process parameters and operating ranges or control limits. Ranges for the indicated parameters should be supported by process development data as described in 3.2.P.2, Pharmaceutical Development, and validation data; submit any supporting data not previously supplied with the proposed ranges.

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

6. We note in Section 3.2.P.3.5.1.2.2, Process Qualification, [REDACTED] (b) (4)  
[REDACTED]  
The results of these studies were not found in the process validation document. Provide the location of data from these studies or submit the data to the BLA.
7. The December 23, 2013, response to question 10c of the December 17, 2013, information requests includes revised acceptance criteria for [REDACTED] (b) (4) for the qualification of replacement WCBs. Update 3.2.S.2.3, Control of Materials, Section 3.2.S.2.3.2.6, Preparation of a Replacement Working Cell Bank, with a revised Table 3.2.S.2.3.2.6-3 that includes the revisions to the critical quality attribute acceptance criteria for replacement WCBs.
8. Regarding the overall approach to qualification of replacement WCBs, Agency experience indicates that an assessment of at least three lots of DS manufactured with a new WCB is necessary to confirm product quality of DS manufactured with a new WCB. Clarify the number of DS lots that are required for qualification of ramucirumab replacement WCBs. Provide a justification for the number of DS lots that will be assessed to support the use of a ramucirumab replacement WCB.

We request a response by January 15, 2014, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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SARAH B KENNETT  
01/09/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, January 08, 2014 5:05 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 clin pharm IR

Hi Deb,

My clin pharm reviewer has the following IR:

Please submit ramucirumab PK parameters generated using a PopPK approach with sparse PK samples collected in trial REGARD to be included in the product labeling for the indicated patient population by January 22, 2014. Apparent differences in PK profiles were observed between Japanese and non-Japanese patients based on the data from JVBN and JVBI studies; therefore the proposed PK information based on the data from JVBW (Japanese patients) may not represent that in the indicated population.

Thank you

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/s/  
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SHARON K SICKAFUSE  
01/08/2014



BLA 125477/0

**INFORMATION REQUEST**

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application:

**Regarding the anti-drug antibody assays:**

1.



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We request a response by January 9, 2014, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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SARAH B KENNETT  
12/31/2013



BLA125477/0

**MID-CYCLE COMMUNICATION**

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

Dear Ms. Norby:

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

We also refer to the teleconference between representatives of your firm and the FDA on December 19, 2013. 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}*

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:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Teleconference Date:** December 19, 2013

**Application Number:** BLA 125477/0  
**Product Name:** Cyramza (ramucirumab)  
**Indication:** Treatment of advanced gastric cancer and gastroesophageal junction adenocarcinoma after prior chemotherapy

**Applicant Name:** Eli Lilly and Co.

**Teleconference Chair:** Steven Lemery, M.D.  
**Teleconference Recorder:** Sharon Sickafuse, M.S.

**FDA ATTENDEES**

**Office of Hematology and Oncology Products**

**Division of Oncology Products 2**

Mimi Biable

Sandra Casak, M.D.

Patricia Keegan, M.D.

Steven Lemery, M.D., M.H.S.

Abhilasha Nair, M.D.

Sharon Sickafuse, M.S.

**Division of Hematology Oncology Toxicology**

Whitney Helms, Ph.D.

**Office of Biotechnology Products**

**Division of Monoclonal Antibodies**

Michele Dougherty, Ph.D.

**Office of Manufacturing and Product Quality**

**Division of Good Manufacturing Practice Assessment**

Francis Godwin, Ph.D.

Biotech Manufacturing Assessment Branch

Candace Gomez-Broughton, Ph.D.

Patricia Hughes-Troost, Ph.D.

Kalavati Suvarna, Ph.D.

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (6)

## **SPONSOR ATTENDEES**

Polina Binder, M.D., Global Patient Safety  
Jonathan Denne, Ph.D., Biostatistics  
Richard Gaynor, M.D., Medical  
Allen Melemed, M.D., Medical  
Robert Metcalf, Ph.D., Global Regulatory Affairs  
Deborah Norby, Global Regulatory Affairs  
AnneMarie O'Connell, Global Regulatory Affairs, CMC  
Vijayapal Reddy, Ph.D., Nonclinical  
Katherine Sugarman, M.D., Global Regulatory Affairs

## **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**

Lilly was advised that a Warning Letter was issued to (b) (4) on (b) (4) (b) (4) has 15 business days to respond to the letter. FDA will review (b) (4) response to determine acceptability and the site will need to be re-inspected.

Lilly stated that they are aware of the Warning Letter and will submit a revised Section 3.2.P.3.1, Manufacturers, withdrawing the (b) (4) site and listing the Lilly Indianapolis IN Technology Center as the sole drug product manufacturing site for ramucirumab. (b) (4)

As previously communicated to Lilly on November 27, 2013, submission of a revised Section 3.2.P.3.1, Manufacturers would not constitute a major amendment.

## **3.0 INFORMATION REQUESTS**

Provide information regarding the incidence of bleeding in patients who received ramucirumab while taking NSAIDs. Lilly agreed to do so and will look at their database of all trials.

## **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

There are no major safety concerns identified at this time and there is currently no need for a REMS.

## **5.0 ADVISORY COMMITTEE MEETING**

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

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

A late cycle meeting is scheduled for February 11, 2014. Revised labeling and request for PMRs/PMCs is due to Lilly by March 24, 2014.

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/s/  
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SHARON K SICKAFUSE  
12/24/2013



BLA 125477/0

## INFORMATION REQUEST

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application:

1. Provide any additional available stability data for drug substance (DS) and drug product (DP) to support setting the expiry dates. We remind you that the data should be provided in the form of a "simple stability update," which is defined as stability data and analyses performed under the same conditions and for the same batches in the same container closure systems as described in the stability protocol provided in the original submission; it will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix of bracketing approaches that deviate from the stability protocol in the original BLA
2. Regarding the [REDACTED]<sup>(b)(4)</sup>, provide summary data in tabular format for all critical quality attributes assessed [REDACTED]<sup>(b)(4)</sup> similar to the data provided in Table Q9b-2 in the November 19, 2013, response to the October 31, 2013 information request.

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9.

10.

We request a response by December 23, 2013, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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/s/  
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SARAH B KENNETT  
12/17/2013

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, December 10, 2013 9:05 AM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 Product Quality/CMC IR

Hi Deb,

My CMC team has the following IR:

1. Provide the method protocols/SOPs and complete method validation reports for the following analytical methods: G1302, G1290, G1301, G1294, G1303, G1380, G1299, G1291, and G1297.
2. The drug substance and drug product release specifications include several compendial methods: visual appearance, color, clarity, osmolality, and pH; (b) (4)  
 is a release assay on the drug product specification. No information regarding the qualification of the indicated compendial methods is found in the submission. Provide information supporting qualification of compendial methods to the BLA.

Please respond by December 13, 2013. Thanks.

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/s/  
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SHARON K SICKAFUSE  
12/10/2013

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

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Memorandum

**Date:** December 2, 2013

**From:** Sharon Sickafuse, RPM

**BLA:** 125477/0

**Product:** Cyramza (ramucirumab)

**Applicant:** Eli Lilly and Co. (Lilly)

**Subject:** Mid-Cycle Review Meeting

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Major Findings/Issues:

- Based on the results of the REGARD study (supported by high-level results of the RAINBOW study), the risk-benefit for the use of ramucirumab for the treatment of second line gastric/GEJ cancer appears favorable.
- Sponsor has proposed a Pregnancy Category of C based on literature submitted in the BLA regarding inhibition of VEGF signaling or knock out of VEGF gene which suggests impairment of fertility in female primates and rodents, and teratogenic effects in fetuses or lethality. Lilly has not conducted any embryofetal development studies. At this point, the non-clinical team is recommended a Pregnancy Category of D, however their review is still ongoing and it was noted that monoclonal antibodies that target the VEGF pathway are Pregnancy Category C.

Status of OSI Inspections:

Inspections of the selected clinical sites (Brazil, Korea, and M.D. Anderson) are completed. No issues were identified. An inspection of all trial documents at Lilly's site in New Jersey was planned for the week of November 17<sup>th</sup>; however OSI was notified a few days before the planned inspection date that Lilly had moved the documents to their Indianapolis location. OSI is hoping to reschedule the applicant inspection for December.

Status of Facility Inspections:

Drug substance is manufactured at the ImClone site in New Jersey. Drug product is manufactured at the Lilly site in Indianapolis and at [REDACTED] (b) (4). Inspections have been completed for the ImClone and Lilly sites and no major issues have been identified.

An inspection of the (b) (4) site, not related to this BLA, was classified as OAI. A Warning Letter is circulating, but it is not known when it will issue. (b) (4)

In the event that the open inspection issues are not resolved by the late cycle meeting, Lilly will submit a revised Section 3.2.P.3.1, Manufacturers, that lists the Lilly Indianapolis IN Technology Center as the sole drug product manufacturing site for ramucirumab.

Labeling Meetings Scheduled:

January 23, 2014	Clinical Studies Indications and Usage Dosage and Administration Warnings and Precautions
February 3, 2014	Warnings and Precautions Adverse Reactions – not including immunogenicity Use in Specific Populations – Pediatric Use Use in Specific Populations – Geriatric Use Overdosage Patient Counseling
February 6, 2014	Adverse Reactions – immunogenicity Drug Interactions Use in Specific Populations if needed Clinical Pharmacology
February 13, 2014	Dosage Forms & Strengths Description How Supplied/Storage and Handling Use in Specific Populations – Pregnancy Use In Specific Populations – Nursing Mothers Nonclinical Toxicology

Labeling needs to be sent to Lilly by March 24, 2014.

Status of PMRs/PMCs:

CMC may request a PMC for re-assessment of specifications for release and stability.

REMS:

At this point, the team does not anticipate that a REMS will be needed. A meeting between the clinical team and OSE is scheduled for December 9, 2013.

Review Due Dates:

Primary reviews: January 23, 2014  
CDTL review: March 26, 2014



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/s/  
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SHARON K SICKAFUSE  
12/06/2013

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, December 03, 2013 1:07 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 - Quality Micro IR

Hi Deb,

My team has the following IR:

Please provide the studies used to support the [REDACTED] (b) (4)  
[REDACTED] maintenance of product temperature at 2-  
8 C during shipment.

Thanks

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/s/  
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SHARON K SICKAFUSE  
12/03/2013

## Hennessey, Lyndsay

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**From:** Hennessey, Lyndsay  
**Sent:** Wednesday, November 27, 2013 8:33 AM  
**To:** Anne.O'Connell@imclone.com  
**Cc:** Hennessey, Lyndsay; Sickafuse, Sharon  
**Subject:** RE: Ramucirumab BLA 125477, Submitted August 23, 2013

Dear Anne Marie,

Please see the reviewers' comment in black below. If you have any further questions, please contact me.

FDA expects to include a request for a simple stability update in an upcoming Information Request . A simple stability update that follows the description outlined in the pre-BLA meeting comments would not constitute a major amendment .

Regarding the inspection issues at the contract drug product manufacturing, (b) (4) FDA agrees that the approach outlined in the email below is acceptable. If the inspection issues at (b) (4) cannot be resolved by the late cycle review, a revised section 3.2.P.3.1, Manufacturers can be submitted to the BLA; the submission would not constitute a major amendment.

Kind regards,  
Lyndsay

**Lyndsay Hennessey**  
Regulatory Health Project Manager  
FDA/CDER/OPS/OBP-IO  
10903 New Hampshire Ave.  
WO Building 21 Room 1523  
Silver Spring, Maryland 20993-0002  
[Lyndsay.Hennessey@fda.hhs.gov](mailto:Lyndsay.Hennessey@fda.hhs.gov)  
240-402-3746

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**From:** Anne Marie O'Connell [mailto:anne.o'connell@imclone.com]  
**Sent:** Friday, November 22, 2013 6:01 PM  
**To:** Kennett, Sarah  
**Cc:** Shiber, Andrew J; Dougherty, Michele  
**Subject:** Ramucirumab BLA 125477, Submitted August 23, 2013

Dear Sarah,

Lilly is approaching the mid-cycle review milestone for Ramucirumab Injection, Solution for Intravenous Infusion (BLA 125477, submitted August 23, 2013), and we would like to follow up with the Agency on our discussion of August 22, 2013 regarding the status of open inspection issues at our contract drug product manufacturer, (b) (4) (see attached draft minutes).

Lilly had requested Agency input on the potential impact to the overall review cycle for the BLA based on open inspection issues at (b) (4)

In the event the open inspection issues are not resolved by the late cycle review milestone (February 11, 2014), to prevent the issuance of a complete response letter, Lilly proposes to submit a revised Section 3.2.P.3.1, Manufacturers, that lists the Lilly Indianapolis IN Technology Center as the sole drug product manufacturing site for Ramucirumab Injection, Solution for Intravenous Infusion. The revised Section 3.2.P.3.1 would be submitted by February 14, 2014, or another date acceptable to the FDA, such that a major amendment can be avoided. Would this approach be acceptable to the FDA?

In addition, at the pre-BLA meeting held January 23, 2013 for Ramucirumab application (see attached minutes), FDA stated a "Simple Stability Update" could be submitted if requested by the FDA during review of the BLA. Lilly has additional time-points for drug substance and drug product lots that are on stability under the protocols submitted in the application and using the same method of analysis. Lilly would like to submit updated Sections 3.2.S.7.1, 3.2.S.7.3.1, 3.2.P.8.1, and 3.2.P.8.3.1 during the week of December 16, 2013. The updated stability is for the same lots of drug substance and drug product in the same container closures systems as described in the stability protocol provided in the original submission. The stability update will use the same tabular presentation as in the original submission as well as the same mathematical analysis and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. The submission will occur within 4 months (no later than December 20) of the submission of the final portion of the BLA (submitted August 23, 2013). Would this information be accepted by the FDA for review such that it would not constitute a major amendment?

Kind Regards,  
Anne Marie

Anne Marie O'Connell  
Associate Vice President, ImClone Regulatory Affairs CMC  
440 Route 22 East  
Bridgewater, NJ 08807  
Phone: 908-243-8849  
Blackberry: (b) (6)  
email: Anne.O'Connell@imclone.com

*Lilly*

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/s/  
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LYNDSAY J HENNESSEY  
11/27/2013



BLA 125477/0

**INFORMATION REQUEST**

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cymruza (ramucirumab).

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

1.

2.

3.

4.

5.

(b) (4)

6.

(b) (4)

We request a written response by December 13, 2013, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Patricia Hughes-Troost  
Team Lead  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA F HUGHES TROOST  
11/26/2013

**From:** Sickafuse, Sharon  
**Sent:** Thursday, November 14, 2013 3:41 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 - stat IR

Hi Deb,

My stat reviewer has the following IR:

Please provide the locations of all data sets used in tcmthadhoc\_fp.sas to create table JVBD.14.12. Please also provide SAS program "asetup.sas" and data set "CP12-0715 prior Tx category\_201211.xlsx" referenced in iadsub.sas.

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/s/  
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SHARON K SICKAFUSE  
11/14/2013



BLA 125477/0

**INFORMATION REQUEST**

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cynamza (ramucirumab).

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

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.



7.

(b) (4)

8.

9.

10.

We request a written response by November 15, 2013, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Patricia Hughes-Troost  
Team Lead  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA F HUGHES TROOST  
11/08/2013



BLA 125477/0

## INFORMATION REQUEST

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

Dear Ms. Norby:

Please refer to your biologics license application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act for Cyramza (ramucirumab).

We have reviewed the chemistry, manufacturing and controls section of your application and have determined that the following information is necessary to take a complete action on your application:

The level of detail and amount and types of data provided in the Manufacturing Process Development and Process Validation sections (3.2.S.2.6 and 3.2.S.2.5) are not sufficient to support the process parameters and controls presented in the Description of Manufacturing Process and Process Controls and Controls of Critical Steps and Intermediates sections (3.2.S.2.2 and 3.2.S.2.4). Additional information and clarification required to evaluate the conclusions made regarding critical quality attributes (CQA), critical process parameters (CPP), and Critical In Process Controls (CIPC) and the subsequent inclusions in sections 3.2.S.2.2 and 3.2.S.2.4 is described in the following comments. It may be necessary to update sections 3.2.S.2.2 and 3.2.S.2.4 to include additional/tighter commitments regarding the manufacturing process and controls in the BLA.

### *Critical Quality Attributes (CQA)*

1. Regarding the quality attribute assessment tool:
  - a. Provide additional clarification regarding what would be considered a “significant clinical event or major safety/toxicological concern” versus “manageable/minor clinical events.”

- b. For the assessment of impact on biological activity in the Impact Score for Quality Attribute Assessment table (3.2.S.2.6.1.1-1), an impact score of high is given to an attribute that results in a greater than (b) (4) change in biological activity and an impact score of medium is given to an attribute that results in a (b) (4) change in biological activity.
- 1) Clarify how biological activity is defined or assessed in the context of the quality attribute assessment.
  - 2) (b) (4)
  - 3) An impact score of “high” is given when an attribute results in a “significant change in PK linked to a quality attribute” and a “significant change in PK with no clear link to a specific quality attribute.” Provide information as to how the determination of a significant change in PK is made.
  - 4) An impact score of “medium” is made when a change of “(b) (4)” (b) (4) Clarify how this correlation was evaluated.
2. The ramucirumab molecule-related quality attributes severity risk assessment presented in Table 3.2.S.2.6.1.4-1 includes an impact risk classification and a knowledge source risk classification.
- a. Clarify what the knowledge source or sources were that support the impact assessment for each attribute.
  - b. If any data are available to support the impact assessment, for example from biological activity assays, provide the data in a clear format.

3. (b) (4)

1 Page Withheld in Full as B4(CCI/TS)  
Immediately Following this Page

*Design of Experiment (DOE) Studies*

7. Regarding the overall approach to classification of process parameters described in figure 3.2.S.2.6.2-2, it is not clear that relevant process parameters were assessed for the potential to impact CQAs.
  - a. For each unit operation, provide a list of the process parameters that were assessed.
  - b. For parameters that were assessed as non-critical, provide a summary of the data that were considered, including operating ranges considered for each parameter, the specific CQAs that were considered in the assessment and acceptance criteria for each, and a summary of the rationale supporting the classification.
  
8. For those parameters that were assessed as a probable risk to a CQA and tested in DoE studies, a “determination of practical significance” was performed as described in figure 3.2.S.2.6.2.2-1.
  - a. It is unclear if the decision tree was used to assess results from both the preliminary and the confirmatory DoE studies. Clarify at what point the decision tree was utilized. If the decision tree was only used to assess results of the confirmatory DoE studies, provide a comprehensive description of the tool or approach that was utilized to assess the practical significance of statistically significant results in the preliminary DoE studies.
  - b. Regarding the tool described in figure 3.2.S.2.6.2.2-1:
    - 1)  (b) (4)
    - 2)
    - 3)

9.

10. Insufficient information regarding the DoE design and analytical approach was provided to allow for an evaluation of the studies performed and the conclusions drawn. Provide additional details of the study design and analysis:
- While it is clear that parameters that were assessed as critical were assessed at the ranges indicated in the BLA, it is not clear what approach was taken to varying the parameter settings across the range identified. Provide a clear and concise accounting of the parameter settings employed in each analysis.
  - Provide the rationale or justification for how each parameter was varied in each of the studies.
  - Identify all CQAs that were assessed in each study.
  - Identify the pre-specified CQA acceptance criteria that were employed in each study.
11. Only high level summary data from the preliminary and confirmatory DoE studies were included in the BLA. Provide more detailed data including a summary of the analyses that includes representative plots and the outcomes of the ANOVA analyses.

3 Pages Withheld in Full as B4(CCI/TS) Immediately  
Following this Page

21.

We request a response by November 19, 2013, in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing.

If you have any questions, please contact Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sarah Kennett, Ph.D.  
Review Chief  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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SARAH B KENNETT  
10/31/2013



BLA 125477/0

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company  
33 ImClone Drive  
Branchburg, NJ 08876

ATTENTION: Deborah L. Norby  
Associate Vice President, Regulatory Affairs

Dear Ms. Norby:

Please refer to your Biologics License Application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351 of the Public Health Service Act, for Ramucirumab, 100 mg/10 mL and 500 mg/50 mL.

We also refer to your August 23, 2013, correspondence, received August 23, 2013, requesting review of your proposed proprietary name, Cyramza. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 23, 2013, 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 Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sharon Sickafuse at (301) 796-1462.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
10/25/2013



BLA 125477/0

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

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

Dear Ms. Norby:

Please refer to your Biologics License Application (BLA) dated August 23, 2013, received August 23, 2013, submitted under section 351(a) of the Public Health Service Act for “Cynamza (ramucirumab).”

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is **April 23, 2014**.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 24, 2014. In addition, the planned date for our internal mid-cycle review meeting is December 2, 2013. Based on the October 10, 2013, teleconference regarding IND 11856, during which agreement was reached that protocol information and the top-line results from the RAINBOW trial that confirm the overall survival effect observed in the REGARD trial may be submitted in November 2013 to this BLA, at this time, we are not planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. Provide a statement whether all sites described in the Audit Summary for Study CP12-0715/14T-IE-JVBD (REGARD), “A Phase 3, Multicenter, Randomized, Double-Blind Study of Ramucirumab plus Best Supportive Care (BSC) vs. Placebo plus BSC in the Treatment of Advanced Gastric or Gastric Esophageal Adenocarcinoma After Disease Progression During or Following First-Line Platinum-or Fluoropyrimidine-Containing Therapy,” conducted the study according to good clinical practices.
2. Submit the following regarding the top-line results from study CP12-0922 (RAINBOW), “Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma”:
  - a. Copies of the pre-Phase 3 meeting minutes for the RAINBOW study.
  - b. Copies of the protocol, all amendments, and the statistical analysis plan.
  - c. *Brief* report describing the major efficacy findings of the primary and secondary endpoints and overall survival estimates in relevant subgroups.
  - d. Datasets that allow us to reproduce efficacy findings *for overall survival* in the intent-to-treat population and in relevant subgroups.
  - e. Safety information, *only* if the information would strengthen the WARNINGS and PRECAUTIONS section of the label (i.e., indicate increased severity of a specific adverse reaction or include a new adverse reaction) and/or that would change the risk/benefit assessment of ramucirumab.

CMC

3.  (b) (4)

4. Regarding the ramucirumab master cell bank (MCB) testing described in Section 3.2.S.2.3, Control of Materials,  (b) (4)

5. Provide the reports for all safety testing performed on the ramucirumab MCB and working cell banks (WCBs).

6.

7.

8.

9.

10.

11.

(b) (4)

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

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

In the HIGHLIGHTS OF PRESCRIBING INFORMATION:

12. Remove the white space between the “HIGHLIGHTS OF PRESCRIBING INFORMATION” and the sentence, “These highlights do not include all the information needed to use CYRAMZA safely and effectively.”
13. Remove the white space between the product title and “Initial U.S. Approval”.
14. Add bulleted subheadings under the DOSAGE FORM AND STRENGTHS section.

In the FULL PRESCRIBING INFORMATION: CONTENTS\*:

15. In the “\*Sections or subsections omitted from the full prescribing information are not listed.” sentence, capitalize the words “full”, “prescribing”, and “information.”

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by October 31, 2013. The resubmitted labeling will be used for further labeling discussions.

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

### **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. Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

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/  
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PATRICIA KEEGAN  
10/22/2013

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** October 10, 2013

**Application Number:** BLA 125477/0

**Product Name:** Cyramza (ramucirumab)

**Sponsor/Applicant Name:** Eli Lilly and Company (Lilly)

**Subject:** Discuss the high level results of study CP12-0922 (RAINBOW), “A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma,” and to discuss the content and format of RAINBOW data to be sent to FDA.

### **FDA Participants:**

Division of Oncology Products 2

Sandra Casak, M.D.

Lola Fashoyin-Aje, M.D.

Steven Lemery, M.D., M.H.S.

Patricia Keegan, M.D.

Missiratch (Mimi) Biable

Monica Hughes, M.S.

Office of Translational Sciences/Office of Biostatistics

Division of Biostatistics V

Hui Zhang, Ph.D.

Kun He, Ph.D.

### **Sponsor/Applicant Participants:**

#### **Lilly Participants**

Deborah Norby, AVP – Global Regulatory Affairs

Katherine Sugarman, Senior Director – Global Regulatory Affairs

Jonathan Denne, Senior Research Advisor – Statistics

Allen Melemed, Senior Director – Medical, Product Development Leader

Michael Emig, Senior Medical Advisor

Benjamin Anderson, VP – Global Product Team Leader

Polina Binder, AVP – Global Patient Safety

Jonathan Schwartz, VP – Clinical Science

Robert Metcalf, VP – Global Regulatory Affairs

Mark Leusch, Advisor – Regulatory Affairs

Richard Gaynor, VP – Oncology Product Development

Kumari Chandrawansa, Director – Biostatistics

## **1.0 BACKGROUND:**

On October 10, 2013, FDA held a teleconference to discuss Lilly's high level results of the Phase 3 Study RAINBOW as agreed to at the January 17, 2013, pre-BLA meeting held for the CP12-0715/14T-IE-JVBD study (REGARD), "A Phase 3, Multicenter, Randomized, Double-Blind Study of Ramucirumab plus Best Supportive Care (BSC) vs. Placebo plus BSC in the Treatment of Advanced Gastric or Gastric Esophageal Adenocarcinoma After Disease Progression During or Following First-Line Platinum-or Fluoropyrimidine-Containing Therapy.", currently under review under BLA 125477. Lilly presented the attached slide deck (emailed to FDA on October 8, 2013) which contained the high level safety and efficacy results for the study. The slide deck also included a proposal as to what will be submitted to the original BLA (BLA 125477/0) with regards to data format and content of the RAINBOW study.

## **2.0 DISCUSSION:**

FDA informed Lilly that the topline RAINBOW results strengthen the application under review (BLA 125477/0) and asked Lilly to submit the following as an amendment to the original BLA:

1. Datasets that allow the Agency to reproduce efficacy findings for overall survival in the intent-to-treat population and in relevant subgroups.
2. Copies of the pre-Phase 3 meeting minutes in reference to the RAINBOW trial.
3. Copies of the protocol, all amendments, and the statistical analysis plan of the RAINBOW trial.
4. Brief report describing the major efficacy findings of the primary and secondary endpoints limited to OS, PFS, and objective response rate and overall survival estimates in relevant subgroups.
5. FDA requested safety information from the RAINBOW trial, in BLA 125477/0, only if the safety information would strengthen the Warnings and precautions Section of the label (specifically more severe risk or a new risk) and/or that would change the risk/benefit assessment of the product (for use under the current application).

Lilly estimated that the above information will be submitted to FDA during the first week of November 2013.

Lilly asked if the submission of the above information, to the original BLA, is considered a major amendment and if it would change the review clock. FDA conveyed to Lily that this topic is currently under internal discussion and will be taken up with management as the submission of the high level RAINBOW results as an amendment to the original BLA does not follow the current PDUFA 5 guidance. FDA stated that even if the submission is considered a major amendment, that the Agency would not necessarily wait until the end of the extended review clock to take action on the application.

Lilly asked if the original BLA was going to be designated a priority review and whether the Agency intended to discuss this application during an ODAC meeting. FDA advised that review

designation determination will be communicated in the filing letter. FDA stated that an application is given a priority review designation based on the primary claim made in the original BLA submission that the product demonstrates a significant improvement in safety or effectiveness compared to currently approved therapies. FDA stated that although the data from the RAINBOW study would not change considerations for priority review, the results strengthen the conclusion that the overall survival effect observed in the REGARD study is a true finding.

FDA also stated that they are unable to comment on the timing of the ODAC prior to filing the BLA; however, FDA stated that inclusion of the results from the RAINBOW trial in the application reduced the chance that FDA will convene an advisory committee to discuss this application. FDA asked when a pre-BLA meeting request can be anticipated for the RAINBOW study as well as when the stand-alone application can be expected. Lilly confirmed that the pre-BLA meeting request will be submitted by end of this month and the stand alone BLA in the first quarter of 2014.

### **3.0 ACTION ITEMS:**

None

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/s/  
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MISSIRATCH BIABLE  
10/16/2013

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, September 24, 2013 12:22 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 clin pharm IR

**Importance:** High

Hi Deb,

The clin pharm reviewer has the following IR:

Please submit the bioanalytical study reports for the modified assay for trials REGARD and JVBW by September 27, 2013.

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/s/  
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SHARON K SICKAFUSE  
09/24/2013

## Planning Meeting Minutes

### BLA 125477/0

Product: Ramuciruib (Cynamza)  
Submission Date: August 23, 2013  
Received Date: August 23, 2013  
Sponsor: Eli Lilly and Co.

**Proposed Indication:** gastric cancer

#### **Review Team/Collaborators for BLA 125477/0:**

Patricia Keegan, M.D., Director DOP2  
*Sharon Sickafuse, M.S., Lead Regulatory Health Project Manager*  
Sandra Casak, M.D., Medical Officer  
Steve Lemery, M.D., Medical Officer (TL and CDTL)  
Hui Zhang, Ph.D., Statistics  
Kun He, Ph.D., Statistics (TL)  
Lillian Zhang, Ph.D., Clinical Pharmacology  
Hong Zhao, Ph.D., Clinical Pharmacology (TL)  
Jee Eun Lee, Ph.D., Pharmacometrics  
Nitin Mehrotra, Ph.D. Pharmacometrics (TL)  
Sachia Khasar, Ph.D., Non-Clinical  
Whitney Helms, Ph.D., Non-Clinical (TL)  
*Lyndsay Hennessey, OBP RPM*  
Michelle Dougherty, Ph.D., Product  
Sarah Kennett, Ph.D., Product (TL)  
Candace Gomez-Broughton, Ph.D., Quality Micro DP  
Kalavati Suvarna, Ph.D., Quality Micro DS  
Patricia Hughes, Ph.D., Quality Micro (TL)  
*Sue Kang, OSE RPM*  
Jibril Abdus-Samad, OSE/DMEPA  
Todd Bridges, OSE/DMEPA (TL)  
Suzanne Robottom, OSE/DRISK  
Cynthia LaCivita, OSE/DRISK (TL)  
Lauren Iacono-Connor, OSI  
*Olga Salis, OPDP RPM*  
Quynh-Van Tran, OPDP

#### **Review Status:**

- Priority Review requested, team agreed to a 8 month review as outlined below.
- Categorical Exclusion requested
- Has Orphan Drug designation, so PREA doesn't apply.
- The clinical development of ramuciruib for gastric cancer has been conducted under IND 11856.

**1. Dates for Milestones and for When Letters Must Issue:**

<b>Milestone</b>	<b>Due</b>
<b>Acknowledgment Letter</b>	Issued 9-5-2013
<b>Filing Action Letter</b>	10-22-2013
<b>Deficiencies Identified Letter (74 Day Letter)</b>	11-5-2013
<b>Send proposed labeling/PMR/PMC/REMS to applicant</b>	3-24-2014
<b>Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant</b>	3-31-2014
<b>Review Target Due Dates:</b>	
<i>Primary Review Due</i>	1-23-2014
<i>Secondary Review Due</i>	
<i>CDTL Review Due</i>	3-26-2014
<i>Division Director Review Due</i>	4-11-2014
<i>Office Director Review Due/Sign-Off</i>	4-23-2014
<b>Compile and circulate Action Letter and Action Package</b>	4-2-2014
<b>FINAL Action Letter Due</b>	4-23-2014

**2. Consults/Collaborative Reviewers:**

OPDP	Olga Salis – RPM Quynh-Van Tran
OSE	Sue Kang - OSE RPM Suzanne Robottom – DRISK Jibril Abdus-Samad - DMEPA
Facility/OMPQ	Kala Suvarna - DS Candace Gomez-Broughton - DP
QT-IRT	Review in DARRTS: 8-19-2013
OSI	Lauren Iacono-Connor assigned, sites selected, site notification has begun.
Pediatric Page/PeRC	Pediatric Page in DARRTS: 9-10-2013
SGEs or Patient Representatives	

2. **ODAC Presentation:** March 13, 2014

Practice sessions TBD

3. **Upcoming Internal Team Meetings:**

**Applicant Orientation Presentation:** Held on June 24, 2013.

**Planning Meeting** held on: September 18, 2013

**Filing Meeting** scheduled for: October 7, 2013

**Team Meeting** scheduled for: November 14, 2013

**Labeling Meeting #1** scheduled for: November 21, 2013

[Indications & Usage, Warnings & Precautions, Adverse Reactions, Patient Counseling]

**Mid-Cycle Meeting** scheduled: for December 2, 2013

[Midcycle communication (telecon) to sponsor: December 19, 2013]

To be scheduled:

Additional labeling meetings

PMR/PMC meeting, if needed

Internal meeting for Late Cycle Meeting

Late Cycle Meeting

Wrap-up Meeting

4. **Discussion:**

Drs. Casak and Lemery stated that Lilly plans to submit topline results of a 2<sup>nd</sup> study of ramucirumab plus paclitaxel for treatment of gastric cancer in late December/early January. If the study results are positive for overall survival, the ODAC meeting scheduled for March 13, 2014, will most likely be canceled and an action taken sooner than April 23, 2014.

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/s/  
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SHARON K SICKAFUSE  
09/18/2013

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, September 11, 2013 11:36 AM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 - clinical IR

Hi Deb:

My clinical reviewer has the following IR:

Please clarify the following discrepancies in the ADVS (vital signs) analysis dataset. As the selected patient visit is the baseline (pretreatment) assessment and the date of the assessment is the same, values in the AVAL and BASE columns should be identical. Similar discrepancies can be found in the systolic blood pressure assessments.

**Ramucirumab arm – diastolic blood pressure**

USUBJID	ADT	AVISIT	AVAL	BASE	VSDTC
CP12-0715/126-0001	08/26/2011	PRE-TREATMENT	90	70	2011-08-26
CP12-0715/139-0001	06/17/2011	PRE-TREATMENT	90	80	2011-06-17
CP12-0715/234-0005	06/24/2011	PRE-TREATMENT	90	70	2011-06-24
CP12-0715/331-0002	11/11/2011	PRE-TREATMENT	90	70	2011-11-11
CP12-0715/410-0006	01/06/2011	PRE-TREATMENT	100	83	2011-01-06
CP12-0715/430-0007	07/14/2011	PRE-TREATMENT	92	89	2011-07-14
CP12-0715/508-0005	08/29/2011	PRE-TREATMENT	90	60	2011-08-29
CP12-0715/526-0003	03/07/2011	PRE-TREATMENT	96	92	2011-03-07
CP12-0715/526-0008	09/27/2011	PRE-TREATMENT	90	83	2011-09-27
CP12-0715/532-0010	08/03/2011	PRE-TREATMENT	97	85	2011-08-03
CP12-0715/534-0005	08/25/2011	PRE-TREATMENT	94	90	2011-08-25
CP12-0715/540-0001	02/08/2011	PRE-TREATMENT	90	70	2011-02-08
CP12-0715/544-0004	09/06/2011	PRE-TREATMENT	96	90	2011-09-06
CP12-0715/552-0001	10/05/2011	PRE-TREATMENT	90	85	2011-10-05
CP12-0715/606-0008	11/17/2011	PRE-TREATMENT	90	80	2011-11-17
CP12-0715/635-0003	03/17/2011	PRE-TREATMENT	95	106	2011-03-17
CP12-0715/660-0002	06/28/2011	PRE-TREATMENT	95	78	2011-06-28
CP12-0715/660-0003	10/04/2011	PRE-TREATMENT	96	99	2011-10-04

CP12-0715/700-0004	07/28/2011	PRE-TREATMENT	90	80	2011-07-28
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**Placebo arm – diastolic blood pressure**

USUBJID	ADT	AVISIT	AVAL	BASE	VSDTC
CP12-0715/234-0003	06/07/2011	PRE-TREATMENT	97	82	2011-06-07
CP12-0715/410-0007	01/10/2011	PRE-TREATMENT	97	81	2011-01-10
CP12-0715/410-0013	07/21/2011	PRE-TREATMENT	100	79	2011-07-21

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SHARON K SICKAFUSE  
09/11/2013



BLA 125477/0

**BLA ACKNOWLEDGEMENT**

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

Dear Ms. Norby:

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:** Cyramza (ramucirumab)  
**Date of Application:** August 23, 2013  
**Date of Receipt:** August 23, 2013  
**BLA Number:** 125477/0  
**Proposed Use:** Treatment of advanced gastric cancer and gastroesophageal junction adenocarcinoma after prior chemotherapy

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

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

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application.

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](mailto: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) 796-230.

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

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SHARON K SICKAFUSE  
09/06/2013

**From:** Sickafuse, Sharon  
**Sent:** Monday, August 19, 2013 12:07 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 Clinical Pharmacology IR

Hi Deb,

My clin pharm team as the following IR:

1. The dataset under the folder i4t-ie-jvbn is not the correct dataset for Study CP12-0402. The folder only includes the data for Study CP12-0401. Please submit the correct dataset.
2. We could locate data for Study CP12-0715 (i4t-ie-jvbd) but noted that they are only from 15 subjects. However, in the clinical pharmacology summary of your submission (Clin-pharm-sum-us-gastric, page16), it states that 58 patients were evaluable for Cmin. Please submit the complete dataset.
3. We note that you used "C" as a flag for excluded observations in the dataset for Study CP12-1705. For an adequate analysis, this flag should be located in a separate column (i.e., first column of the dataset).

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SHARON K SICKAFUSE  
08/19/2013

**From:** Sickafuse, Sharon  
**Sent:** Monday, July 22, 2013 12:46 PM  
**To:** Deborah Norby (Deborah.Norby@imclone.com)  
**Subject:** BLA 125477/0 immunogenicity methods IR

Hi Deb,

My CMC team has the following IR:

Provide the method protocols for the following methods: (b) (4)

[REDACTED] If

additional validation reports will be submitted to support the assessment of ramucirumab immunogenicity, provide the corresponding method protocol.

Thanks

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SHARON K SICKAFUSE  
07/22/2013



BLA 125477/0

**BLA PRESUBMISSION ACKNOWLEDGEMENT**

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

Dear Ms. Norby:

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: Cyramza (ramucirumab)

Date of Submission: March 26, 2013

Date of Receipt: March 27, 2013

Our Reference Number: BLA 125477/0

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.

The BLA Secondary Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of 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.

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](mailto: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 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

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SHARON K SICKAFUSE  
03/29/2013

**From:** Sickafuse, Sharon  
**Sent:** Thursday, February 21, 2013 4:59 PM  
**To:** 'Deborah Norby'  
**Subject:** RE: IND 11856, Ramucirumab; February 28, Clin Pharm Follow Up Telecon

Hi Deb,

The clin pharm team has the following response to your question of "Does FDA agree that the proposed PK content (Table1) is adequate to inform a risk/benefit assessment for the proposed use?":

FDA Response: Your proposed pharmacokinetic content to be included in the initial BLA submission in support of the proposed gastric adenocarcinoma indication appears acceptable. However, the adequacy of the PK content will be determined upon the review of your BLA submission.

---

**From:** Deborah Norby [<mailto:Deborah.Norby@imclone.com>]  
**Sent:** Monday, February 18, 2013 1:36 PM  
**To:** Sickafuse, Sharon  
**Subject:** IND 11856, Ramucirumab; February 28, Clin Pharm Follow Up Telecon

**Hi Sharon,**  
**In anticipation of the follow up telecon scheduled with the Clin Pharm group, Lilly is providing this brief pre-read to facilitate the discussion with the FDA on Feb 28th.**

**The list of planned attendees is provided below.**

**Planned Attendees**

**Lan Ni, Ph.D., Senior Director PK/PD, Drug Disposition**  
**Ling Gao, Ph.D., Associate Director, Clinical Pharmacology, Global Medical Sciences-Biometrics**  
**Patricia Brown-Augsburger, Ph.D., Research Advisor, Drug Disposition**  
**Michelle Burgess, BSc Hons, Clinical Pharmacology and Biopharmaceutics**  
**Robert Konrad, MD, Distinguished Medical Fellow, Lilly Laboratory for Experimental Medicine**  
**Allen Melemed, MD, Senior Medical Director**  
**Colleen Mockbee, PharmD, Senior Director, Regulatory Affairs Oncology**  
**Mark Leusch, PhD, Director, Regulatory Affairs Oncology**  
**Deborah Norby, BSN, Associate Vice President, Global Regulatory Affairs**  
**Katherine Posther Sugarman, MD, Advisor, Regulatory Affairs Oncology**  
**Dong Geng, Ph.D., Associate Director Pharmacology and Clinical Pharmacology**

**Please let me know if you have any questions.**  
**Thanks,**

Deb

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/s/  
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SHARON K SICKAFUSE  
03/01/2013

IND 011856

**MEETING PRELIMINARY COMMENTS**

ImClone LLC  
Attention: Colleen Mockbee, Rph  
Senior Director, GRA-US Oncology  
Eli Lilly and Company  
33 ImClone Drive  
Branchburg, NJ 08876

Dear Ms. Mockbee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Ramucirumab [Human Monoclonal Antibody (IMC-1121B) to the Kinase Domain Insert Receptor (KDR) and Chemotherapy.”

We also refer to your November 9, 2012, correspondence, received November 9, 2012, requesting a meeting to discuss concurrence from the Agency on the structure, content and timing of submission of the Quality module (Modules 2.3 and 3) of the BLA.

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.

If you have any questions, call me, at (301) 796-4798.

Sincerely,

*{See appended electronic signature page}*

CDR Andrew Shiber, Pharm.D.  
United States Public Health Service  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research  
Andrew.Shiber@fda.hhs.gov

## PRELIMINARY MEETING COMMENTS

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** January 23, 2013 at 2PM Eastern  
**Meeting Location:** FDA White Oak Building 21  
Conference Room 1539  
10903 New Hampshire Ave  
Silver Spring, MD 20993

**Application Number:** 11856  
**Product Name:** Ramucirumab  
**Indication:** **Gastric Junction Cancer (GEJ)**  
**Sponsor/Applicant Name:** ImClone, LLC

### **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 January 23, 2013, at FDA White Oak, Silver Spring, Maryland between ImClone, LLC and the Division of Monoclonal Antibodies. 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. 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). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

### **1.0 BACKGROUND**

**Purpose:** To discuss concurrence from the Agency on the structure, content and timing of submission of the Quality module (Modules 2.3 and 3) of the BLA.

The meeting package describes the sponsor's intent to register the C1 drug substance manufacturing process, alternate vial and container closure suppliers, addition of the 10 ml vial drug product presentation, and the manufacture of a new working cell bank. A high level view

of the lot genealogy to support the C1 drug substance and drug product comparability, validation and expiry is provided.

## 2. DISCUSSION

### Question 1

*Lilly intends to provide the procedure for preparation of a new working cell bank (WCB) and proposed acceptance criteria for release of a new WCB in the BLA, and once qualified, implement use of a new WCB made according to the filed process in commercial production. A certificate of analysis for the new WCB will be submitted in the first Annual Report to the BLA. Does the Agency agree with this approach?*

### FDA Response

If the manufacturing and qualification of the new working cell bank are performed under an approved protocol, the report may be submitted in the Annual Report.

We note that while the information provided describing the safety characterization or evaluation of a new ramucirumab working cell bank appears to be acceptable, no information is provided regarding comparability of the new working cell bank with respect to product quality attributes of ramucirumab manufactured using the current working cell bank and regarding the integrity/genetic stability of the new cell bank. The additional characterization tests needed to address these points and acceptance criteria should be included in the protocol for manufacturing and qualification of a new working cell bank. In addition, include detailed descriptions of all non-compendial assays (e.g., viral contaminant and identity) performed to support the safety qualification of the new working cell bank with the protocol.

### Question 2

*Lilly anticipated Process C2 would be the commercial launch process, which differs from Process C1* (b) (4)

*Viral clearance validation studies were conducted in accordance with ICH guidelines, using representative Process C2 material. The change* (b) (4)  
*is not expected to impact the validity of the viral clearance studies.* (b) (4)

*does the Agency agree that the approach using* (b) (4)  
*Process C2* (u) (4) *in viral clearance studies is acceptable?*

### FDA Response

The proposal to conduct viral clearance validation studies using C2 process (b) (4) to support commercialization of the C1 process may be acceptable. When the validation study reports are submitted, provide a detailed comparison of protein concentration, process-related impurities, and product quality attributes for (b) (4) the C1 and C2 processes. Any differences noted between (u) (4) the two processes should be assessed for potential impact to the viral clearance results. (b) (4)

(b) (4) provide a detailed comparison of the operating parameters and an assessment of the potential impact on viral clearance.

### Question 3

Based on FDA feedback from the Nov. 2011 Type C meeting, Lilly is proposing (b) (4) (b) (4) Does the Agency agree that the proposed approach to validation of (b) (4) during drug substance manufacture is acceptable?

#### FDA Response

Yes, the proposed validation approach (b) (4) during drug substance manufacture is acceptable. The (b) (4) example that was provided appears to be acceptable to support the validation. Include in the BLA the actual (b) (4) (b) (4) for all validation runs. The (b) (4) defined in the BLA should be supported by data collected either at or beyond the specified limit. Also include the (b) (4) values for product quality parameters in addition to bioburden and endotoxin.

### Question 4

Does the Agency agree with Lilly's approach to removing specific impurity specifications from the drug substance release specifications based on the combination of risk assessment, and data collected from development studies and confirmed through clinical production history and process validation to demonstrate clearance of impurities (b) (4)

#### FDA Response

The approaches described to assessing clearance of process-related impurities to below the level of detection/quantitation appear to be appropriate and may be acceptable to support removing the identified process-related impurities from the drug substance specification. Since complete knowledge of the raw materials used in the ramucirumab drug substance manufacturing process is not available at this time, additional process-related impurities that may need to be assessed for clearance may be identified during the BLA review. A final decision regarding the need for a specification for any particular process-related impurity can only be made following review of data submitted to the BLA. Provide a description of the risk assessment approach utilized and summarize the rationale for the safety level defined for each impurity. The small scale study details provided in the BLA should include a comparison of critical operating parameters between the validated commercial manufacturing process and the small scale model and the qualification data for the scale-down model. Regarding the (b) (4) assay, provide a detailed summary of the origin of the anti-host cell protein antibody(ies) and provide the qualification data demonstrating the specificity and calculated coverage of the assay.

### Question 5

Lilly is proposing to add a specification for (b) (4) (b) (4) to the release and stability testing protocols. (b) (4)

(b) (4) ? Does the Agency agree with Lilly's approach

### FDA Response

The proposed approach (b) (4) appears to be reasonable. The outcome of the comparability study for process C0 and C1 drug substance and drug product and the (b) (4) stability data will play roles in the final assessment of acceptability. In addition, in our response to the April 13, 2012 submission, we suggested that a side-by-side stressed study be performed; studies performed on DS and DP may provide valuable information to help link the (b) (4) and the clinical and commercial materials. FDA notes that Table 16, proposed ramucirumab drug product stability protocol-registration batches, does not include the (b) (4) analysis. We recommend including the (b) (4) analysis in the stability protocol for DP registration batches.

### **Question 6**

*Lilly proposes to provide justification in the BLA to support a request for FDA to waive the in vivo rabbit pyrogen test in favor of an in vitro bacterial endotoxin test (BET) using the Limulus ameobocyte lysate reagent (LAL) as provided for in 21CFR§610.9, Equivalent Methods and Processes. The justification will be based on the studies proposed below. Does the Agency agree with this approach?*

### FDA Response

Yes, the approach is acceptable.

Regarding the bacterial endotoxins test, it has come to our attention that conduct of the bacterial endotoxins test as described in USP <85> may not in all cases provide an accurate measure of bacterial endotoxins. Specifically, recent information indicates that some products show a lower than acceptable endotoxin recovery when a known amount of endotoxin is spiked into the product or product sample and tested after different hold times. In the BLA, confirm the accuracy of your endotoxin reported values by providing evidence that the results are not susceptible to a time-dependent masking effect.

### **Question 7**

*Does the Agency agree that the drug substance and drug product release specifications are adequate to support approval of the planned BLA?*

### FDA Response

The majority of the test methods identified in the drug substance and drug product specifications appear to be generally appropriate. The need for any additional test methods that may be necessary to monitor product quality attributes at release of ramucirumab can only be determined after review of the data submitted to the BLA. The acceptance criteria set for any individual test method or quality attribute should be appropriately justified, taking into account clinical experience and manufacturing experience. The use of (b) (4) for setting release specification acceptance criteria is not clear; note that a (b) (4) is not an acceptable justification for widening acceptance criteria. Determination of the final release specifications for ramucirumab drug substance and drug product will be a BLA review issue.

The endotoxin specification acceptance criterion for DP, (b) (4). We recommend (b) (4) the endotoxin specification acceptance criterion for DP if possible.

We also recommend the container closure integrity test be performed in lieu of the sterility test for stability samples annually and at expiry.

Regarding the acceptance criteria for (b) (4) drug substance and drug product release and stability specifications, we recommend adding a qualitative acceptance criterion (e.g., comparable to reference standard) to the specification in addition to the quantitative limits already defined in order to ensure that the DS and DP do not vary significantly from lot to lot or throughout the stability protocol. The need for a qualitative acceptance criterion can be reassessed once a more robust data set generated with the (b) (4) is available and it is determined that the quantitative criteria that are set are sufficient for the identification of any significant differences.

**Question 8:** Stability:

*A) Does the Agency agree that the proposed stability package (12 months drug substance stability and 6 months drug product stability) will be adequate to support the initial proposed application?*

*Does the Agency agree with Lilly's proposal to provide updated stability results (18 months drug substance results and 12 months drug product results) during the review period in support of setting the expiry date?*

FDA Response

The proposed stability package appears to be adequate to support the initial application.

Regarding the proposed timing of the stability data submission, as per the PDUFA V legislation, agreement must be reached regarding data to be submitted subsequent to the submission of the BLA, and these data must be submitted within 30 days of the submission of the complete BLA. With respect to the timeline for submission of the drug substance and the drug product stability data described in the meeting package, as were included in the preliminary responses for the January 17 pre-BLA meeting, we have the following comments:

FDA may request a "simple stability update" to support a proposed dating period for drug product and drug substance." A simple stability update is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission; it will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. If FDA requests this information, the simple stability update would need to be submitted within 4 months of the submission of the final portion of the BLA or, if designated standard review, within 7 months of the submission of the final portion of the BLA. A simple stability update submitted at FDA's request within these timeframe may be reviewed and considered in shelf life determinations.

*B) Lilly proposes to use the following specifications to monitor the quality of ramucirumab drug substance and drug product on stability. Does the Agency concur that the proposed tests and specifications are appropriate for monitoring the stability of commercial batches?*

#### FDA Response

The post-approval drug substance and drug product stability protocols found in Tables 18 and 19 appear to be generally appropriate to monitor ramucirumab product quality during the shelf-life. The need for any additional test methods in the stability protocols can only be assessed following review of data presented in the BLA. The acceptance criteria for product quality attributes on stability should be appropriately justified and will be a BLA review issue. As was stated during the November 15, 2011 meeting, we recommend that the container closure integrity test be performed annually and at expiry. Please see the response to question 5 for additional comments regarding the stability registration protocols (Tables 15 and 16).

#### **Question 9**

*Lilly intends to submit representative [REDACTED] (b) (4) [REDACTED] in the BLA in sections 3.2.S.4.3, Validation of Analytical Procedures, and 3.2.S.5, Reference Standard or Materials. In addition, these data will be provided in section 3.2.S.2.6, in the side-by-side results of comparability studies performed for Process C0 and C1. Therefore, Lilly proposes to not include any additional chromatograms and gels in Section 3.2.S.7, Stability. Does the Agency agree with this approach?*

FDA Response:

No, we do not agree with the approach. Gels and chromatograms generated during the stability studies should be included in 3.2.S.7 and in 3.2.P.8. While the quantitative data monitors the presence of impurities in DS and DP, the relative identity of the impurities and the presence of novel impurities can only be assessed by visual examination of the gels and chromatograms. At a minimum, the gels and chromatograms for the first and last available timepoints should be included in the BLA.

#### **Question 10**

*Does the Agency agree with the proposal to submit in the BLA [REDACTED] (b) (4) [REDACTED]*

FDA Response:

No, the approach is not acceptable. Submit a batch record for one lot from each site where drug product is manufactured.

#### **Question 11**

*Does the FDA agree that the proposed Tables of Contents for Modules 2.3 and 3 of the BLA provides the appropriate structure and content to support review of the BLA, and at this time, no issues are apparent that would result in a “Refusal to File”?*

FDA Response:

From the product quality perspective, the high level information provided regarding the proposed table of contents for Modules 2.3 and 3 of the BLA appears to be acceptable; however, we note that Table 20 of the meeting package identifies section 3.2.S.3.2 as ‘Summary of Impurities. As per the ICH M4Q(R1) guidance, the section is titled ‘Impurities’ and should contain complete information regarding impurities present in the drug substance or active links to the appropriate sections where the information can be found and not just a summary of information related to impurities. Please see the ICH M4Q Implementation Working Group Questions and Answers document, section 3, for additional information.

When submitting completed reports, for example, comparability or method validation reports, include the associated protocols.

For additional details related to the Quality Microbiology content please refer to the table below:

**Table of contents Boilerplate for Quality Micro information**

<b>ECTD section</b>	
<b><i>Module 1</i></b>	<b><i>Administrative information</i></b>
1.1	Forms
1.2	Cover letter
1.3	Administrative information ➤ <i>A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections.</i>
1.4	Reference Section
1.6	Meetings
1.12	Other correspondence
1.14	Labeling
1.16	Risk management plans
<b><i>Module 2</i></b>	<b><i>Technical Document Summaries</i></b>
<b><i>Module 3</i></b>	<b><i>Quality</i></b>
<b>3.2.S</b>	<b>Drug Substance</b>
<b>3.2.S.1</b>	<b>General information</b>
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General properties
<b>3.2.S.2</b>	<b>Manufacture</b>
3.2.S.2.1	Manufacturer(s) ➤ <i>A complete list of the manufacturing and</i>

	<i>testing sites with their corresponding FEI numbers</i>
3.2.S.2.2	Description of Manufacturing Process and Process Controls
3.2.S.2.3	Control of Materials
3.2.S.2.4	Controls of Critical Steps and Intermediates ➤ <i>Pre-determined in-process bioburden and endotoxin limits and data</i>
3.2.S.2.5	Process Validation and/or Evaluation ➤ <i>Three successful consecutive product (b) (4) validation runs at manufacturing scale.</i> ➤ <i>(b) (4) sanitization and storage validation</i> ➤ <i>Bioburden and endotoxin data obtained during manufacture of the three conformance lots</i> ➤ <i>Data summaries of shipping validation studies</i>
3.2.S.2.6	Manufacturing Process Development
<b>3.2.S.3</b>	<b>Characterization</b>
<b>3.2.S.4</b>	<b>Control of Drug Substance</b>
3.2.S.4.1	Specification ➤ <i>Bioburden and endotoxin</i>
3.2.S.4.2	Analytical Procedures ➤ <i>Bioburden and Endotoxin</i>
3.2.S.4.3	Validation of Analytical Procedures ➤ <i>Bioburden and endotoxin test qualifications</i>
3.2.S.4.4	Batch Analyses
3.2.S.4.5	Justification of Specification
<b>3.2.S.5</b>	<b>Reference Standards or Materials</b>
<b>3.2.S.6</b>	<b>Container Closure System</b>
<b>3.2.S.7</b>	<b>Stability</b>
3.2.S.7.1	Stability Summary and Conclusions
3.2.S.7.2	Post-approval Stability Protocol and Commitment
3.2.S.7.3	Stability Data
<b>3.2.P</b>	<b>Drug Product</b>
<b>3.2.P.1</b>	<b>Description and Composition of the Drug Product</b>
<b>3.2.P.2</b>	<b>Pharmaceutical Development</b>
3.2.P.2.3	Manufacturing Process Development
3.2.P.2.4	Container Closure System
3.2.P.2.5	Microbiological Attributes ➤ <i>Container Closure Integrity test validation and data</i> ➤ <i>The worst-case (b) (4) parameters validated with the container closure integrity test</i>

3.2.P.2.6	Compatibility
<b>3.2.P.3</b>	<b>Manufacture</b>
3.2.P.3.1	Manufacturer(s) ➤ <i>A complete list of the manufacturing and testing sites with their corresponding FEI numbers</i>
3.2.P.3.2	Batch Formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls
3.2.P.3.4	Controls of Critical Steps and Intermediates
3.2.P.3.5	Process Validation and/or Evaluation ➤ <i>Bacterial filter retention study for the sterilizing filter</i> ➤ <i>Sterilization and depyrogenation validation of sterile product-contact equipment and components, and equipment requalification program</i> ➤ <i>In-process controls and hold times</i> ➤ <i>Isolator decontamination, if applicable</i> ➤ <i>Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs,</i> ➤ <i>A description of the routine environmental monitoring program</i> ➤ <i>The lyophilization process and sterilization validation, if applicable</i> ➤ <i>Shipping validation</i>
<b>3.2.P.4</b>	<b>Control of Excipient</b>
3.2.P.4.1	Specification
3.2.P.4.2	Analytical Procedures
3.2.P.4.3	Validation of Analytical Procedures
3.2.P.4.4	Justification of Specification
3.2.P.4.5	Excipients of Animal Origin
3.2.P.4.6	Novel Excipient
<b>3.2.P.5</b>	<b>Control of Drug Product</b>
3.2.P.5.1	Specification ➤ <i>Bioburden, sterility and endotoxin</i>
3.2.P.5.2	Analytical Procedures ➤ <i>Bioburden, sterility and endotoxin</i>
3.2.P.5.3	Validation of Analytical Procedures ➤ <i>Bioburden, endotoxin, and sterility test qualifications</i>
3.2.P.5.4	Batch Analyses
3.2.P.5.5	Characterization of Impurities
3.2.P.5.6	Justification of Specification
<b>3.2.P.6</b>	<b>Reference Standards or Materials</b>
<b>3.2.P.7</b>	<b>Container Closure System</b>
<b>3.2.S.8</b>	<b>Stability</b>
3.2.P.8.1	Stability Summary and Conclusions

	➤ <i>Microbial attributes</i>
3.2.P.8.2	Post-approval Stability Protocol and Commitment ➤ <i>Include container closure integrity test performed in lieu of the sterility test for stability samples annually and at expiry.</i>
3.2.P.8.3	Stability Data
<b>3.2.A</b>	<b>Appendices</b>
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
<b>3.2.R</b>	<b>Regional Information</b>
<b>3.3</b>	<b>Literature References</b>

### Question 12

*Based on the similarity of the C1 and C2 manufacturing processes, does the Agency agree that pre-approval inspection can be conducted during either Process C1 or Process C2 manufacture?*

FDA response:

The pre-approval inspection should occur while the manufacturing facility is in operation for C1 or C2 manufacturing. The decision to waive the inspection (b) (4) will be made after submission is received.

**Question 13:** Fast Track Designation was provided by DA for this application, and a request for a rolling submission was submitted with the request for the pre-BLA meeting to occur on January 17, 2013. Lilly anticipates manufacturing ramucirumab drug substance and drug product from (b) (4). A more detailed manufacturing schedule will be provided at the pre-BLA CMC meeting on January 23, 2013. The list of manufacturing, packaging and testing facilities is provided in Table 21. Based on the proposed timing for manufacture, the list of facilities outlined in Table 21, and the proposed submission date of August 2013 for the Quality Modules, Lilly would like to discuss Agency plans for inspection of the facilities.

FDA response: It is too premature to comment on the plans for inspections. The drug substance manufacturing site, ImClone, LLC, will most likely be inspected and should be in operation during the 2nd - 4th month of the BLA review cycle.

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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.**  
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/s/  
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ANDREW J SHIBER  
01/18/2013



IND 11856

**MEETING PRELIMINARY COMMENTS**

ImClone LLC  
Attention: Colleen Mockbee, RPh  
Senior Director, GRA-US Oncology  
Eli Lilly and Company  
33 ImClone Drive  
Branchburg, NJ 08876

Dear Ms. Mockbee:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Ramucirumab."

We also refer to your October 23, 2012, correspondence, received October 23, 2012, requesting a meeting to discuss pharmacology/toxicology, clinical pharmacology, statistical, and clinical issues related to a proposed BLA submission for the treatment of gastric adenocarcinoma.

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.

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

## PRELIMINARY MEETING COMMENTS

**Meeting Type:** Type B  
**Meeting Category:** pre-BLA

**Meeting Date and Time:** January 17, 2013

**Application Number:** IND 11856  
**Product Name:** Ramucirumab  
**Indication:** Treatment of gastric adenocarcinoma  
**Sponsor/Applicant Name:** ImClone LLC

### 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 January 17, 2013, between ImClone LLC 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. 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). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

### BACKGROUND

On October 23, 2012, ImClone submitted a request for a clinical pre-BLA meeting (SDN 963) to discuss their intention to submit a BLA based on results from study CP12-0715/14T-IE-JVBD (REGARD), "A Phase 3, Multicenter, Randomized, Double-Blind Study of Ramucirumab plus Best Supportive Care (BSC) vs. Placebo plus BSC in the Treatment of Advanced Gastric or Gastric Esophageal Adenocarcinoma After Disease Progression During or Following First-Line Platinum-or Fluoropyrimidine-Containing Therapy." The REGARD study enrolled 355 patients with disease progression during or after first-line platinum- or fluoropyrimidine-containing therapy, randomized 2:1, to receive either 8 mg/kg ramucirumab every 2 weeks and BSC or placebo and BSC. The primary objective was to evaluate the overall survival (OS) of ramucirumab-treated versus placebo-treated patients. Secondary objectives were to evaluate the following: progression-free survival (PFS), including 12-week PFS rate, objective response rate, duration of response, quality of life, pharmacodynamic profile, and immunogenicity.

ImClone states that the primary analysis was performed using a stratified log-rank test. At the time of data cut-off, with 278 events, OS was statistically significantly improved [HR=0.776 (95% CI 0.0603, 0.998), p =0.0473] in patients receiving ramucirumab (median OS 5.2 months, 95% CI 4.4, 5.7) as compared to patients receiving placebo (median OS 3.8

months, 95% CI 2.8, 4.7),. PFS was also statistically significantly improved [HR=0.483 (95% CI 0.37, 0.62),  $p < 0.0001$  ] in patients receiving ramucirumab (median PFS 2.1 months, 95% CI 1.5, 2.7) as compared to those receiving placebo (median PFS 1.3 months, 95% CI 1.3, 1.4) and a.

There is an ongoing study (CP12-0922), RAINBOW (Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab in Patients with Metastatic Gastric Adenocarcinoma). This study randomized (1:1) subjects with metastatic gastric and gastroesophageal junction (GEJ) cancer who had disease progression during or following first-line therapy with any platinum and fluoropyrimidine therapy. In the last annual report (submitted on October 26, 2012, with data up to September 1, 2012), ImClone stated that 604 of the planned 662 patients have been enrolled in the study.

ImClone was granted Fast Track status on November 14, 2012, for ramucirumab as a single agent for the treatment of patients with unresectable or metastatic gastric adenocarcinoma, including adenocarcinoma of the GEJ, that has progressed following first-line chemotherapy.

During the meeting, ImClone wishes to reach agreement with FDA on the following:

- The proposed data package to support filing of a complete application under the PFUFA V program.
- Overall content and format of the proposed BLA.
- The proposed submission plans to enable a rolling submission of the BLA under the Fast Track program including the timeline for submission of complete modules and Lilly's request for priority review.
- Proposed BLA planned amendments including the 120 day safety update.
- Proposed expanded access program for ramucirumab for patients with advanced gastric cancer.

The meeting package was submitted on December 18, 2012, as SDN 995. Draft FDA responses were communicated to ImClone on January 15, 2013.

## **SPONSOR QUESTIONS AND FDA RESPONSES**

### **Overall**

1. *Does FDA agree that the results from the pivotal study REGARD demonstrate the safety and efficacy of ramucirumab as a single agent for treatment of patients with advanced gastric cancer and are sufficient to support the proposed indication?*

#### FDA Response:

FDA cannot answer this question at this time. The major issue identified to date regarding this application will be whether this study showing a modest effect on OS that is not statistically robust as discussed in FDA guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>) can provide substantial evidence of effectiveness as a single study, also noting the more modest effect in the North American subgroup.

Given that this is a new molecular entity, and given the effects observed in the REGARD study, the Agency anticipates that your general question will be the primary topic for discussion at an ODAC meeting in order to determine whether the Agency should wait for

the results of the RAINBOW study prior to determining whether ramucirumab should be approved for the treatment of patients with gastric cancer. The need for an ODAC meeting may be readdressed if FDA receives top-line summary results from the RAINBOW trial that corroborates the OS effects observed in the REGARD trial.

Data from the RAINBOW study may also provide important data regarding the ramucirumab treatment effects in an exploratory subgroup analysis in women and whether the hazard ratio observed in this subgroup of the REGARD study was potentially a real finding or whether the effect was an outlier estimate based on a small non-randomized subgroup.

The following responses are based on a BLA submitted on the results of REGARD only and may change if the BLA contains the results of both REGARD and RAINBOW.

### **Efficacy**

2. *Does FDA agree with the proposed approach for the Summary of Clinical Efficacy?*

#### FDA Response:

The approach for the Summary of Clinical Efficacy (SCE) appears reasonable. Please refer to FDA Guidance regarding the integrated summary of effectiveness

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>) and the locations of both the Integrated Summaries of Effectiveness and Safety within the CTD

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>). If appropriate, because the application will be based on a single study (e.g., based on the size of the SCE), the text portion of the Summary of Clinical Safety can be incorporated in Module 2 of the BLA with tables and figures. The Integrated Summary of Efficacy should be more extensive than the SCE, and include not only text with tables and figures, but additional appendices of tables, figures, and datasets as well.

### **Safety**

3. *Does FDA agree with the planned safety populations, safety analyses, and assessment of adverse events of special interest (AESIs) proposed for the Summary of Clinical Safety?*

#### FDA Response:

No. In general, the proposed approach for the Summary of Clinical Safety appears reasonable. However, FDA expects ImClone to submit safety data from any ramucirumab study, including combination-chemotherapy studies, if the data may reasonably be considered to possibly affect statements of contraindications, warnings, precautions, or adverse reactions in the draft labeling. Certain rare adverse reactions [for example, reversible posterior leukoencephalopathy syndrome (RPLS)] may only be evident following an analysis of the entire safety database.

Additionally, please refer to the Guidance above

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>) regarding the information and data that FDA expects in Modules 2 and 5 of the BLA.

4. *Does FDA agree with the criteria for identifying patient narratives and case report forms (CRFs) that will be included in the submission?*

FDA Response:

FDA generally agrees with the criteria for identification of CRFs to be included in the BLA; however, FDA also requests submission of CRFs for all patients across the safety database who experienced RPLS, perforation, fistula, thrombotic microangiopathy, or  $\geq$  Grade 4 hemorrhage.

Regarding patient narratives, please also supply patient narratives for those patients who prematurely terminated study drug for the following reasons: “other”, lost to follow-up, physician decision, or subject decision.

To facilitate review, FDA recommends that narratives contain hyperlinks to CRFs and include the following components:

- subject age and gender
- signs and symptoms related to the adverse event being discussed
- an assessment of the relationship of exposure duration to the development of the adverse event
- pertinent medical history
- concomitant medications with start dates relative to the adverse event
- pertinent physical exam findings
- pertinent test results (for example: lab data, ECG data, biopsy data)
- discussion of the diagnosis as supported by available clinical data
- a list of the differential diagnoses, for events without a definitive diagnosis
- treatment provided
- re-challenge and de-challenge results (if performed)
- outcomes and follow-up information
- an informed discussion of the case, allowing a better understanding of what the subject experienced.

5. *Does FDA agree with the planned approach for assessing infusion reactions to inform labeling for premedication?*

FDA Response:

Insufficient information was provided for the Agency to answer this question. Although the majority of patients received pre-medication, approximately, 20% of patients did not. Therefore, some information can be submitted in the BLA regarding the incidence rate of infusion reactions in this population and whether premedication should be recommended prior to the first dose of ramucirumab versus initiating premedication following the first instance of an infusion reaction.

6. *Does FDA agree with the proposal for updated safety information to be provided in the 4-month safety update?*

FDA Response:

No. In addition to the proposal, please also submit any information from any trial (single-agent or not) that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling.

Please also submit an updated analysis of OS at the time of the 4-month safety update or at the time that you submit the final module (if the data are available earlier) that provides for an updated analysis when 80% of patients have experienced an event on the study.

Please note that the 120 safety update should be submitted 120 days from the date that the application is complete rather than 120 days after submission of the initial module.

### **Statistics**

7. *Does FDA agree with the proposed studies for which electronic datasets will be submitted?*

FDA Response:

Yes, this is acceptable. Please also see FDA's response to Question #8 for additional comments.

8. *Does FDA agree with Lilly's plan to submit those SAS programs used to create the derived datasets for the efficacy endpoints, or used for the efficacy analysis, for REGARD as well as those used to produce any analyses proposed for inclusion in the label, and to make other programs available upon request?*

FDA Response:

No. FDA has the following requests:

- a. Please include the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
- b. Please provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.
- c. Provide a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses. Variables used for sensitivity analyses and subgroup analyses should be included as well.

### **Clinical Pharmacology/Pharmacokinetics (PK)**

9. *Does FDA agree that the proposed PK data package will be adequate to support FDA review of the biologics license application (BLA) and inform labeling for ramucirumab?*

FDA Response:

The proposed PK data package appears acceptable. However, the adequacy and entirety of PK data package will be reviewed during your original BLA submission. In the BLA submission, provide a scientific rationale to justify not conducting dedicated studies to evaluate the effect of hepatic or renal impairment on ramucirumab pharmacokinetics.

10. *Does FDA agree that the planned immunogenicity data package will be adequate to support FDA review of the BLA and inform labeling for ramucirumab?*

FDA Response:

No. An assessment of the impact of anti-drug antibodies on ramucirumab pharmacokinetics, efficacy and safety as well as the neutralization results should be included in the original BLA submission for FDA review and to inform labeling for ramucirumab. The immunogenicity incidence should be provided for individual trials and for all the submitted clinical trials combined.

Submit validation reports for each anti-drug antibody assay at the time of the submission of the corresponding clinical data. In addition, submit the validation protocols and the protocols for the anti-drug antibody assays if they are not included as part of the validation reports. Refer to the FDA Guidance for Industry, "Assay Development for Immunogenicity Testing of Therapeutic Proteins," at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf).

11. *Are the format and composition of the planned clinical pharmacology datasets sufficient to enable FDA review of the clinical pharmacology package with regard to:*
- Pharmacokinetic datasets?*
  - QT datasets, waveforms, etc.?*

FDA Response:

ImClone's proposal to submit the CSR and QT datasets and waveforms to the BLA by the end of June 2013 as part of the rolling submission is acceptable. Please note that FDA does not consider this to be a BLA amendment, but rather a separate module which should be identified as such in the rolling submission schedule.

Submit the following items for QTc study/assessment at the time of your original BLA submission:

- Clinical protocol
- Investigator's Brochure
- Annotated CRF
- A Define file which describes the contents of the electronic data sets.
- Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses.
- ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
- Highlights of Clinical Pharmacology Table

In addition, FDA has the following advice in preparing the clinical pharmacology sections of the BLA submission:

- a. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies. Refer to the FDA Guidance for Industry, "Bioanalytical Method Validation," at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf).
- b. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK and pharmacodynamics (PD). For example, domains related to safety (e.g., AEs) and efficacy, demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.
- c. Provide all concentration-time and derived PK parameter datasets as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- d. Present the PK parameter data as geometric mean with coefficient of variation (and mean  $\pm$  standard deviation) and median with range as appropriate in the study reports.
- e. Provide a table listing of patients with renal or hepatic impairment who have received the product, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc. for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.
- f. Submit the following datasets to support the population PK analysis:
  - SAS transport files (\*.xpt) for all datasets used for model development and validation.
  - A description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
  - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with \*.txt extension (e.g., myfile\_ctl.txt, myfile\_out.txt).

- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports, submit:

- The standard model diagnostic plots.
- Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
- Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
- A summary of the report describing the clinical application of modeling results.

Refer to the pharmacometric data and models submission guidelines at [www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm) for more information.

- g. Submit the results of analyses exploring the exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for ramucirumab in the targeted patient population and include the results of this exploratory analysis in the BLA submission. Refer to FDA Guidances for Industry found at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf) and [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf) for more information.

## Nonclinical

12. *Does FDA agree that the nonclinical pharmacology studies are adequate to support the filing and with Lilly's plan to include only those studies directly linked to the clinical indication in the BLA?*

### FDA Response:

Yes, the nonclinical pharmacology studies described in meeting package and ImClone's plan to include only those studies directly linked to the clinical indication appear acceptable to support the submission of a BLA for the proposed indication.

IND 11856

13. *Does FDA agree that nonclinical PK studies will be adequate to support FDA review of the BLA and inform labeling for ramucirumab?*

FDA Response:

Yes, the nonclinical PK studies to be submitted in the BLA, as described in the meeting package, appear acceptable to support the submission of a BLA for the proposed indication.

14. *Does FDA agree that the proposed toxicology studies will be adequate to support FDA review of the BLA and inform labeling for ramucirumab?*

FDA Response:

The set of completed and ongoing toxicology studies described in the meeting package appears acceptable to support the submission of a BLA for the proposed indication with the exception of reproductive toxicology which has not been addressed. FDA refers to the June 29, 2012, letter in response to your February 22, 2011, request for waiver of reproductive toxicology studies which states the following:

“FDA encourages ImClone to submit the data and information described above to the IND for FDA review. If FDA determines that ImClone’s assessment is not adequate, then a combined embryo-fetal/peri-postnatal developmental toxicity study in animals, as described in the ICH S6(R1) Guidance for Industry, “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals,” will be required.”

### **Registration Package**

15. *Does FDA agree that the proposed contents of the BLA will be complete and adequate for FDA review of the BLA (that is, there are no filing deficiencies)?*

FDA Response:

ImClone intends to discuss the contents of the Quality module of the BLA during the CMC pre-BLA meeting scheduled for January 23, 2013. Comprehensive comments regarding the completeness and adequacy of the proposed contents will be provided in the context of the CMC pre-BLA meeting. However, FDA notes that the Administrative Information section (section 1) does not include section 1.4 (“Reference Section”); any supporting letters of authorization, for example, for container closure component master files, would be expected to be submitted to this section.

In addition, the absence in the BLA of reproductive toxicology studies or an adequate scientific assessment of the reproductive effects of ramucirumab that can be used from both a scientific and regulatory perspective as an alternative to these studies will be considered a filing deficiency. Refer to FDA’s June 29, 2012 letter in response to ImClone’s February 22, 2011, request for waiver of reproductive toxicology studies for further information.

16. *On November 14, 2012, FDA granted Fast Track designation for ramucirumab as a single agent for the treatment of patients with unresectable or metastatic gastric*

*adenocarcinoma, including adenocarcinoma of the gastroesophageal junction that has progressed following first-line therapy. Does FDA agree with the proposed contents and timeline for the rolling submission of the following modules?*

- a. Nonclinical module (Modules 2.4, 2.6 and 4) and related administrative items (Module 1).*
- b. Clinical module (Modules 2.5, 2.7 and 5) and related administrative items (Module 1) including labeling.*
- c. Quality module (Modules 2.3 and 3) and related administrative items (Module 1).*

**Table 14. Proposed Rolling Submission Timeline for the BLA**

<b>Module Description</b>	<b>Module Number</b>	<b>Proposed Submission Date</b>	<b>Rationale for Supplementing the Module with Additional Information during FDA's Review &amp; Timing of Submitting Additional Information</b>
Nonclinical	<ul style="list-style-type: none"> <li>• 2.4 Nonclinical Overview</li> <li>• 2.6 Nonclinical Written and Tabulated Summary</li> <li>• 4 Nonclinical Study Reports</li> <li>• Related administrative items in Module 1</li> </ul>	February 2013	Not applicable
Clinical	<ul style="list-style-type: none"> <li>• 2.2 Introduction to Summary</li> <li>• 2.5 Clinical Overview</li> <li>• 2.7 Clinical Summaries</li> <li>• 5 Clinical Study Reports</li> <li>• Related administrative items in Module 1 (including labeling)</li> </ul>	April 2013	<p>Lilly will provide the final CSR for the Phase 2 study in ovarian cancer I4T-IE-JVBR (IMCL CP12-0711) at the time of the 4-month safety update in August 2013 (see Section 6.6). These data should not impact labeling.</p> <p>Lilly will provide the final Phase 2 JVBK CSR, QT datasets, and waveforms by the end of June 2013. Because there was no observed prolongation of QT interval above the threshold of regulatory concern (&gt;10 msec) with ramucirumab compared with baseline based on the available results of Study JVBK and that the absence of a QT finding is unlikely to affect the safety review, this is considered a minor component of the data package and would not be anticipated to delay FDA beginning its review of the BLA.</p>
Quality	<ul style="list-style-type: none"> <li>• 2.3 Quality Overall Summary</li> <li>• 3 Quality</li> <li>• Related administrative items in Module 1</li> </ul>	August 2013	<p>Lilly will provide 6-month drug product stability and 12-month drug substance stability data from our intended commercial processes in the BLA. Lilly will provide 9- and 12-month drug product stability data from our intended commercial process during the BLA review (November 2013). As described in FDA's Fast Track guidance (FDA 2006), Module 3 would consist of final reports and be a reviewable unit at the time of submission. Because Fast Track designation has been granted, it is Lilly's understanding that the additional 12-month drug product stability data would not constitute an extension to the BLA review period.</p>

Abbreviations: BLA = Biologics License Application; CSR = clinical study report; PK = pharmacokinetic.

IND 11856

FDA Response:

No, please FDA's responses to Questions #6 and #11.

Please also revise your submission timeline to include a module with the cardiac electrophysiology clinical study report (CSR) and associated datasets.

Regarding the proposed data on page 61 of the meeting package for the submission of the final CSR, these data should be provided in the clinical module (Module 5) or ImClone can provide a separate submission for this CSR in the rolling submission timeline. It is inappropriate to submit this information in the 120 day safety update.

The proposed timeline for submission of the Quality module appears to be acceptable. Please see general comments in FDA's response to Question #15 regarding the proposed contents of the Quality module. Regarding the proposed timing of stability data submission, as per the PDUFA V legislation, agreement must be reached regarding data to be submitted subsequent to the submission of the BLA. In addition, ImClone should plan to submit the additional, agreed upon data sets within 30 calendar days after the submission of the BLA. With respect to the timeline for submission of the drug product stability data described in Table 14 of the meeting package, FDA has the following comments:

FDA may request a "simple stability update" to support a proposed dating period for the drug product and drug substance. A simple stability update is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission; it will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. If FDA requests this information, the simple stability update would need to be submitted within 4 months of the submission of the final portion of the BLA or, if designated standard review, within 7 months of the submission of the final portion of the BLA. A simple stability update submitted at FDA's request within these timeframes may be reviewed and considered in shelf life determinations.

In addition, FDA notes that ImClone proposes an application orientation meeting for the quality module; please be aware that it is unlikely that a separate meeting will be necessary.

17. *Does the FDA agree that this application would be considered for a priority review based on the totality of the data, unmet medical need, orphan drug designation, and magnitude of the benefit?*

FDA Response:

FDA agrees that the Agency will consider the application for priority review; however, the designation of priority review will be determined when the application is received.

IND 11856

18. *Does FDA agree that REGARD is the only study considered a covered study under the financial disclosure requirements?*

FDA Response:

Yes, FDA agrees.

19. *Does FDA agree with Lilly's plan to provide a comprehensive and readily located list of all clinical sites and manufacturing facilities for studies included in the BLA to support the Office of Scientific Investigation (OSI)'s preapproval clinical and manufacturing inspection planning?*

FDA Response:

Although FDA agrees with the general proposal to include the clinical site information in the BLA, please see Appendix 1 for instructions regarding how the Agency would prefer this information to be submitted in the application.

From the product quality perspective, the information in Table 16 of the meeting package and the proposed placement in module 3.2 are acceptable to satisfy the PDUFA V requirements. Please note that establishment information is also a required component of FDA Form 356h (section 29). Please see FDA's additional advice under Manufacturing Facilities.

20. *Does FDA have any comments on the potential labeling concepts outlined in the Target Product Profile (TPP)?*

FDA Response:

Yes. When possible, please use command language in product labeling (for example, rather than stating "TRADENAME should be prepared", state "prepare TRADENAME").

Please only include *adverse reactions* in product labeling. Adverse reactions are those events for which there is some basis to believe there is a casual relationship between the occurrence of an adverse event and the use of the drug. Listing any adverse event occurring at  $\geq 5\%$  in the REGARD trial does not meet this definition as many of these events may have occurred at a higher incidence in the placebo arm and there may be no basis to believe that ramucirumab caused the adverse event.

Additionally, in some cases, FDA recommends that ImClone use specific vital sign measurements or laboratory measurements to describe the incidence of certain findings (e.g., hypertension and proteinuria) if these measurements more accurately describe adverse effects of ramucirumab compared to physician-reported adverse events.

21. *Given the results of the REGARD study and unmet medical need, does FDA agree that an expanded access program in advanced gastric adenocarcinoma after prior chemotherapy could be established in the United States prior to approval? If FDA agrees that an expanded access program could be initiated, does FDA have any*

*comments on Lilly's proposal to collect serious adverse events (SAEs) and not collect detailed safety or efficacy information?*

FDA Response:

FDA does not object to ImClone's proposal to initiate an expanded access program, provided that the program does not interfere with recruitment in the ongoing RAINBOW trial. However, safety data should include all Grade 3-5 adverse events, regardless of relatedness and the physician's assessment of seriousness. OS data should be collected.

22. *Does FDA agree that, based on the initial review of safety data and the inherent limited distribution and administration by specialists trained in oncology, inclusion of a REMS plan in the BLA is not necessary?*

FDA Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, FDA does not anticipate that a REMS will be necessary if ramucirumab is approved. FDA will make a final determination for the need for a REMS during the review of your application.

Additionally, because ramucirumab will be administered in infusion centers and prescribed by oncologists who routinely obtain informed consent from patients prior to administering anti-cancer therapeutics, FDA does not anticipate the need for a MedGuide.

**ADDITIONAL FDA CLINICAL PHARMACOLOGY COMMENTS:**

Please address the following clinical pharmacology related questions in the BLA submission:

23. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
24. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
25. What are the exposure-response relationships (dose-response, exposure-response) for safety?
26. How is the QT prolongation potential assessed? What are the conclusions and proposed labeling description?
27. What are the pharmacokinetic characteristics of ramucirumab?

IND 11856

28. What influence do the intrinsic factors (as listed below but not limited to) have on ramucirumab exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- gender
  - race
  - weight
  - disease
  - genetic polymorphism
29. What influence do the extrinsic factors (e.g., concomitant medications, etc.) have on ramucirumab exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
30. What is the impact of immunogenicity on ramucirumab exposure and/or its pharmacodynamic response? What is the clinical impact?

## **DATA STANDARDS**

CDER strongly encourages IND sponsors and BLA and NDA applicants to consider the implementation and use of data standards for the submission of applications. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. These resources are intended to assist submitters in the preparation and submission of standardized study data to CDER. This webpage will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>).

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our October 29, 2012, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

## **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

## **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

#### **OFFICE OF SCIENTIFIC INVESTIGATIONS**

Please see attachment in Appendix 1.

## Appendix 1

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (**Item I and II**).

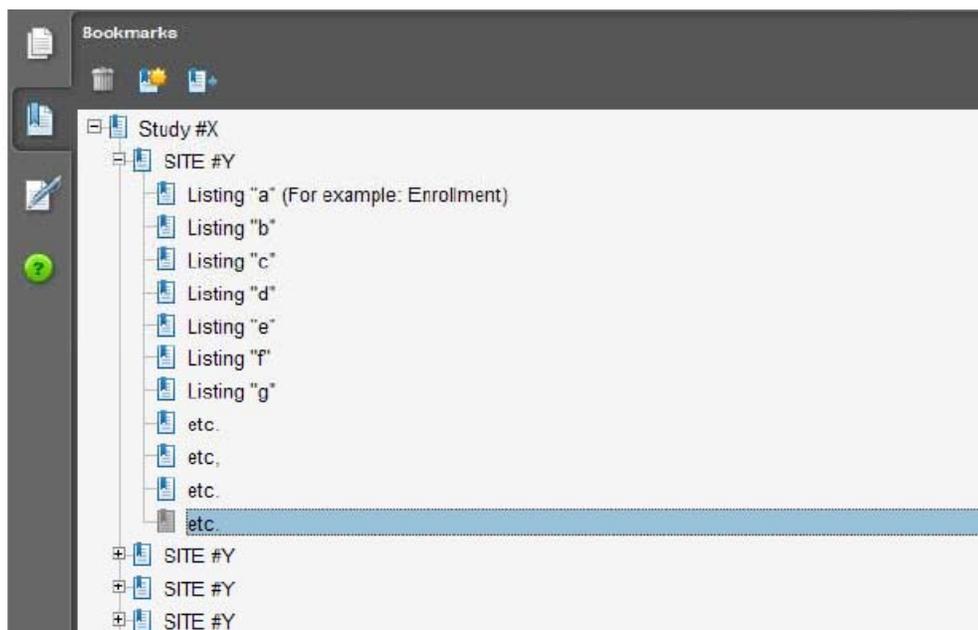
The dataset that is requested as per **Item III** below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (**Attachment 2**, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**
1. Please include the following information in a tabular format in the original BLA for each of the completed Phase 3 clinical trials (pivotal):
    - a. Site number
    - b. Principal investigator
    - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  2. Please include the following information in a tabular format by site in the original BLA for each of the completed Phase 3 clinical trials:
    - a. Number of subjects screened for each site by site
    - b. Number of subjects randomized for each site by site
    - c. Number of subjects treated who prematurely discontinued for each site by site
  3. Please include the following information in a tabular format in the BLA for each of the completed Phase 3 clinical trials:
    - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    - b. Name, address, role and contact information of all CROs used in the conduct of the clinical trials
    - c. Location of Charter(s) for Centralized Efficacy Assessments, as appropriate.
    - d. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
    - e. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
  4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
  5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the BLA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



## III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to **Attachment 1**, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## **Attachment 1**

### Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### INTRODUCTION

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### **Site-Specific Efficacy Results**

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

IND 11856

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

IND 11856

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

## Attachment 2

### Technical Instructions:

### Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-sNDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study  (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

IND 11856

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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/s/  
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SHARON K SICKAFUSE  
01/15/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 11856

ImClone Systems, Incorporated  
Attention: Cheryl Anderson  
Vice President, Regulatory Affairs  
33 ImClone Drive  
Branchburg, NJ 08876

Dear Ms. Anderson:

Please refer to your Investigational New Drug Application (IND) for “Human Monoclonal Antibody (IMC-1121B) to the Vascular Endothelial Growth Factor Receptor 2.”

We also refer to the May 20 2008, meeting between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached 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) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Sharon Sickafuse, M.S.  
Regulatory Project Manager  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** May 20, 2008

**APPLICATION:** IND 11856

**SPONSOR:** ImClone Systems, Inc.

**DRUG NAME:** Human Monoclonal Antibody (IMC-1121B) to the Kinase Domain Insert Receptor

**INDICATION:** (b) (4)

**TYPE OF MEETING:** Type B

**MEETING RECORDER:** Sharon Sickafuse

### **FDA ATTENDEES:**

#### **Office of Oncology Drug Products**

Division of Biologic Oncology Products

Anne Pilaro, Ph.D.

Sharon Sickafuse, M.S.

#### **Office of Clinical Pharmacology**

Division 5

Leslie Kenna, Ph.D.

Hong Zhao, Ph.D.

#### **Office of Biotechnology Products**

Division of Monoclonal Antibodies

Chana Fuchs, Ph.D.

Sarah Kennett, Ph.D.

Patrick Swann, Ph.D.

### **SPONSOR ATTENDEES:**

#### **ImClone Systems, Inc.**

Richard Crowley, Ph.D., Senior Vice President, Biopharmaceutical Operations

Karen Fleshman, Senior Director, Regulatory CMC

Floyd Fox, Ph.D., Assistant Vice President, Clinical Pharmacology

Joel Goldstein, Ph.D., Assistant Vice President, Formulation Development

Elizabeth Yamashita, Ph.D., Vice President, Regulatory CMC & Operations

Quinwei Zhou, Ph.D., Senior Director, Bioanalytical Sciences

**BACKGROUND:**

On February 19, 2008, ImClone submitted a meeting request (amendment 73) to discuss 1) the comparability plan for drug substance and drug product site, scale, and process changes to support use of the (b) (4) material in Phase 3; 2) proposed chemistry and manufacturing plans to support the BLA; 3) immunogenicity assay; and 4) drug-drug interaction study. The meeting package was submitted on April 18, 2008, as amendment 83. Draft FDA responses were communicated to ImClone on May 19, 2008.

**MEETING OBJECTIVES:** Discuss CMC issues regarding Phase 3 studies and the pending BLA, the design of the drug-drug interaction study, and the immunogenicity assay format.

**FDA INTRODUCTORY COMMENTS:**

FDA's responses are highly dependent on whether the Process C material is introduced into the Phase 3 trials early vs. late in accrual with a large vs. a small amount of clinical experience with the new process material. In FDA's draft responses, FDA assumed that a significant majority of patients in the Phase 3 studies will receive Process C material.

**SPONSOR QUESTIONS AND FDA RESPONSES:**

- 1. Does the Agency agree that the comparability analytical characterization program is acceptable to demonstrate biochemical comparability of IMC-1121B drug substance (DS) Process B (b) (4) to Process C (b) (4), ImClone) to support use of Process C DS for Phase 3 clinical trials and subsequently for licensure?*

FDA Response:

ImClone should implement acceptance criteria for the purpose of comparability based on the lot release data from process B. Additionally, current acceptance criteria for certain assays, e.g. (b) (4) are such that a significant variability in relative antibody attributes could still be within the acceptance criteria. Additional parameters should be added to the acceptance criteria to ascertain that processes B and C result in comparable products.

For the stability parameter of the comparability studies, we are unclear as to the container in which the (b) (4) will be stored, but assume that as this study is intended to show comparability, containers for process B and C will be the same. The (b) (4) stability protocols (Tables 7 and 15, respectively) should be modified to include the potency bioassay, and the HPLC should have % aggregates and % fragments reported as well.

Discussion:

ImClone informed FDA that the analytical comparability study has been completed, so it cannot implement the changes identified in the FDA response. ImClone agreed to include the cell based potency assay as part of the stability program (b) (4). ImClone will also implement reporting of % aggregates and % fragments for the HPLC assay.

ImClone clarified that the containers (b) (4) made by process B are (b) (4) while the containers (b) (4) made by process C are (b) (4). Most of the process C (b) (4) is in (b) (4). The same timepoints will be used for process B and process C. FDA stated that this plan was acceptable.

2. *Does the Agency agree that the design and acceptance criteria of the proposed monkey pharmacokinetic (PK) study are acceptable to support comparability of the IMC-1121B DS Process B ( (b) (4) to Process C (b) (4) , ImClone) and to support use of Process C DS for Phase 3 clinical trials?*

FDA Response:

While the majority of the proposed monkey PK study design is acceptable, the current study design does not include immunogenicity testing. Please include immunogenicity testing for samples obtained from all animals exposed to either Process B- or Process C-derived, IMC-1121B at the following time points: pre-dose, 14-21 days post-dose, and at a final time point at which either IMC-1121B product is anticipated to be completely cleared.

Depending on the results of the comparability studies, a human PK comparability study may be necessary.

Discussion:

ImClone stated that the in-life portion of the monkey PK study has been completed. Samples are available from pre-dose, day 14, and day 21 timepoints for immunogenicity analysis.

ImClone will use either the current (b) (4) immunogenicity assay (which needs to be validated) or the older (b) (4) immunogenicity assay to measure the samples.

3. *Use of drug product (DP) manufactured from Process C DS in the Phase 3 studies will not occur until the monkey PK data are available. Does the Agency concur that it is acceptable to introduce the DP manufactured from Process C materials into the Phase 3 studies based on acceptable results from the monkey PK study and concurrent with or prior to collection of clinical PK data for Process C material in the proposed drug-drug interaction (DDI) and QTc studies?*

FDA Response:

The proposal is acceptable from a Clinical Pharmacology perspective. Please submit the CMC and non-clinical PK comparability data for review and concurrence of comparability prior to use of process C materials in clinical trials.

Discussion:

FDA stated that they will review the data as quickly as possible, but are unable to commit to a specific timeframe. FDA stressed that the submission needs to be complete.

4. *Does the Agency concur that it is sufficient to submit a summary of the monkey PK study in an IND amendment to support use of the Process C material for Phase 3 clinical trials?*

FDA Response:

No, FDA does not agree that summary data will be sufficient to assess non-clinical comparability. ImClone must provide the complete study report, including the summary tables and line-listed data for individual animals in the monkey PK comparability study.

Discussion:

ImClone agreed to provide the complete study report.

5. *Does the Agency concur that the program outlined for the qualification of (b) (4) at ImClone Systems for commercial manufacture of IMC-1121B DS is appropriate to support licensure?*

FDA Response:

Yes. ImClone's plans to demonstrate consistency (b) (4) is acceptable.

Discussion:

(b) (4)

6. *Does the Agency concur that the proposed DS stability plan to demonstrate comparability of (b) (4) and provide flexibility in choice of container/closure systems for the post-approval annual commitment batches is acceptable?*

FDA Response:

As mentioned in FDA's draft response to question number 1, FDA is unclear on the container use planned to show stability for the comparability/development (b) (4) and requests further clarification.

In addition to the proposed stability testing, ImClone should include an assessment of leachables for (b) (4) containers to assure both are interchangeable over the (b) (4) storage timeline.

Discussion:

ImClone stated that an assessment of leachables is planned for the (b) (4) as part of the development program. An assessment of leachables for the (b) (4) will also be included for the registrational program.

(b) (4)  
[Redacted]  
FDA stated that this plan was acceptable.

Post-meeting addition:

Following the meeting, FDA asked for additional clarification on the use of the (b) (4) containers as it was still not clear whether these are intended solely for storage of stability samples or also for storage of (b) (4). Dr. Elizabeth Yamashita clarified in an email dated May 20, 2008, that ImClone “plan to only use the (b) (4) on the stability program. All (b) (4) at commercial scale will be in the (b) (4). Therefore, FDA is modifying our reply. ImClone will not need to do a leachables assessment of the (b) (4) container, nor will they need to add an additional stability registrational lot split between (b) (4) as proposed during the meeting.

7. *Does the Agency concur that the proposed plan to demonstrate control of the polysorbate (Tween 80) levels (b) (4) is appropriate to support product approval?*

FDA Response:

Demonstration of control (b) (4) would be appropriate (b) (4) for Tween 80. (b) (4)

Discussion:

[Redacted] (b) (4)

8. *Does the Agency concur that the proposed DP stability program for the BLA is appropriate to support product approval?*

FDA Response:

The storage conditions as presented in Tables 13 and 14 of the meeting package appear appropriate to support product approval. The specifications used for stability studies, as identified in Table 15, should be modified as follows:

- a. The potency bioassay should be added as a stability test.
- b. HPLC acceptance criteria should have % aggregates and % fragments reported as well.
- c. Please include (b) (4) in the DP stability testing to monitor (b) (4) with time.

Re-assessment of release testing acceptance criteria is appropriate at this stage of product development. Any changes in DP release specifications should be considered when assessing the appropriateness of DP stability specifications.

Discussion:

ImClone agreed to implement FDA's recommendations.

9. *Does the Agency agree that the drug-drug interaction (DDI) study design plan is acceptable to determine the relative effect of docetaxel on the PK of IMC-1121B?*

FDA Response:

The DDI study synopsis did not indicate when samples will be drawn to characterize the PK of IMC-1121B in subjects in Arm A or Arm B. Please clarify the sampling plan for IMC-1121B. Based on preliminary information provided on the PK of IMC-1121B in patients observed in Study CP12-0401 and Study CP12-0402 in your submission of April 23, 2008, the half life of a 10 mg/kg dose of IMC-1121B is approximately 200 hours. FDA recommends that ImClone collect PK samples to measure the concentration of IMC-1121B for 5 half lives of elimination.

The study synopsis did not indicate when samples will be drawn to characterize docetaxel PK in subjects enrolled in Arm B. The study synopsis did not explicitly state the days on which docetaxel concentration will be measured in patients in Arm A. Please clarify the sampling plan for docetaxel.

Discussion:

ImClone stated that the 200 hour half life is correct for the final infusion where IMC-1121B is nearing steady state. However, for the first infusion the half life is approximately 100 hours; 5 times this value yields a dosing interval of approximately 3 weeks which results in an approximately 3 week dosing cycle as proposed in the current design for the DDI study.

The sampling plan, which was inadvertently omitted from the DDI study description, is as follows.

Cycle 1:

Arm A - docetaxel monotherapy: baseline, 0.25 hours prior to the end of infusion, and 0.25, 1, 2, 5, 23, 168, 336, and 504 hours post-infusion.

Arm B - IMC-1121B monotherapy: baseline and 0.25, 1, 2, 5, 23, 168, 336, and 504 hours post-infusion.

Cycle 2:

Arms A and B (docetaxel and IMC-1121B combination): Sampling times are identical to those in cycle 1.

Cycles 3, 5, 7, and 9: pre-infusion and 1 hour post-infusion.

30-Day follow-up: single serum sample.

FDA advised that the proposed DDI study design is acceptable.

10. *Does the Agency agree that when the (b) (4) assay is successfully validated to detect anti-IMC-1121B antibodies in the presence of drug as described, it will be acceptable?*

FDA Response:

A final assessment of acceptability can only be made when reviewing the full immunogenicity section in the BLA. However, based on the description provided in the meeting package, the (b) (4) looks promising as a sensitive immunogenicity detection assay. A detailed description of the validation plan is sparse in the meeting package, but many of the same parameters identified (b) (4) should be assessed for this assay too (b) (4)

The information in the BLA should also include similar points as identified in the February 7, 2006, (b) (4) (b) (4), and should provide the appropriate data in support of the parameters identified.

ImClone should re-analyze assay cutpoints once patient serum sample data is available to assure that there are not major differences resulting from the disease state that would require additional consideration.

It is critical that a neutralizing assay be in place to assess positive anti-drug antibody samples identified (b) (4).

Discussion:

ImClone did not have any questions or comments.

11. (b) (4)

FDA Response:

Based on information in previous submissions, it is FDA's understanding that blood samples for the determination of anti-IMC-1121B antibodies will be collected in all study patients at baseline, prior to the cycle 3 infusion, prior to the cycle 5 infusion, and at the 30-day follow up visit. In the event that anti-IMC-1121B antibodies are detected, the patient's serum IMC-1121B concentration will be analyzed to determine if there is any alteration in IMC-1121B PK. In the event of an infusion reaction, samples for immunogenicity testing will be collected as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

As stated during the August 7, 2007, meeting, if the immunogenicity assay is able to detect anti-IMC-1121B antibodies in the presence of study drug, it will be acceptable to collect the last patient sample one month after the last dose.

Discussion:

ImClone did not have any questions or comments.

**ADDITIONAL FDA COMMENTS REGARDING CMC ISSUES:**

12. In addition to a comparability assessment, prior to using process C material in clinical trials, please submit a re-assessment of viral clearance, including retroviral load, and the ability of any small-scale viral clearance validation studies to support viral clearance of ImClone's [REDACTED] (b) (4) (process C).

Discussion:

ImClone agreed to provide the requested information.

13. Prior to initiating Phase 3 clinical trials, please update the release specifications and reassess the acceptance criteria to assure appropriateness. For example, the acceptance criteria for the HPLC assay is currently [REDACTED] (b) (4). The specification should be reassessed for appropriateness based on manufacturing history, and a limit for fragments as well as a limit for aggregates should be incorporated into the acceptance criteria. At this stage of product development, a potency bioassay should be included as part of release and stability testing for BDS and DP. [REDACTED] (b) (4) should be a quantitative assay rather than qualitative; the current acceptance criterion is [REDACTED] (b) (4)

Discussion:

ImClone clarified that process C material will not be used at the beginning of Phase 3 studies.

ImClone will reassess specifications for BDS and DP prior to the implementation of Process C clinical supplies.

[REDACTED] (b) (4)

14. [REDACTED] (b) (4) should be included in the release testing of DP. In addition, please include [REDACTED] (b) (4) to the DP stability testing [REDACTED] (b) (4)

Discussion:

ImClone agreed [REDACTED] (b) (4) in the release testing of DP.

15. The current DS acceptance criteria for bioburden are (b) (4)

[Redacted content]

Discussion:

ImClone agreed with FDA's recommendations.

Linked Applications

Sponsor Name

Drug Name

-----  
IND 11856

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IMCLONE SYSTEMS INC

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Human Monoclonal Antibody (IMC-1121B)  
to the Kinase Domain Insert Receptor  
(KDR) and Chemotherapy

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/s/  
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SHARON K SICKAFUSE

06/18/2008

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125477/0

**LATE-CYCLE MEETING MINUTES**

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

Dear Ms. Norby:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 11, 2014.

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

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager at (301) 796-2320.

Sincerely,

*{See appended electronic signature page}*

Steven Lemery, M.D.  
Lead Medical Officer  
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

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date:** February 11, 2014

**Application Number:** BLA 125477/0

**Product Name:** Cyramza (ramucirumab)

**Applicant Name:** Eli Lilly and Co. (Lilly)

**Meeting Chair:** Steven Lemery, M.D., M.H.S.

**Meeting Recorder:** Sharon Sickafuse, M.S.

**FDA ATTENDEES**

**Office of Hematology and Oncology Products**

Jonathan Jarow, M.D.

Richard Pazdur, M.D.

Division of Oncology Products 2

Mimi Biable

Sandra Casak, M.D.

Lola Fashoyin-Aje, M.D.

Patricia Keegan, M.D.

Steven Lemery, M.D.

Sharon Sickafuse, M.S.

Division of Hematology Oncology Toxicology

Whitney Helms, Ph.D.

**Office of Biostatistics**

Division 5

Hui Zhang, Ph.D.

**Office of Clinical Pharmacology**

Division 5

Lillian Zhang, Ph.D.

Hong Zhao, Ph.D.

**Office of Biotechnology Products**

Division of Monoclonal Antibodies

Michele Dougherty, Ph.D.

Sarah Kennett, Ph.D.

**Office of Compliance**  
**Office of Manufacturing and Product Quality**  
Division of Good Manufacturing Practices  
Biotech Manufacturing Assessment Branch  
Patricia Hughes, Ph.D.  
Kalavati Suvarna, Ph.D.

**Office of Surveillance and Epidemiology**  
Division of Risk Management  
Cynthia LaCivita

Division of Pharmacovigilance II  
Afrouz Nayernama  
Peter Waldron, M.D.

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (6), Independent Assessor  
(b) (6), Independent Assessor

**APPLICANT ATTENDEES**

Richard Gaynor, M.D., Ph.D., Medical Development  
Robert Konrad, M.D., Laboratory for Experimental Medicine  
Mark Leusch, Ph.D., Global Regulatory Affairs  
Bruce Meiklejohn, Ph.D., Research and Development  
Allen Melemed, M.D., Medical  
Robert Metcalf, Ph.D., Global Regulatory Affairs  
Talia Muram, M.D., Laboratory for Experimental Medicine  
Deborah Norby, Global Regulatory Affairs  
Anne Marie O'Connell, CMC Global Regulatory Affairs  
Robert Ortmann, M.D., Diagnostic and Experimental Medicine  
Katherine Sugarman, M.D., Global Regulatory Affairs

**BACKGROUND**

BLA 125477/0 was submitted on August 23, 2013, for Cyramza (ramucirumab).

Proposed indication: Treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma after prior chemotherapy

PDUFA goal date: April 23, 2014

FDA issued a Background Package in preparation for this meeting on January 29, 2014.

## DISCUSSION

### LCM AGENDA

1. Introductory Comments - 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues - 15 minutes

The following information requests are outstanding:

- a. Request made on January 23<sup>rd</sup> to clarify if the surface sample data includes samples collected from personnel during the (b) (4) simulation. If not, please provide personnel monitoring data. Also provide a summary of any environmental monitoring excursions.

Discussion:

No discussion occurred because the requested information was received on January 29th.

- b. Request made on January 24<sup>th</sup> to submit the MedWatch reports for all cases of reversible posterior leukoencephalopathy syndrome (RPLS) reported in any trial in the ramucirumab development program. These reports were submitted to the IND but we also need them submitted to the BLA.

Discussion:

Lilly stated that there were 2 cases of RPLS; both were from the colorectal carcinoma trial. The first case was submitted in the original BLA. The second case was submitted as a BLA amendment on January 31, 2014.

3. Postmarketing Requirements - 15 minutes

FDA plans to request the following postmarketing requirements:

- To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for accurate detection of binding antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The validation report will be submitted (b) (4) by Month/Year (Lilly to provide date).

Discussion:

FDA stated that the intent of this PMR could be satisfied either by developing a new assay as described above or by providing data showing acceptable drug tolerance of the ADA assay between (b) (4) of ADA. Lilly agreed to provide the data as requested above as a PMR.

FDA will provide Lilly with proposed revised PMR language within a week.

- To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ramucirumab, including procedures for accurate detection of neutralizing antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement by Month/Year (Lilly to provide date).

Discussion:

Lilly stated that it may be difficult to improve the drug tolerance of the current assay. FDA will internally discuss the need for this PMR and contact Lilly with an answer within a week.

- To accurately analyze patient serum samples from the Cyramza clinical trials for the presence of anti-ramucirumab antibodies and neutralizing antibodies using the more sensitive and validated assays described above. The report will be submitted by Month/Year (Lilly to provide date).

Discussion:

FDA will revise the PMR to indicate that the PMR can be satisfied either by submitting adequate data on the drug tolerance of the current ADA assay or by re-analyzing patient serum samples with the new assay if the data on the drug tolerance of the current assay is not acceptable.

FDA will provide Lilly with proposed revised PMR language within a week.

Lilly verified that patient samples from Study REGARD and other previous clinical trials have been archived and are available for re-testing.

3. Postmarketing Commitments - 15 minutes

FDA plans to request the following postmarketing commitments:

- To re-evaluate ramucirumab drug substance lot release and stability specifications after <sup>(b)(4)</sup> lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Lilly to provide date).

Discussion:

Lilly stated that they are transitioning from process C1 to C2 and inquired if it would be acceptable to provide a re-evaluation of drug substance specifications from lots manufactured using C1 and C2. FDA agreed with this approach if comparability is established.

Lilly will provide a written agreement with the proposed PMC and will provide milestones for completion of the PMC to the BLA.

- To re-evaluate ramucirumab drug product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Lilly to provide date).

Discussion:

Lilly stated that they are transitioning from process C1 to C2 and inquired if it would be acceptable to provide a re-evaluation of drug product specifications from lots manufactured using C1 and C2. FDA agreed with this approach if comparability is established.

Lilly will provide a written agreement with the proposed PMC and will provide milestones for completion of the PMC to the BLA.

- To confirm product stability (b) (4) using small scale studies. These studies will include (b) (4). The final study reports will be provided by Month/Year (Lilly to provide date).

Discussion:

Lilly agreed to perform the studies and proposed to assess two lots manufactured by process C1 and one lot manufactured by process C2. FDA agreed with this approach.

Lilly will provide a written agreement with the proposed PMC and will provide milestones for completion of the PMC to the BLA.

- To perform a shipping study to confirm validation of the commercial ramucirumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, rSDS-PAGE, mSDS-PAGE, IEX, (b) (4), and potency of ramucirumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers. The final study report will be provided by Month/Year (Lilly to provide date).

Discussion:

Lilly will perform the shipping study as requested.

Lilly will provide a written agreement with the proposed PMC and will provide milestones for completion of the PMC to the BLA.

4. Major labeling issues - 5 minutes

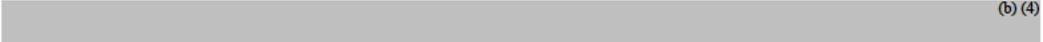
Labeling is under review. Comments regarding the carton and container were conveyed to Lilly on January 28, 2014. Comments regarding the package insert will be conveyed to Lilly by March 24, 2014.

Discussion:

Lilly submitted revised carton and container labeling on February 7, 2014. This is under review.

FDA conveyed the following high level comments regarding the proposed package insert:

- Inclusion of a Boxed Warning for hemorrhage.
- Revision of the indication to specify fluoropyrimidine and cisplatin prior therapy.
- The Dosage and Administration section will be reorganized. FDA will request justification as to why the in-line filter is necessary in order to include the use of the filter in product labeling. .
- Revise the hemorrhage subsection in Warnings to include information on NSAIDS.

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

Delete PFS curves for brevity, but FDA will include statements in their reviews that Lilly may use the PFS curves in promotional materials.

5. Review Plans - 5 minutes

Complete review of information that FDA requested.  
Complete labeling negotiations.

Complete PMR/PMC negotiations.

6. Wrap-up and Action Items - 10 minutes

Lilly asked if their proposed expiry period of  (b) (4) for drug substance and 36 months for drug product is acceptable. FDA review teams stated that there were no major concerns with the proposed expiry periods at this time; however, final determination cannot be communicated until the application has been reviewed by the signatory authorities.

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
FDA will propose revised language for the binding antibody assay PMR.	FDA	2-19-2014
FDA will contact Lilly regarding the need for the neutralizing antibody assay PMR.	FDA	2-19-2014
FDA will propose revised language for the immunogenicity PMR.	FDA	2-19-2014
Lilly will submit written agreements regarding the 4 PMCs and milestones for each	Lilly	TBD

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/  
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STEVEN J LEMERY  
02/19/2014



BLA 125477/0

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

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

Dear Ms. Norby:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 11, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please call Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date:** February 11, 2014

**Application Number:** BLA 125477/0

**Product Name:** Cyramza (ramucirumab)

**Indication:** Treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single-agent after prior 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

No substantive review issues have been identified to date.

## **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues requiring modifications to the proposed risk management plan have been identified to date.

## **LCM AGENDA**

1. Introductory Comments - 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues - 15 minutes

The following information requests are outstanding:

- a. Request made on January 23<sup>rd</sup> to clarify if the surface sample data includes samples collected from personnel during the (b) (4) simulation. If not, please provide personnel monitoring data. Also provide a summary of any environmental monitoring excursions.
- b. Request made on January 24<sup>th</sup> to submit the MedWatch reports for all cases of reversible posterior leukoencephalopathy syndrome reported in any trial in the ramucirumab development program. These reports were submitted to the IND but we also need them submitted to the BLA.

3. Postmarketing Requirements - 15 minutes

FDA plans to request the following postmarketing requirements:

- To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for accurate detection of binding antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement by Month/Year (Lilly to provide date).
- To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ramucirumab, including procedures for accurate detection of neutralizing antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement by Month/Year (Lilly to provide date).

- To accurately analyze patient serum samples from the Cyramza clinical trials for the presence of anti-ramucirumab antibodies and neutralizing antibodies using the more sensitive and validated assays described above. The report will be submitted by Month/Year (Lilly to provide date).

3. Postmarketing Commitments - 15 minutes

FDA plans to request the following postmarketing commitments:

- To re-evaluate ramucirumab drug substance lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Lilly to provide date).
- To re-evaluate ramucirumab drug product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Lilly to provide date).
- To confirm product stability (b) (4) using small scale studies. These studies will include (b) (4). The final study reports will be provided by Month/Year (Lilly to provide date).
- To perform a shipping study to confirm validation of the commercial ramucirumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, rSDS-PAGE, mSDS-PAGE, IEX, (b) (4) and potency of ramucirumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers. The final study report will be provided by Month/Year (Lilly to provide date).

4. Major labeling issues - 5 minutes

Labeling is under review. Comments regarding the carton and container were conveyed to Lilly on January 28, 2014. Comments regarding the package insert will be conveyed to Lilly by March 24, 2014.

5. Review Plans - 5 minutes

Complete review of information that FDA requested.

Complete labeling negotiations.

Complete PMR/PMC negotiations.

6. Wrap-up and Action Items - 10 minutes

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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.**  
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/s/  
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PATRICIA KEEGAN  
01/29/2014