CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125477Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

REVIEW ADDENDUM

Date:	**March 3, 2014**
To:	Administrative File, STN 125477
From:	Candace Gomez-Broughton, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsed:	Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject:	New Biologic License Application: Primary review addendum to update the Environmental Assessment
US License:	1891
Applicant:	Eli Lilly and Company
Facility:	Eli Lilly and Company, Indianapolis, IN USA (FEI#1819470)
Product:	Cyramza (ramucirumab)
Dosage:	Sterile liquid for intravenous infusion 500 mg/50 mL and 100 mg/10 mL
Indication:	Treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Due date:	April 23, 2014

Recommendation: The BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

This is an addendum to for the drug product quality microbiology review memo entered into DARRTS on 3-Feb-2014 for BLA 125477 to update the Environmental Assessment of the primary review.

ENVIRONMENTAL ASSESSMENT

Ramucirumab is an IgG1 monoclonal antibody and is eliminated from the body by degradation to smaller peptides and amino acids by various proteolytic processes in the cells followed by receptor-mediated endocytosis. Therefore, excretion from humans is unlikely. The end degradation products occur naturally in the environment and the use of ramucirumab will not alter their distribution in the environment. Therefore, the Sponsor claims a categorical exclusion from submitting an environmental assessment, 21 CFR 25.31 (c).

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/s/

CANDACE GOMEZ-BROUGHTON
03/03/2014

PATRICIA F HUGHES TROOST
03/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

REVIEW ADDENDUM

Date:	February 12, 2014
To:	Administrative File, STN 125477
From:	Candace Gomez-Broughton, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsed:	Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject:	Amended Biologic License Application
US License:	1891
Applicant:	Eli Lilly and Company
Facility:	Eli Lilly and Company, Indianapolis, IN USA (FEI#1819470)
Product:	Cyramza (ramucirumab)
Dosage:	Sterile liquid for intravenous infusion 500 mg/50 mL and 100 mg/10 mL
Indication:	Treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Due date:	April 23, 2014

Recommendation: An amendment to this BLA was reviewed from a product quality microbiology perspective and the BLA as amended is recommended for approval.

This is an addendum to for the drug product quality microbiology review memo entered into DARRTS on 3-Feb-2014 for BLA 125477. Information requests were sent to the sponsor on 8-Nov-2013 and 23-Jan-2014 and the responses were received on 15-Nov-2013 and 29-Jan-2014. The responses were included in Amendments 0019 and 0030 (sequences #13 and #29). The information requests and responses are discussed below.

Reviewer Question: 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.

Sponsor Response in Amendment 0030: The sponsor confirmed that the surface sample data included in Section 3.2.P.3.5.2.4.10, Summary of Environmental Monitoring Conducted During Process Simulations, does include samples taken from personnel during (b) (4) simulations. In addition, there were no environmental monitoring excursions.

Reviewer Question: Please provide shipping validation data for the minimum and maximum loads using commercial shipper and the summer winter profiles for shipments. Provide the protocol to be used for commercial shipment (b) (4) .

Sponsor Response in Amendment 0012: The sponsor states that ramucirumab is shipped (b) (4) Therefore, summer and winter profiles on minimum and maximum loads are not necessary to validate shipping. The study report for the shipping validation, TR-1128, was provided as Attachment Q8-2. Drug product vials were packaged into the commercial configurations and shippe (b) (4) The vials were sampled and inspected for physical damage, analyzed for drug product quality attributes and monitored to verify the shipment temperature (2-8°C) was maintained.

Results show that all testing results were satisfactory and met microbial specifications (container closure and temperature maintenance). All sampled vials were subjected to container closure integrity testing and there were no failures. (b) (4) (b) (4) (b) (4) the sponsor based on the passing drug quality test results.

These results show that ramucirumab drug product is not adversely affected by shipping.

Reviewer's comment: The sponsor's responses to the information requests are adequate. All information requests for drug product quality microbiology have been adequately addressed.

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/s/

CANDACE GOMEZ-BROUGHTON
02/12/2014

PATRICIA F HUGHES TROOST
02/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date:	**January 23, 2014**
To:	Administrative File, **STN** 125477
From:	Candace Gomez-Broughton, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsed:	Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject:	New Biologic License Application
US License:	1891
Applicant:	Eli Lilly and Company
Facility:	Eli Lilly and Company, Indianapolis, IN USA (FEI#1819470)
Product:	Cyramza (ramucirumab)
Dosage:	Sterile liquid for intravenous infusion 500 mg/50 mL and 100 mg/10 mL
Indication:	Treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy
Due date:	April 23, 2014

Recommendation: The BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

REVIEW SUMMARY

BLA 125477 was submitted in eCTD format on 13-Sep-2013 to license ramucirumab for treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy. Ramucirumab is a human DNA-derived monoclonal antibody that targets the extracellular domain of the kinase insert domain receptor (KDR, or human vascular endothelial growth factor receptor-2 or VEGFR-2). The drug substance (DS) is manufactured at ImClone Systems LLC in Branchburg, New Jersey. The drug product (DP) is manufactured at Eli Lilly and Company in Indianapolis, Indianapolis.

This review covers the product quality microbiology of the DP as presented in BLA section 3.2.P. The product quality microbiology review for the DS was completed by Kalavati Suvarna, Ph.D. in a separate memo.

Amendments reviewed in response to information requests

An information request was sent to the sponsor on 26-Nov-2013. The response was submitted in eCTD format on 13-Dec-2013 in Amendment 0018 under sequence #0016.

DRUG PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Ramucirumab is a sterile, preservative-free, 10 mg/mL solution for intravenous infusion. The DP is formulated in (b) (4) solution at pH 6.0 and is provided in two presentations, 500 mg/50mL and 100mg/10mL (referred to as the 10 mL and 50 mL presentations for simplicity). Prior to infusion, the DP is diluted with 0.9% sodium chloride. The DP composition is described in the table below and was provided in section P.1 (Table 3.2.P.1-1).

Table 3.2.P.1-1 Unit Formula for Ramucirumab Drug Product, 500 mg/50 mL and 100 mg/10 mL

Ingredient	Quantity (mg/mL)	Function	Reference to Standards
Active Ingredient			
Ramucirumab	10	Active Ingredient	In-house
Other Ingredients			
(b) (4) Histidine	0.65	(b) (4)	USP, Ph.Eur, JP
(b) (4) Histidine Monohydrochloride	1.22		Ph.Eur, JP
Glycine	9.98		USP, Ph.Eur, JP
Sodium Chloride	4.38		USP, Ph.Eur, JP
Polysorbate 80	0.10		USP-NF, Ph.Eur, JP
Water for Injection	(b) (4)		USP, Ph.Eur, JP
(b) (4)			

SATISFACTORY

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

The ramucirumab DP is filled into a single-use Type I glass vial with a (b) (4) (b) (4) stopper, and a (b) (4) seal. The DP is sterilized (b) (4). Excipients and drug substance are tested for both bioburden and endotoxin. Container closure integrity (CCI) tests using the dye ingress and microbial ingress test methods have been completed.

Dye Ingress Test

Vial units from the process validation batches at both manufacturing facilities were subjected to the dye ingress test for CCI. The test procedure is described in Section 3.2.P.8.3.1.10.2.1. Results

show that all of the vials used in the study met acceptance criteria. Results are shown below in the table provided in Section P.2.5 (Table 3.2.P.5-1).

Table 3.2.P.2.5-1 Container Closure Test Results – Dye Ingress

(b) (4)

Microbial Ingress

The microbial ingress test method was also used in order to demonstrate container closure integrity. Vials from both manufacturing sites were (b) (4) tested for microbial growth. Media was tested for growth promotion. No growth was shown in any of the test vials or negative control vials. A description of the microbial ingress studies is provided in Table 3.2.P.2.5-2 in the submission and also shown below.

Table 3.2.P.2.5-2 Microbial Ingress Method Details

(b) (4)

Reviewer's Question: 1. Provide the sensitivities [redacted] of the microbial ingress test used to qualify the container closure integrity test for the ramucirumab drug product. The sensitivity of the microbial ingress test should be correlated to that of the dye ingress test using the same challenge conditions [redacted] and evaluated. Please provide a description on how the positive controls were prepared for the microbial ingress test. Indicate if the worst-case [redacted] were simulated in the container closure studies.

Sponsor Response in Amendment 0018

1a. Provide the sensitivities [redacted] *of the microbial ingress test used to qualify the container closure integrity test for the ramucirumab drug product.* The [redacted] (positive control) used in this study was [redacted] kept in place throughout the testing process.

1b. The sensitivity of the microbial ingress test should be correlated to that of the dye ingress test using the same challenge conditions [redacted] *and evaluated. Please provide a description on how the positive controls were prepared for the microbial ingress test.* Lilly did not complete ramucirumab-specific direct comparison studies to correlate the microbial ingress and dye ingress test sensitivities. Instead, a technical assessment and literature review, along with evaluation of ramucirumab dye ingress method validation data, were performed to address such a correlation. When compared with microbial ingress testing, the dye ingress affords inherent advantages. Molecule-size methylene blue dye tracers provide superior penetrability through CCI breaches than microorganisms used in microbial testing. Detection of the dye has been validated and is more reliable than probabilistic microbial growth and no incubation periods are needed. For these reasons, the dye ingress test is considered equivalent or better with respect to sensitivity than the microbial ingress test. This conclusion has been supported by published correlation studies where identical sets of defect samples were tested using both methods. The results demonstrate that when the same challenge conditions are used, the dye ingress methods yielded equivalent or better leak detection than microbial ingress testing.

The dye ingress test was validated specifically for ramucirumab in both the 10 and 50 mL vials. The methylene blue dye was determined to be suitable because it does not interact with the drug product and has appropriate detection sensitivity. [redacted] Challenge conditions, detection sensitivity and the use of a [redacted] positive control for routine testing are aligned with those of the microbial ingress methods commonly used in industry. Lilly considered the method is suitably validated based on these considerations.

[redacted]

Table Q1-1. LOD, LOQ and Repeatability Validation for Dye Ingress Method

(b) (4)

2c. Indicate if the worst-case (b) (4) *were simulated in the container closure studies.* Both the 10- and the 50 mL presentation vials were challenged with worst case (b) (4) at Lilly. Vials were tested for container closure integrity using the dye ingress method. This particular method was a qualified development method (b) (4) (b) (4) The results from this study are summarized in Table Q1-2 and provided below.

Table Q1-2 (b) (4) Parameter Study (Lilly)

(b) (4)

[redacted]

Reviewer's Comments: In the CCI microbial ingress method validation study the positive control was prepared (b) (4) [redacted] *. A request to complete the study using a positive control with* (b) (4) *will not be made because the dye ingress method was shown to be effective in detecting* (b) (4) [redacted].

P.3 Manufacture

The facilities involved in drug product manufacturing, testing, labeling, and packaging are listed in Table 3.2.P.3.1-1 and shown below:

Table 3.2.P.3.1-1 Manufacture and Control Facilities for Ramucirumab Drug Product

Site	Responsibilities
Eli Lilly and Company Indianapolis, Indiana 46285 USA Establishment Identification Number: 1819470	Drug product manufacture. Release testing and stability testing for drug product. Secondary packaging / labeling of drug product.
ImClone Systems LLC 33 ImClone Drive Branchburg, NJ 08876 USA Establishment Identification Number: 3002889358	Release testing and stability testing for drug product.

Reviewer comments: Refer to the cGMP section of this BLA for the facilities' compliance status.

P.3.3 Description of Manufacturing Process and Process Controls

Ramucirumab drug substance is shipped from ImClone Systems (b) (4) upon receipt. The manufacturing process steps are listed below:

(b) (4)

Reviewer's comment: *The manufacturing process has been adequately described.*

SATISFACTORY

P.3.4 Control of Critical Steps and Intermediates

A risk evaluation was completed in order to determine the level of criticality of process parameters and in-process controls for ramucirumab drug product manufacturing. Operating ranges and acceptance criteria were developed for parameters and controls that were determined to be critical. The risk analysis is described in Section P.2.3.1, Ramucirumab Drug Product Control Strategy. In-process controls (IPCs) have been established to monitor microbial quality and are summarized in Table 3.2.P.3.4.2.2-1 provided in Section P.3.4.

Table 3.2.P.3.4.2.2-1 In-Process Specifications for Manufacture of Ramucirumab Drug Product

(b) (4)

In addition, (b) (4) have been established in order to maintain quality. The (b) (4) were provided in Section P.3.4 and provided below.

Table 3.2.P.3.4.2.3-1 Processing (b) (4) for Ramucirumab Drug Product

(b) (4)

SATISFACTORY

P.3.5 Process Validation

Ramucirumab drug product manufacturing was prospectively validated at commercial scale and according to the processes described in Section P.3.3. In addition, critical systems were qualified prior to the execution of the process validation (PV) protocol. The PV approach included a total of four drug product validation batches. Two PV batches of each commercial presentation were manufactured using maximum and minimum batch sizes. Four drug substance batches were used in the manufacture of validation batches. The drug product PV matrix is summarized in the table shown below.

Drug Product Presentation (Batch Number)	500 mg/50 mL (C067686)	100 mg/10 mL (C067691)	100 mg/10 mL (C067690)	500 mg/50 mL (C067683)
Target Batch Size	(b) (4)			
DS Lot No.	601504	601357	601580	601512
Date of Manufacture	4-Sep-12	17-Sep-12	8-Sep-12	28-Aug-12
Theoretical Batch Size in vials	(b) (4)			
Total filled vials				
Total samples				
Inspection discards				

The theoretical batch size is calculated (b) (4)

P.3.5.1.2 Process Validation Strategy

The process validation strategy included three stages: (1) Process Design - Assessment of process parameters from each unit operation, experience from historical clinical trial batch performance, data from developmental studies, and data from platform knowledge were used to develop and optimize the commercial manufacturing process. Several studies were completed in order to support the commercial manufacturing process. (2) Process Qualification - A sampling plan and acceptance criteria were developed to assess variability within and between batches. The plan included sampling points, number of samples for each unit operation and the relevant quality attributes to be monitored. The process validation criteria allowed for a science and risk based determination of the ability of the process to consistently produce quality product. (3) Continued Process Verification - A monitoring plan has been established and will be maintained in order to ensure that the process is in control. Any changes to the process will be governed by the internal quality change management system and regulatory reporting requirements.

P.3.5.2 Sterilization Process and Validation Summary

Information and data supporting ramucirumab (b) (4) is provided in this section. Non-product-specific data is maintained in Drug Master File (b) (4) and is also provided with BLA. A letter of authorization for the DMF was submitted in Section 1.4.1 Letters of Authorization.

Buildings and Facilities

Ramucirumab drug product is manufactured (b) (4)

(b) (4)

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Release Testing

Release results of the process validation batches show that all batches met the acceptance criteria. Endotoxin levels were (b) (4) for all batches (acceptance criteria: (b) (4)). All batches passed the sterility test.

SATISFACTORY

(b) (4)

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(b) (4)

Reviewer's comment: There is currently only one drug product manufacturing site for ramucirumab.

SATISFACTORY

P.3.5.2.4.11 Actions Concerning Product When Process Simulations Fail

If acceptance criteria are not met (b) (4), an investigation is completed to determine that cause of the failure. The impact to the product lots (b) (4) is determined during the investigation. (b) (4)

(b) (4)

P.3.5.2.5 Microbiological Monitoring Of the Environment

Environment monitoring is described in Section 3.2.A.1, Facilities and Equipment.

P.3.5.2.6 Container Closure and Package Integrity

Container closure is monitored for drug product on stability and is described in the product stability protocol, Section 3.2.P.8.2, Post-Approval Stability Protocol and Stability Commitment. Container closure integrity has been demonstrated by microbial immersion and dye ingress testing. Results are provided in Section 3.2.P.2.5 Microbiological Attributes.

P.3.5.2.7 Sterility Testing Method

Sterility is determined using a method compliant with USP <71> and Ph. Eur. 2.6.1. Method qualification for the sterility test is described in Section 3.2.P.5.3.4.

P.3.5.2.8 Bacterial Endotoxin Testing Method

Bacterial endotoxin is tested by a method compliant with USP <85> and Ph. Eur. 2.6.14. The method qualification is described in Section 3.2.P.5.3.3.

P.3.5.2.9 Drug Product Shipping Validation

A shipping study is planned to validate the shipping strategy (b) (4)

Filled vials will be packaged at the Lilly Technology Center (LDC). (b) (4) Product and packaging will be sampled for inspection and testing. Temperature monitor data will be analyzed for excursions outside of the 2-8°C temperature range. Container closure integrity will be evaluated on vials for both presentations. The results from the shipping validation will be summarized in a technical report.

Reviewer's question: If available, please submit results from the shipping validation study.

The sponsor's response to this request is pending and will be addressed in an addendum to this review.

P.5 Control of Drug Product

The release and end of shelf-life microbial specifications for ramucirumab drug product are endotoxin (b) (4) and sterility. Container closure integrity is conducted at the end of shelf life.

SATISFACTORY

P.5.2 Analytical Procedures

The drug product is formulated at 10mg/mL from the drug substance (b) (4).
The difference between the drug substance and drug product (b) (4).
Methods used for microbial control are compendial methods. Qualification of these methods is provided in Section 3.2.P.5.3.3 and 3.2.P.5.3.4.

Non-compendial methods used for the control of the drug product quality will be reviewed by OBP.

(b) (4)

Qualification studies were done using three batches of ramucirumab drug product and results showed that there was no interference with the assay (b) (4)
Acceptance criteria for the interference test were:

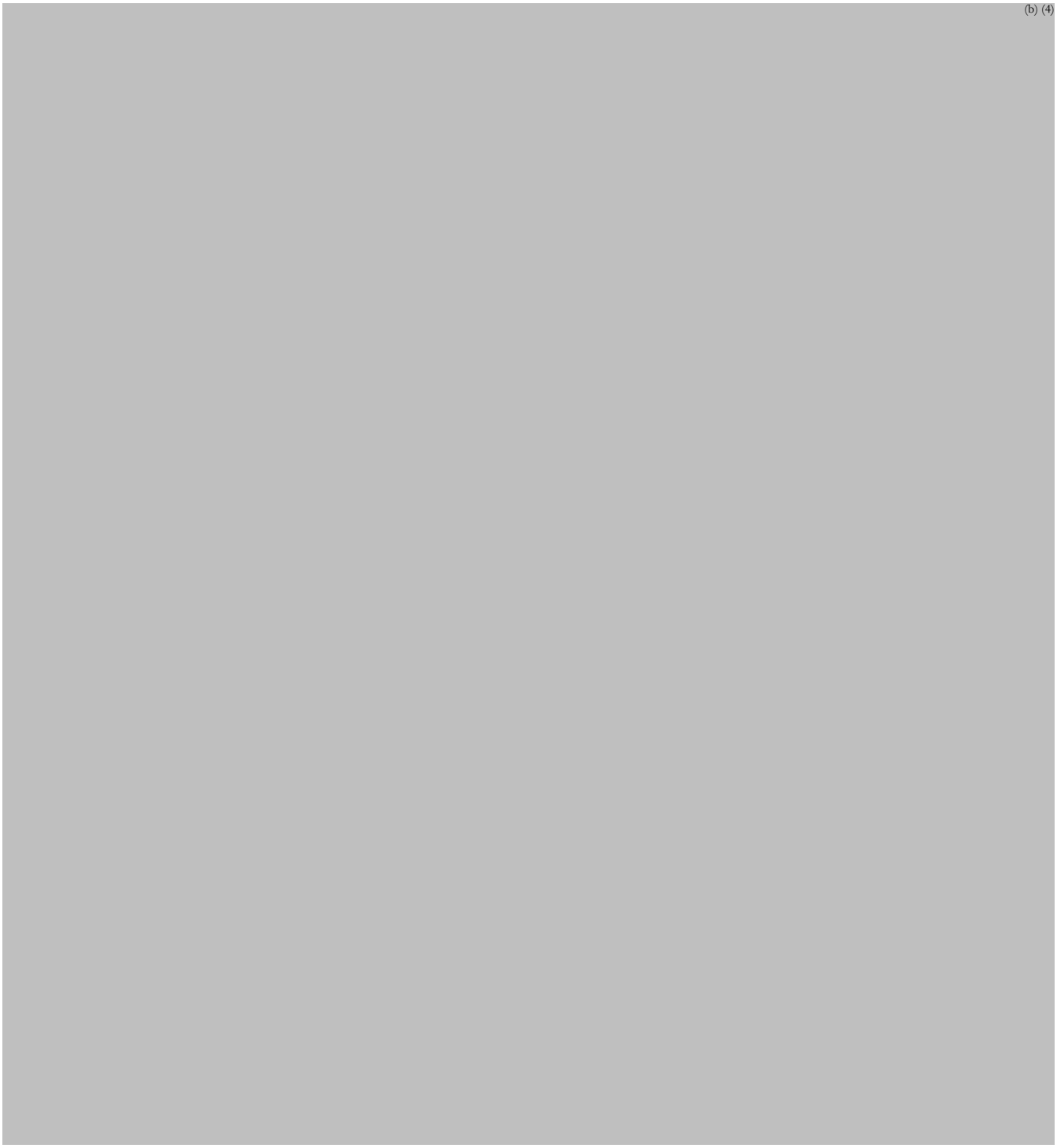
(b) (4)

(b) (4) All acceptance criteria were met.

Lots C067683, C067686, and C067691 were manufactured using commercial process and subjected to the BET and a rabbit pyrogen test. The results are compared in Table 3.2.P.5.3.3.1-2 which is provided below.

Table 3.2.P.5.3.3.1-2 Summary of Bacterial Endotoxins and Rabbit Pyrogen Test Data

(b) (4)



SATISFACTORY

P.3.5.3.4 Determination of Sterility of Ramucirumab Drug Product

Three batches of drug product were used for the sterility test method qualification. The sterility test was done in the presence or absence of drug product. Microbial recovery in drug product samples were compared to positive control media. Challenge organisms included those listed in USP <71>:

- *S. aureus (ATCC 6538)*

- *P. aeruginosa* (ATCC 9027)
- *B. subtilis* (ATCC 6633)
- *C. sporogenes* (ATCC 19404)
- *C. albicans* (ATCC 10231)
- *A. brasiliensis* (ATCC 16404)

Results show comparable growth in the presence and absence of the drug product.

P.5.4 Batch Analysis

Batch analysis for batches manufactured at Lilly is provided in Section 3.2.P.5.4. Results related to the microbial quality of drug product batches met acceptance criteria. Results of the sterility tests met USP/Ph. Eur./JP requirements and endotoxin level were (b) (4) for each batch. Batches C067683 and C067686 represent the 500 mg/50 mL product strength and batches C067690 and C067691 represent the 100 mg/10 mL product strength. All four batches were manufactured in August and September 2012.

SATISFACTORY

P.5.6 Justification of Specifications

Release and end of shelf life specifications for sterility are set according to USP <71>. The acceptance criterion complies with the compendial requirements.

Endotoxin specification is set at (b) (4)

P.7 Container Closure System

Ramucirumab drug product is packaged in a Type I tubing glass vial with a (b) (4) stopper (b) (4). Supplier information is provided in Table 3.2.P.7.3-1 and shown below.

Table 3.2.P.7.3-1 Component Supplier Information

(b) (4)

[a] Letters of Authorization to DMFs are provided in Section 1.4.1, Letters of Authorization.

SATISFACTORY

P.8 Stability

Stability protocols include long-term storage under the recommended storage conditions (2-8°C), accelerated (23-27°C), and (38-42°C) stressed storage studies. The drug product lots currently on stability include eight drug product lots manufactured at full scale at the proposed commercial manufacturing site (Eli Lilly and Company). All of the drug product lots were manufactured using the commercial container closure system. The sponsor proposes an expiry of 36 months for drug product stored at 2-8°C. Container closure integrity testing (dye ingress method) is performed at the 0, 12, 24, and 36 month time points for stability samples stored at 2-8°C. One lot of each vial presentation (100mg/10mL and 500mg/50 mL) will be added to the stability program annually.

Reviewer's comment: The stability protocol includes container closure integrity testing initially, annually, and at expiry for sample stored at 2-8°C. The remainder of the stability data, protocol, and proposed expiry should be reviewed by OBP.

SATISFACTORY

ENVIRONMENTAL ASSESSMENT

The supplement did not involve the introduction of a new unlicensed molecular entity or an increase in the production of the previously licensed drug substances; therefore, Environmental Assessment information is not required.

cGMP STATUS

Please refer to the TB-EER response in DARRTS.

CONCLUSION

I. The BLA, as amended, is recommended for approval from a product quality microbiology perspective.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. No inspectional follow-up items were identified.

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/s/

CANDACE GOMEZ-BROUGHTON
01/23/2014

PATRICIA F HUGHES TROOST
01/23/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Kalavati Suvarna, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA	125477/0
APPLICANT	Eli Lilly and Company
US LICENSE NUMBER	1891
SUBMISSION REVIEWED	Original BLA
PRODUCT	CYRAMZA (Ramucirumab, rHuman MAb to VEGFR-2; IMC-1121B; LY3009806)
MANUFACTURING FACILITY	ImClone Systems LLC, 33 ImClone Drive, Branchburg, NJ 08876. USA. FEI: 3002889358.
INDICATION	Treatment of patients with advanced gastric cancer or gastric-esophageal junction adenocarcinoma after prior chemotherapy.
DOSAGE FORM	Solution for Intravenous Infusion (500 mg/50 mL and 100 mg/10 mL vials)
SUPPORTING DOCUMENTS	IND 011856, (b) (4)
CDER RECEIPT DATE	August 23, 2013
REVIEW ASSIGN DATE	August 26, 2013
REVIEW COMPLETE DATE	December 23, 2013
GRMP GOAL DATE	January 23, 2014
PDUFA GOAL DATE	April 23, 2013
PROJECT MANAGER	Sickafuse Sharon
DIVISION	Division of Oncology Products 2
TO	S:\archive\BLA\125477\STN125477.rev.mem.BLA.12-23-2013.doc

1. PRODUCT QUALITY MICROBIOLOGY SUMMARY

I. EXECUTIVE SUMMARY

The subject of this BLA is ramucirumab, a recombinant human IgG1 anti-vascular endothelial growth factor receptor-2 monoclonal antibody expressed in murine myeloma cells (NS0). It inhibits ligand simulated activation of VEGF receptor and p44/p42 mitogen activated kinases and neutralizes ligand induced proliferation and migration of endothelial cells. Manufacture of ramucirumab involves (b) (4) (b) (4) The drug substance is formulated (b) (4) The drug product is available in two presentations, 500 mg/50 mL and 100 mg/10 mL. This review covers microbial control of the drug substance manufacturing process described in the original BLA (eCTD sequence 0003 dated 8-23-2013) and amendments (eCTD sequence 0009 dated 11-4-2013, 0013 dated 11-15-2013, and 0017 dated 12-9-2013). For a review of the microbial controls in drug product manufacture and sterility assurance of drug product, please see the review by Dr. Candace Gomez-Broughton. The drug substance is manufactured at ImClone Systems LLC, 33 ImClone Drive, Branchburg, NJ 08876. USA. The site was inspected from November 4-13, 2013 and the inspection has been initially classified as NAI. The proposed shelf-life for drug substance is (b) (4)

II. Recommendation and Conclusion on Approvability

Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective. The drug substance manufacturing site, ImClone Systems LLC, 33 ImClone Drive, Branchburg, NJ 08876. USA, was inspected by a team of investigators from November 4-13, 2013. No FDA Form 483 was issued and the inspection has been classified as NAI.

2. PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Introduction:
Ramucirumab is a recombinant human IgG1 anti-vascular endothelial growth factor receptor-2 monoclonal antibody. It inhibits ligand simulated activation of VEGF receptor and p44/p42 mitogen activated kinases and neutralizes ligand induced proliferation and migration of endothelial cells. Manufacture of ramucirumab involves (b) (4) The drug substance is formulated (b) (4) The drug product is available in two presentations, 500 mg/50 mL and 100 mg/10 mL. The drug product is diluted with 0.9% Sodium Chloride Injection prior to administration by intravenous infusion. The proposed dose of CYRAMZA as a single-agent is 8 mg/kg every 2 weeks administered as an intravenous infusion over approximately 60 minutes ((b) (4) The proposed shelf-life for drug substance is (b) (4)

The CMC section of the original BLA was submitted under eCTD sequence 0003 dated 8-23-2013. In addition, the following amendments are reviewed here: eCTD sequence numbers 009 dated 11-4-2013 (b) (4)), 0013 dated 11/15/2013 (quality microbiology information) and 0017 dated 12/9/2013 (shipping validation data).

3.2.S. DRUG SUBSTANCE

3.2.S.1. GENERAL INFORMATION
Ramucirumab is a recombinant human monoclonal antibody of the IgG1 subclass that targets the extracellular domain of the human vascular endothelial growth factor receptor-2 or VEGFR-2) expressed in NS0 cells (murine myeloma cell line). The average molecular mass of ramucirumab (b) (4) is 146,756 Da. Ramucirumab drug substance is formulated (b) (4) (b) (4)

This section is reviewed by the OBP reviewer

3.2.S.2. MANUFACTURE

3.2.S.2.1. MANUFACTURE(S)

The drug substance manufacturing, testing and release sites were provided in Table 3.2.S.2.1-1 in section 3.2.S.2.1 of the BLA and are shown below:

Table 3.2.S.2.1-1: Manufacture and Control Facilities for Ramucirumab Drug Substance.

Manufacturing Facility	The drug substance is manufactured in accordance with current Good Manufacturing Practices at the following facility: ImClone Systems LLC 33 ImClone Drive Branchburg, NJ 08876 USA Establishment Identification Number: 3002889358
Storage Facility	ImClone Systems LLC 33 ImClone Drive Branchburg, NJ 08876 USA Establishment Identification Number: 3002889358
Control Facilities	The drug substance is tested at the following facilities: Release testing and stability testing for bulk drug substance and sterility testing for (b) (4) re performed at: ImClone Systems LLC 33 ImClone Drive Branchburg, NJ 08876 USA Establishment Identification Number: 3002889358 (b) (4)

(b) (4)

Table 3.2.S.2.1-1: Continued

(b) (4)

Review comment: For the compliance status of the manufacturing and testing sites, please see final TB-EER.

3.2.S.2.2. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

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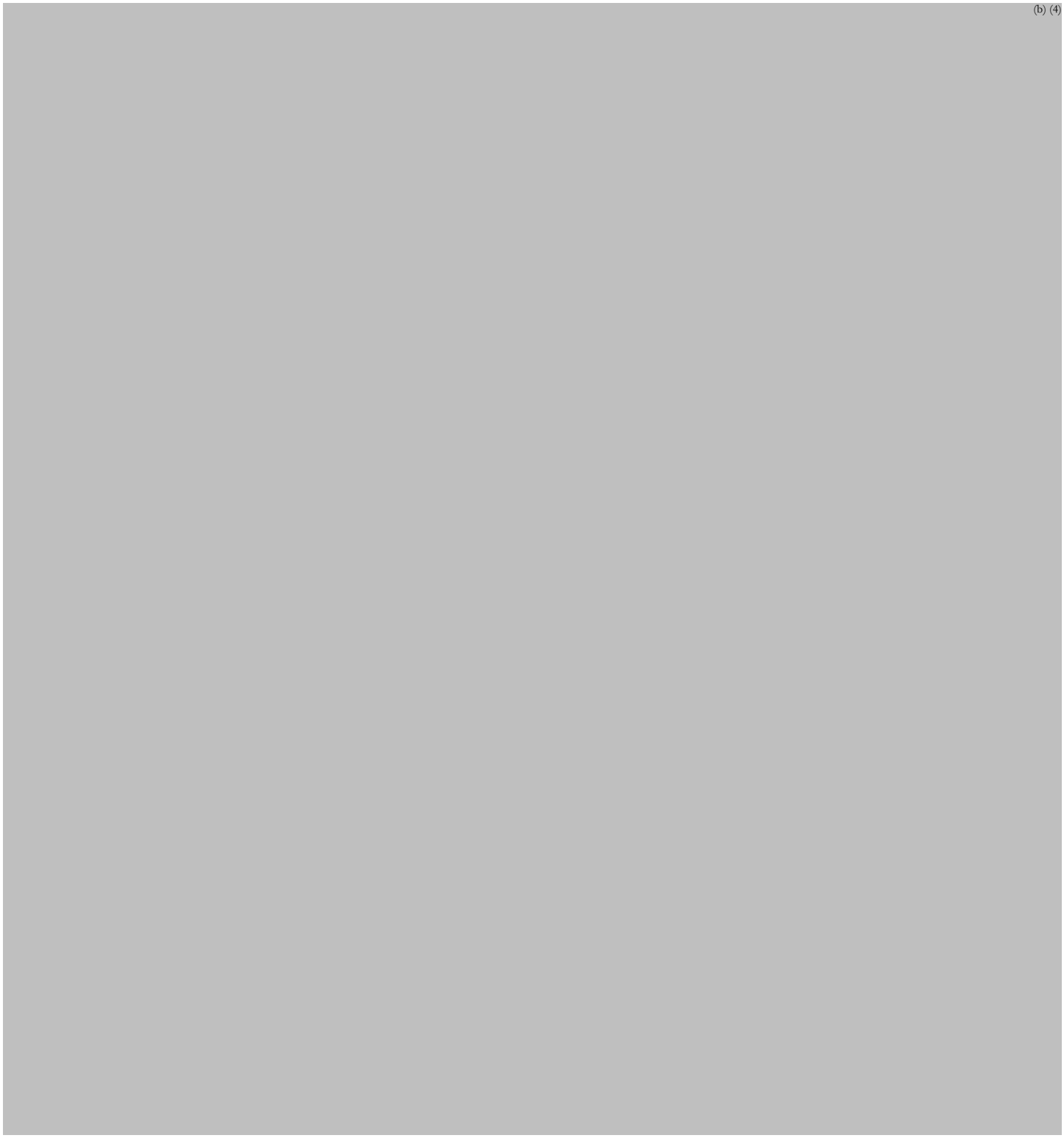

CGMP STATUS:
Please refer to the final TB-EER for the compliance status of the manufacturing and testing facilities.

CONCLUSION:

I. Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective.

II. CMC product specific information and data should be reviewed by the OBP reviewer.

III. Please refer to the final TB-EER for the compliance status of the manufacturing and testing facilities.

SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Kalavati Suvarna, Ph.D. Date:
Concurring BMAB Team Leader: Patricia. F. Hughes, Ph.D. Date:

cc:
OND/OHOP/DOP II RPM/Sickafuse, Sharon
OC/OMPQ/BMAB TL/Hughes, Patricia
OND/OHOP/DOP II MO/Casak, Sandra
OND/OHOP/DOP II CDTL /Lemery, Steven

APPEARS THIS WAY ON ORIGINAL

Information request included in 74 day letter dated 10-22-2013

1. Provide information on (b) (4) storage conditions (container, temperature, and duration) and data supporting microbial control (b) (4).

Information request 11-5-2013

1. Please provide a Table with the duration of each manufacturing process step (b) (4) .
2. Please provide details of how (b) (4) are sterilized.
3. Please provide a process flow diagram (b) (4) for bioburden and endotoxin. Also, clarify the volume of sample tested for bioburden and endotoxin at each unit operation.
4. Please revise the established (b) (4) based on worst case manufacturing scale data ((b) (4) Data to support microbial control (b) (4) should be provided.
5. Please provide the protocols to be used for concurrent validation (b) (4) .
6. Please provide the microbial data obtained (b) (4)
7. Please provide the protocol to be used (b) (4)
8. Please provide shipping validation dat (b) (4) . The protocol to be used for commercial shipment (b) (4) should be defined.
9. Please provide the protocol and information (b) (4) used for qualification of the endotoxin test method (b) (4) and drug substance. The qualification raw data for each lot of (b) (4) and drug substance tested along with lot number should be submitted. (b) (4) The sample storage conditions for routine testing and that used during qualification studies should be specified.
10. Please provide the sample volume and lot numbers of (b) (4) and drug substance tested during bioburden qualification. The protocol used should be provided and the sample storage conditions for the qualification studies and for routine testing should be specified.

Information request 12-3-2013

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

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

/s/

KALAVATI C SUVARNA
01/10/2014

PATRICIA F HUGHES TROOST
01/10/2014

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125477	Eli Lilly and Company	9/13/2013
Established/Proper Name: Ramucirumab	**BLA/NDA Type:** Original	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
❑ including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
❑ PI –non-annotated	Y	
❑ PI –annotated	Y	
❑ PI (electronic)	Y	
❑ Medication Guide	Y	
❑ Patient Insert	Y	
❑ package and container	Y	
❑ diluent	Y N	No diluent
❑ other components	Y	
❑ established name (e.g. USAN)	Y	
❑ proprietary name (for review)	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing arrangement	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	Y N	
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info ○ nomenclature ○ structure (e.g. sequence, glycosylation sites) ○ properties	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control ○ batch numbering and pooling scheme ○ cell culture and harvest ○ purification ○ filling, storage and shipping	Y	
❑ control of materials ○ raw materials and reagents ○ biological source and starting materials ○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing	Y	Defer to OBP
❑ control of critical steps and intermediates ○ justification of specifications ○ stability	Y	
❑ process validation (prospective plan,		

CTD Module 3 Contents	Present?	If not, justification, action & status
results, analysis, and conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y Y	[redacted] (b) (4) and microbial control data to support [redacted] (b) (4) was not included.
❑ characterization of drug substance		Defer to OBP
❑ control of drug substance		
○ specifications	Y	
○ justification of specs.	Y	Defer to OBP
○ analytical procedures		
○ analytical method validation		Microbial method validation information for intermediates and the drug substance was included.
○ batch analyses	Y	
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability	Y N	
❑ summary	Y	Defer to OBP
❑ post-approval protocol and commitment	Y	
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	Y	No preservative
○ container-closure integrity		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y Y Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y	
○ Validation of aseptic processing (media simulations)	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ Environmental Monitoring Program	Y	
○ Lyophilizer validation	Y N	
○ Other needed validation data (hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)		Defer to OBP
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	Defer to OBP except for microbial specifications
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7]		
○ specifications (vial, elastomer, drawings)		
○ availability of DMF & LOAs		
○ administration device(s)	Y	
❑ stability	Y	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
○ protocol	Y	
○ results		
○ method validation		
Diluent (vials or filled syringes) [3.2P′]		
❑ description and composition of diluent	Y N	N/A
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
○ Filter validation		

CTD Module 3 Contents	Present?	If not, justification, action & status
○ Component, container, closure depyrogenation and sterilization validation	Y N	
○ Validation of aseptic processing (media simulations)	Y N	
○ Environmental Monitoring Program		
○ Lyophilizer sterilization validation	Y N	
○ Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards		
❑ container closure system		
○ specifications (vial, elastomer, drawings)	Y N	
○ availability of DMF & LOAs	Y N	
❑ stability		
❑ summary		
❑ post-approval protocol and commitment	Y N	
❑ pre-approval		
○ protocol		
○ results		
Other components to be marketed (full description and supporting data, as listed above):		
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	N/A
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment		
○ manufacturing flow; adjacent areas	Y	
○ other products in facility		
○ equipment dedication, preparation, sterilization and		

CTD Module 3 Contents	Present?	If not, justification, action & status
storage ○ procedures and design features to prevent contamination and cross-contamination		
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	Y N	Defer to OBP
❑ novel excipients		Defer to OBP
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y N	
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y Y Y Y	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Defer to OBP
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please provide information on (b) (4) storage conditions (container, temperature, and duration) and data supporting microbial control (b) (4).

Kalavati Suvarna, Ph.D. (Drug Substance)
Candace Gomez-Broughton, Ph.D. (Drug Product)

Product Quality Reviewer(s) Date

Patricia Hughes, Ph.D. (Team Leader)

Branch Chief/Team Leader/Supervisor Date

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

/s/

CANDACE GOMEZ-BROUGHTON
10/03/2013

KALAVATI C SUVARNA
10/03/2013

PATRICIA F HUGHES TROOST
10/03/2013