CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

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

Date:	**November 10, 2015**
To:	Administrative File, STN 125547/0
From:	Candace Gomez-Broughton, Ph.D., Reviewer, CDER/OPQ/OPF/DMA
Endorsed:	Patricia Hughes, Ph.D., Actg Branch Chief, CDER/OPQ/OPF/DMA
Subject:	Original Biologic License Application Review Memo – Drug Substance
US License:	1891
Applicant:	Eli Lilly and Company
Facility:	Drug Substance: ImClone Systems LLC, Branchburg, New Jersey (FEI number: 3002889358)
Product:	PORTRAZZA® (necitumumab)
Dosage:	Liquid solution for intravenous infusion (16mg/mL)
Indication:	For use in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer
Due date:	December 2, 2015

Recommendation: The supplement is recommended for approval from a microbiology product quality perspective with the following Post-Marketing commitment:

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

INTRODUCTION

Necitumumab is a recombinant monoclonal antibody (immunoglobulin G subclass 1(IgG1)) that binds to human epidermal growth factor receptor (EGFR) thereby inhibiting its activation. The proposed indication for necitumumab is for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer. Necitumumab drug substance is manufactured at ImClone Systems LLC in Branchburg, New Jersey. Drug product is manufactured at Eli Lilly and Company in Indianapolis, Indiana.

This assessment covers the drug substance sections of the BLA from a microbial control perspective. Drug product sections were reviewed by Lakshmi Narasimhan, Ph.D. in a separate review memo.

ASSESSMENT

Amendments Reviewed For Drug Substance Quality Microbiology

- SDN 0047
- SDN 0035

S DRUG SUBSTANCE

S.1 General Information

Necitumumab is an anti-EGFR recombinant monoclonal antibody. Necitumumab drug substance is formulated (b) (4) containing (b) (4) (b) (4) 40 mM sodium chloride, 133mM mannitol, and 0.01% (w/v) polysorbate 80, pH 6.0.

S.2 Manufacture

S.2.1 Manufacturer(s)

Necitumumab drug substance is manufactured at ImClone Systems, LLC. Storage and testing facilities for drug substance are listed in the table below:

Facility	FEI Number (s)	Responsibility
ImClone Systems LLC	3002889358	Drug substance manufacturing; MCB and WCB storage, release and stability testing
Eli Lilly and Company	1819470	Back up MCB and WCB storage
(b) (4)		

Reviewer's comment: The ImClone Systems LLC facility was inspected on March 6-9, 2015 by Peter Qiu, Ph.D., OPQ/OPF/DIA and was VAI.

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S.4 Control of Drug Substance

S.4.1 Specification

Microbial release specifications for necitumumab drug substance is are as follows:

- Endotoxin: ≤ (b) (4) EU/mg
- Bioburden: ≤ (b) (4) CFU/100 mL

S.4.2 Analytical Procedures

The analytical procedures used in release testing are listed below:

- Endotoxin: USP <85>, Ph. Eur. 2.6.14
- Bioburden USP <61>, Ph. Eur. 2.6.12

Bioburden testing is performed (b) (4)

S.4.3 Validation of Analytical Procedures

Bioburden Method Suitability

Method validation was performed (b) (4) All samples met the acceptance criteria demonstrating the test is qualified for its intended use. Data are provided in validation report GR-13185 included in the BLA.

Endotoxin Inhibition/Enhancement Testing

The bacterial endotoxin concentration in drug substance samples is determined by using the kinetic chromogenic Limulus Amoebocyte Lysate (LAL) test. Validation studies were completed to demonstrate that this method is suitable (b) (4) Qualification was completed (b) (4) These results demonstrate that this method is suitable for testing bacterial endotoxin in drug substance (b) (4) All acceptance criteria were met.

S.4.3.1 Endotoxin Hold Time Study for Necitumumab Drug Substance

In accordance with the Agency's requests, an endotoxin hold time study was completed in order to determine if a Low Endotoxin Recovery (LER) effect was observed due to the DS formulation. Studies were done to simulate worst case hold conditions (b) (4) The initial studies were completed using naturally occurring endotoxin (NOE) prepared in-house (b) (4) A second study was completed using lipopolysaccharide (LPS) in response to comments from the Agency (b) (4)

S.4.3.1.1 Low Endotoxin Recovery Study Using Lipopolysaccharide

(b) (4)

(b) (4)

Results are summarized in Table 3.2.S.4.3.1.1-1 which has been provided below.

Table 3.2.S.4.3.1.1-1 LPS Hold Time Study Results for Necitumumab Drug Substance (% T0 basis)

(b) (4)

Reviewer comments: The endotoxin hold time studies done with bulk drug substance (BDS) show (b) (4) *The sponsor was asked to establish an endotoxin sample hold time of not more than (NMT)* (b) (4) *hours and to amend the BLA accordingly.*

The sponsor has amended the BLA (sequence #0031) with a final study report (b) (4)

(b) (4)

(b) (4)

The LPS recovery data from this study are summarized in the table below.

Table 4: Results of Endotoxin Hold Testing using Lipopolysaccharide (LPS) Inoculum

(b) (4)

This data supports the validated (b) (4) hold time (b) (4) The results from this study show (b) (4)

Reviewer comment: The results from the endotoxin recovery studies are inconsistent. Therefore the sponsor will complete these studies using three drug substance batches manufactured during a recent campaign as a post-marketing commitment. The studies will be completed (b) (4)

The studies must be done (b) (4)

SATISFACTORY

S.4.4 Batch Analyses

Analytical data was provided for commercial process lots (511091, 511011, 511010, 511009, 510910, 510909, 508444, 508429, and 508425). Bacterial endotoxin results were < (b) (4) EU/mg and no growth was detected bioburden assay for all batches.

S.4.5 Justification of Specification
The endotoxin specification is ≤ (b) (4) EU/mg. Based on the proposed does of 800 mg, assuming an average body weight of 70 kg, an acceptance criterion of < (b) (4) EU/mg would be acceptable to ensure that the maximum tolerance limit allow by USP (5 EU/kg) is not exceeded. (b) (4)

The bioburden specification of ≤ (b) (4) CFU/100 mL was determined to discriminate between background microbial counts and contamination. This specification reflects the microbiological control required within a closed bioprocess containment system and ensures quality and safety of the product.

S.5 Reference Standards or Materials

This section will be reviewed by the OBP reviewer.

S.6 Container Closure System
Necitumumab DS is filled (b) (4)

The (b) (4) system was qualified to evaluate its suitability. Endotoxin (acceptance criteria: < (b) (4) EU/ml), bioburden, and sterility testing (acceptance criteria: (b) (4) sterility assurance level) are performed for by the vendor. Biological reactivity, physiochemical, particulates testing is also done.

Reviewer's comment: Data on leachables and biological reactivity should be reviewed by OBP.

S.7 Stability
This section will be reviewed by the OBP reviewer.

SATISFACTORY

CONCLUSION

I. The BLA is recommended for approval from a microbiological product quality perspective with the following Post-Marketing Commitment:

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

II. CMC product specific information and date should be reviewed by OBP.

III. No additional inspectional follow-up items were identified.

FDA Information Requests for STN 125547/0 Microbial Quality

S.4.2 Analytical Procedures

Please submit the following documents:

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

S.2.4.2 Microbiological Controls

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

S.4.3.1 Endotoxin Hold Time Study for Necitumumab Drug Substance

The endotoxin hold time studies done with bulk drug substance (BDS) show (b) (4) Please establish an endotoxin sample hold time of not more than (NMT) (b) (4) hours. Please amend the BLA accordingly.

SIGNATURES

Candace Y. Gomez-broughton -S

Digitally signed by Candace Y. Gomez-broughton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640207, cn=Candace Y. Gomez-broughton -S
Date: 2015.11.16 07:13:27 -05'00'

Patricia F. Hughestroost -S

Digitally signed by Patricia F. Hughestroost -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096547, cn=Patricia F. Hughestroost -S
Date: 2015.11.16 11:56:54 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date:	September 22, 2015
To:	Administrative File, STN 125547/0
From:	Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement:	Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/ OPQ/OPF/DMA
Subject:	Biological License Application (BLA)
US License:	# 1891
Applicant:	Eli Lilly and Company
Facility:	Eli Lilly, Indianapolis, IN (FEI# 1819470)
Product:	Portrazza (necitumumab)
Dosage:	Sterile, liquid formulation in a vial for intravenous injection, 16 mg/mL provided as an 800 mg/50 mL presentation for single use
Indication:	For the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) in combination with gemcitabine and cisplatin
Due Date:	December 02, 2015

Recommendation for Approvability: The drug product section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval with the following PMC. The sponsor has agreed to fulfill the PMC and submit the study report in the first annual report.

> Qualification of the endotoxin and sterility test methods was performed with two nonclinical demonstration/engineering batches of drug product. As a post-marketing commitment, perform the endotoxin and sterility test method qualification studies with two additional drug product batches and submit the information and summary data in the first annual report.

SUMMARY:

Eli Lilly and Company (Lilly) has submitted a new biologics license application, STN 125547 to license the use of necitumumab in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). Drug substance is manufactured by ImClone Systems LLC, Branchburg, New Jersey and drug product is manufactured at Lilly, Indianapolis, Indiana, USA.

The application was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 and Module 3 (drug substance and drug product sections), appendices (3.2.A.1, Facilities and Equipment and 3.2.A.2, Adventitious Agents Safety Evaluation), and a regional section (3.2.R). Letter of authorization (LOA) for Lilly's Type V DMF 21219 to reference the information regarding (b) (4) operations at the Indianapolis site and a LOA for (b) (4) Type V DMF (b) (4)

INTRODUCTION

Necitumumab drug product (DP) is manufactured (b) (4) from Necitumumab drug substance (DS). The proposed commercial manufacturer for the necitumumab drug product is Lilly Indianapolis, Indiana, USA.

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0012	April 14, 2015	Amendment
0028	August 03, 2015	Amendment
NA	August 12, 2015	Teleconference
0030	August 13, 2015	Amendment
0031	August 19, 2015	Amendment
0034	September 17, 2015	Amendment

ASSESSMENTS:

3.2.P DRUG PRODUCT

Necitumumab drug product

DP is manufactured at Lilly, Indianapolis, Indiana, USA. The proposed commercial necitumumab drug product, 800 mg/50 mL, is supplied as a sterile solution in 50 mL Type I glass vials, intended for single use.

3.2.P.1 Description and Composition of the Drug Product

DP is formulated in an aqueous (b) (4) solution at pH 6.0, containing (b) (4) (b) (4) 40mM sodium chloride, 133mM glycine, 50mM mannitol, and 0.01% w/v polysorbate 80. The drug product is diluted in 0.9% sodium chloride injection USP in an infusion container prior to administration by intravenous infusion.

The composition of DP provided in Table 3.2.P.1-1 is reproduced below.

Table 3.2.P.1-1 Unit Formula for Necitumumab Drug Product, 800 mg/50 mL

Ingredient	Quantity (mg/mL)	Function	Reference to Standards
Active Ingredient:			
Necitumumab	16	Active Ingredient	In-house
Other Ingredients:			
Sodium Citrate, Dihydrate	2.55	(b) (4)	USP-NF, Ph.Eur, JP
Citric Acid, Anhydrous	0.256		USP, Ph.Eur, JP
Glycine	9.984		USP, Ph. Eur, JP
Sodium Chloride	2.338		USP, Ph. Eur, JP
Mannitol	9.109		USP-NF, Ph. Eur, JP
Polysorbate 80	0.1		USP-NF, Ph.Eur, JP
Water for Injection	*q.s.* (b) (4		USP, Ph.Eur, JP

q.s. = quantity sufficient

Satisfactory

Labeling

FDA question (April 14, 2015): The proposed labeling claims that diluted drug product may be stored for up to 24 hours at 2-8°C. Please submit microbiological studies in support of the 24 hour post-dilution storage time at 2-8°C. Describe the test methods and results that employ a minimum countable inoculum ([redacted] CFU) to simulate potential microbial contamination that may occur during storage. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-dilution storage period is not more than [redacted] hours at 2-8°C.

Firm's Response in amendment dated August 03, 2015 in sequence # 0028: The microbiological challenge study protocol (SDP15037) and report (SDR15037) are attached to the response. [redacted]

The challenge organism's inoculum level was confirmed to be within the target range. The following table showing the results of the challenge study is reproduced below.

Necitumumab Microbial Challenge Data

[redacted]

Reviewer's comments: Although the results are expressed as CFU for the tested time points, no [redacted] log increase of growth was observed in any of the challenge organisms for the time points tested. The submitted microbiological challenge study data supports the storage period of up to 24 hours at 2 to 8°C for the infusion solution.

Satisfactory

3.2.P.2 Pharmaceutical Development

Container Closure System

DP is filled into a Type I glass tubing vial, closed with a 20 mm [redacted] stopper, and secured with a 20 mm aluminum [redacted] seal. The

secondary packaging (carton) provides protection to the light sensitive DP.

Satisfactory

3.2.P.2.5 Microbiological Attributes

Integrity of the container closure system (CCS) of the DP has been demonstrated using both dye ingress and microbial ingress test methods.

Dye ingress test

This dye test was performed using vial units (b) (4) manufactured at Lilly. The CCI test results presented in Table 3.2.P.2.5-1 are reproduced below.

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

(b) (4)

Dye ingress testing was performed per the method provided in Section 3.2.P.8.3.1.3.2.1, Container Closure Integrity Dye Ingress, which is reviewed below.

(b) (4)

(b) (4)

Method validation data and information for the dye ingress CCI testing of vials, filled with Necitumumab, was provided in section 3.2.P.8.3.1.3.2.2 is also reviewed here. The validation was performed using proposed commercial drug product presentation. (b) (4)

Microbial Ingress

The microbial ingress test method was performed (b) (4)

The details of microbial ingress method used for testing samples from both the manufacturing sites (Lilly and (b) (4)) provided in Table 3.2.P.2.5-2 and microbial ingress results provided in Table 3.2.P.2.5-3 are duplicated below:

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

(b) (4)

Table 3.2.P.2.5-3 Microbial Ingress Test Results

(b) (4)

The microbial challenge CCI test results at both sites met the acceptance criteria. No growth was observed in any of the negative controls or test vials, while positive controls and the growth promotion testing for the media were positive for growth.

Comparison Study Correlating Sensitivities of Microbial Ingress and Dye Ingress

(b) (4)

The microbial and dye ingress CCI test results provided in the submission is reproduced below.

Table 3.2.P.2.5-4 Results of the Microbial Ingress and Dye Ingress Sensitivity Comparison

(b) (4)

FDA question (April 14, 2015):

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

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

Firm's Response in amendment dated April 21, 2015 in sequence # 0012:

1. One negative control unit not exposed to the test conditions is used as per Lilly method G1273, "Container Closure Integrity Dye Ingress".
2. Dye ingress CCI testing for the necitumumab batches manufactured at both [(b) (4)] and Lilly sites are performed at Lilly's Indianapolis site and the challenge conditions, positive control preparation, and sensitivity are the same.
3.

Reviewer's comments: CCI test method has been qualified using worst case pressure/vacuum conditions.

Satisfactory

Capping Force:

Summary of Lilly Study

A development study with commercial CCS of necitumumab drug product was conducted to evaluate the capping process using worst-case capping pressures and machine speeds. [(b) (4)] All the samples passed the dye ingress test, Table 3.2.P.2.5-5, reproduced below and a capping force in the range of [(b) (4)] psig will be used during routine production at the Lilly drug product manufacturing facility.

Table 3.2.P.2.5-5 Capping Process – Dye Ingress Results (Lilly)

[(b) (4)]

Reviewer's comments: Although a positive control [(b) (4)] *is used for the dye ingress CCI testing, considering the high sensitivity of the test method, additional studies will not be requested.*

Satisfactory

3.2.P.3.1 MANUFACTURER(S)

The manufacturing, packaging, labeling, and control facilities listed in Table 3.2.P.3.1-1 is duplicated below:

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

Site	Responsibilities
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 USA Establishment Identification Number: 1819470	Drug product manufacture. Release testing and stability testing of 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 of drug product.

Reviewer's comments: Lilly's Indianapolis facility was inspected conducted by the district on July 27- August 04, 2015.

3.2.P.3.2 BATCH FORMULA

The proposed commercial batch size of Necitumumab Drug Product is approximately (b) (4) L (b) (4)

3.2.P.3.3 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

Manufacturing Process

(b) (4)

[redacted]

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Satisfactory

3.2.P.4 CONTROL OF EXCIPIENTS:
This section should be reviewed by OBP

3.2.P.5 CONTROL OF DRUG PRODUCT
3.2.P.5.1 Specifications
The microbial for the drug product release specifications are Necitumumab should be sterile with endotoxin limit of ≤ (b) (4) EU/mg.
The proposed commercial dose of Necitumumab drug product is a flat dose of 800 mg (doses are not scaled for bodyweight). Based on this dose, the proposed specification of ≤ (b) (4) EU/mg for the release of the drug product provides (b) (4) fold of safety factor.
The DP, 50 mL (800mg) solution is diluted in 0.9% sodium chloride injection USP prior to administration by intravenous infusion.

Satisfactory

3.2.P.5.2 Analytical procedures

Endotoxin: The presence of endotoxin in drug product samples is determined using kinetic chromogenic method in compliance with USP, Ph. Eur and JP. (b) (4)

Sterility: Sterility testing of Necitumumab drug product for release is performed (b) (4) according to the USP, Ph. Eur and JP.

Bioburden: (b) (4) bioburden testing is used for bulk drug product lots.

3.2.P.5.3 Validation of Analytical procedures

Endotoxin Method Qualification: Method Verification Summary Kinetic Chromogenic Bacterial Endotoxin Test: (b) (4) The results are shown in the table below, which was provided in the submission.

Table 3.2.P.5.3.1.1-1 Summary of Validation Data for Bacterial Endotoxins Testing

(b) (4)

Reviewer's comment: The study met the USP <85> acceptance criterion for (b) (4) *% recovery. Report also indicates that the sample and system acceptance criteria were met for the 3* (b) (4) *lots C262169, C266766 and C296125.*

FDA question (23 July 2015): Please clarify if the endotoxin assay method qualification studies were performed with commercial manufacturing DP lots. Submit the endotoxin assay method qualification information and results from studies performed using 3 commercial formulated bulk drug product lots.

Firm's Response in amendment dated August 03, 2015 in sequence # 0028: The three lots used for method verification are representative of commercial manufacturing. Necitumumab with a target concentration of 16 mg/mL and commercial formulation were filled into 50 mL vials for all three lots. Batch C1200159 is a Registration stability batch manufactured [redacted] (b) (4) at commercial scale [redacted] (b) (4) Batches C262169 and C266776 are non-clinical demonstration/engineering batches manufactured at Lilly within proposed commercial batch volume ranges [redacted] (b) (4).

Reviewer's comments: Qualification of the endotoxin test method was performed with two non-clinical demonstration/engineering batches of drug product. Endotoxin assay method qualification data from two additional commercial batches drug product will be requested as a PMC.

PMC: Qualification of the endotoxin test method was performed with two nonclinical demonstration/engineering lots of drug product. A post-marketing commitment is proposed to provide endotoxin assay method qualification data from two additional drug product batches. The data should be provided in the first annual report.

Firm's Response in amendment dated September 17, 2015 in sequence # 0034: The sponsor has agreed to fulfill the PMC and submit the study report in the first annual report.

Satisfactory

Rabbit pyrogen test:

Report, LY3012211 Necitumumab Rabbit Pyrogen and Bacterial Endotoxins Test Method Equivalency Data which includes CofA of Rabbit pyrogen testing performed with three lots of Necitumumab drug Product (C1200159, C262169, and C266776) is provided. [redacted] (b) (4)

FDA question (23 July 2015): Please clarify if the Rabbit pyrogen test studies were performed with commercial manufacturing DP lots

Firm's Response in amendment dated August 03, 2015 in sequence # 0028: The three lots used for rabbit pyrogen testing are representative of commercial manufacturing.

Satisfactory

Endotoxin Hold Time Study

Hold time study was performed simulating worst case hold conditions using DP vials to determine if a Low Endotoxin Recovery (LER) effect was observed when DP vials were tested for endotoxin. Initial studies were performed with naturally occurring endotoxin (NOE). [redacted] (b) (4) [redacted] (b) (4) Additional studies using lipopolysaccharide (LPS) were also performed.

LER study using LPS: [redacted] (b) (4)

(b) (4) The test results are shown in the table 3.2.P.5.3.2.1-1 below, which was reproduced from section 3.2.P.5.3.

Table 3.2.P.5.3.2.1-1 LPS Hold Time Study Results for Necitumumab Drug Product (% T0 basis)

(b) (4)

The samples met the acceptance criteria for endotoxin recovery (b) (4) .

LER study using NOE: (b) (4) The results of the LER study with NOE are shown below in Table 3.2.P.5.3.2.2-1, reproduced from submission.

Table 3.2.P.5.3.2.2-1 Endotoxin Hold Time Study Results for Necitumumab Drug Product (% T0 basis)

(b) (4)

The samples met the acceptance criteria for recovery (b) (4)

FDA question (April 14, 2015): Your Endotoxin Hold Time Study (b) (4) Please clarify if the hold time of the DP endotoxin samples was limited to < (b) (4) hours (b) (4)

Firm's response in April 21, 2015 amendment (Sequence 012): Lilly acknowledged that the endotoxin hold time study demonstrated (b) (4)

FDA question (28 July 2015):

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

b. *The endotoxin hold time studies have demonstrated* (b) (4) *You have stated in your response dated April 21, 2015 that* (b) (4) *will be proposed* (b) (4) *Please submit your proposal* (b) (4).

Firm's Response in amendment dated August 03, 2015 in sequence # 0028:

a. The endotoxin hold time study was performed (b) (4)

b. (b) (4) The results of this recent study shown in Table Q3B-1 are reproduced below:

Table Q3B-1: LPS Recovery over Time Using a (b) (4) EU/mL LPS Target in Preparation for a Rabbit Pyrogen Test

(b) (4)

All four DP batches demonstrated (b) (4)% recovery (b) (4)

These results were in contrast to the data provided in the BLA and led to further investigation (b) (4) Lilly anticipated (b) (4) hold time data to be available from this study by August 7th, 2015 and has requested a meeting with FDA on or after August 10th, 2015, to discuss the data and the proposed (b) (4) for Necitumumab Drug Product.

Teleconference on August 12, 2015 and amendment dated August 13, 2015 in sequence # 0030:
The following documents were submitted for discussion:

- Agenda for the teleconference to discuss recent endotoxin recovery results for necitumumab drug product
- Interim Report for Recoverability of LPS in Necitumumab (LY3012211) Drug Product (PRD-01901-TR)

- Presentation: Necitumumab Drug Product USP <85> Spike and Recovery Studies: Data Review and Testing Proposal

After the teleconference, Lilly submitted the Final report for PRD-01901, Recoverability of LPS in Necitumumab (LY3012211) Drug Product in amendment dated August 19, 2015 in sequence # 0031.

(b) (4)

An investigative study was conducted to identify the possible cause(s) for the observed discrepancies between the two studies (b) (4)

Results in Table 3 reproduced below, indicates (b) (4)

Table 3: Comparison of LPS Recovery in Two Necitumumab Drug Product Batches with Varying LPS Spiking Amounts*

(b) (4)

To confirm these results, a new hold study using three commercially representative DP batches shown in Table 3.2.P.5.3.2-1, reproduced below, was conducted. (b) (4)

Table 3.2.P.5.3.2-1 Necitumumab Drug Product Lots Used in Study PRD-01901

(b) (4)

The % recovery of endotoxin in this study is calculated using two methods. (b) (4)

Table 5: LPS Recovery Calculated (b) (4)

(b) (4)

Reviewer's comments: Batches manufactured at Lilly listed in this table have two batch numbers, an Imclone's batch number and a Lillys' batch number provided in the parenthesis. Appendix I of the report includes a disposition notification for the traceability of ImClone and Lilly lot numbers.

Table 6: LPS Recovery Calculated [redacted]

Three necitumumab DP batches with different manufacturing dates and production sites achieved [redacted]% LPS recovery [redacted] The percentage of LPS recovery estimated by these two different calculation methods were comparable [redacted]

Reviewer's comments: Data from Table 5 and Table 6 showed that the % recovery of endotoxin from the spiked DP batches manufactured at [redacted] *and Lilly by the commercial process was within* [redacted] *% recovery* [redacted] *This study demonstrated* [redacted] *in three DP lots.*

Satisfactory

Sterility test Method Qualification:
Three lots of drug product were used in the method verification studies. The study was performed [redacted]

(b) (4)

The study met the acceptance criteria, which were as follows:

- Plate counts from (b) (4) CFU per plate for yeast and bacteria. Plate counts from (b) (4) CFU per plate for mold.
- Challenge organism inoculum < (b) (4) CFU per canister.
- Growth within (b) (4) days for fungal cultures and within (b) (4) days for yeast and bacterial cultures. Comparable growth in the test canister and the corresponding control canister.
- Microscopic confirmation of yeast and bacterial culture growth. Visual detection of fungal mycelia in the fungal-inoculated canisters.
- No growth in the negative control canisters.

FDA question (April 14, 2015): Please provide the lot numbers of the Necitumumab drug product used for the sterility test method verification study.

Firm's response in April 21, 2015 amendment (Sequence 012): One lot manufactured (b) (4) (C1200159) and two development lots (C262169 and C266776) manufactured at Lilly during commercial development were used for method verification.

FDA question (23 July 2015): Please clarify if the sterility assay method qualification studies were performed with commercial manufacturing DP lots.

Firm's Response in amendment dated August 03, 2015 in sequence # 0028: The three lots used for method verification of sterility assay are representative of commercial manufacturing. Necitumumab with a target concentration of 16 mg/mL and commercial formulation were filled into 50 mL vials for all three lots. Batch C1200159 is a registration stability batch manufactured (b) (4) at commercial scale (b) (4) Batches C262169 and C266776 are non-clinical demonstration/engineering batches manufactured at Lilly within proposed commercial batch volume ranges (b) (4)

Reviewer's comments: Qualification of the endotoxin test method was performed with two non-clinical demonstration/engineering batches of drug product. Sterility test method qualification data from two additional commercial batches drug product will be requested as a PMC.

PMC: Qualification of the sterility test method was performed with two engineering lots of drug product. A post-marketing commitment is proposed to provide sterility test method qualification data from two additional drug product batches. The data should be provided in the first annual report.

Firm's Response in amendment dated September 17, 2015 in sequence # 0034: The sponsor has agreed to fulfill the PMC and submit the study report in the first annual report.

Satisfactory

Bioburden test:

FDA question (April 14, 2015): Provide the details of bioburden testing and method qualification summary data from 3 formulated bulk drug product lots.

Firm's response in April 21, 2015 amendment (Sequence 012): (b) (4)

(b) (4) The data for Necitumumab bioburden method verification provided in Table Q17-1 is reproduced below. All recovery results met the acceptance criteria of ≥ (b) (4)%. One lot manufactured at (b) (4) (C1200159) and two development lots manufactured at Lilly (C262169 and C266776) were used for this method verification.

Table Q17-1. Bioburden Percent Recovery Data

(b) (4)

Reviewer's comments: Not clear if one lot manufactured at (b) (4) (C1200159) and two development lots (C262169 and C266776) manufactured at Lilly represent the commercial manufacturing lots.

FDA question (23 July 2015): It is not clear whether the bioburden test method qualification studies were performed with commercial manufacturing lots. Please clarify and submit bioburden test method qualification information and results from studies performed using 3 commercial formulated bulk drug product lots.

Firm's Response in amendment dated August 03, 2015 in sequence # 0028: The three lots used for method verification of bioburden test are representative of commercial manufacturing. . Batch C1200159 is a registration stability batch and lots C262169 and C266776 are non-clinical demonstration/engineering batches.

Reviewer's comments: Bioburden test (b) (4) use of engineering batches for the method qualification is acceptable.

Satisfactory

3.2.P.5.4 Batch Analyses

All Necitumumab drug product lots manufactured met the endotxoxin (< (b) (4) EU/mL) and sterility acceptance criteria.

Reviewer's comments: Results other than sterility and endotoxin should be reviewed by OBP reviewer.

Satisfactory

3.2.P.5.6 Justification of Specification

Endotoxin

The endotoxin specification is ≤ (b) (4) EU/mg. The proposed commercial dose of Necitumumab Drug Product is currently a flat dose of 800 mg (doses are not scaled for bodyweight). Based on this dose, an endotoxin limit < (b) (4) EU/mg would be acceptable for the proposed commercial specification to ensure that the maximum tolerance limit (5 EU/kg) is not exceeded (assuming an average body weight of 70 kg).

The proposed specification of ≤ (b) (4) EU/mg for the release of the drug product provides (b) (4) fold of safety factor.
The DP, 50 mL (800mg) solution is diluted in 0.9% sodium chloride injection USP prior to administration by intravenous infusion.
FDA question (April 14, 2015): Please clarify if the endotoxin contribution from the 0.9% saline was considered when setting the release endotoxin specification of the drug product.

Firm's response in April 21, 2015 amendment (Sequence 012): The potential contribution of endotoxin present in the 0.9% saline solution was not considered when setting the release endotoxin specification for drug product. Necitumumab Drug Product is released as single cartons each containing a 50 mL vial and is not packaged with saline solution for administration. The maximum necitumumab dose is 800 mg and is infused over a minimum (b) (4) minutes; therefore, the threshold limit is NMT (b) (4) EU/mg. The NMT (b) (4) EU/mg specification represents a (b) (4) fold safety factor over the allowed USP limit.

Satisfactory

3.3.P.7 CONTAINER CLOSURE SYSTEM
The Type I clear tubing glass 50 mL vials are manufactured (b) (4) (b) (4) Stoppers are gray The stopper is further sealed in place with aluminum seal with (b) (4) flip-top. The components may be tested in house or accepted on the basis of the supplier's Certificate of Analysis or Certificate of Conformance. The (b) (4) are received from the vendor with Certificates of Analysis confirming endotoxin results met the acceptance criteria.
A letter of authorization to (b) (4) Type V DMF (b) (4) was provided in the BLA (b) (4) The referenced (b) (4) product is (b) (4) Gray (b) (4) Serum Stopper and it falls into (b) (4) family.
The above components are described in the DMF- (b) (4) revision, dated January 24, 2013.
FDA question (April 14, 2015): Please provide endotoxin acceptance criteria for the (b) (4) stoppers.
Firm's response in April 21, 2015 amendment (Sequence 012): Per Lilly incoming specification, the acceptance criteria for endotoxin on (b) (4) stoppers is no more than (b) (4) EU/stopper.

Satisfactory

3.2.P.8 STABILITY
DP lots were evaluated at the recommended (2-8°C), accelerated (b) (4) and stressed (b) (4) storage conditions. Based on these data, a 24-month shelf life is proposed for the DP and when (b) (4) month stability data is available, a (b) (4) month shelf life may be requested.

POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT
At least one lot of Necitumumab Drug Product per year will be placed at (b) (4) °C storage conditions. In the post approval stability program microbiological tests (CCI test and sterility) are performed (b) (4). CCI and Sterility results from release testing will be reported (b) (4)
FDA question (April 14, 2015): Please implement CCI at (b) (4) month time point in the stability protocol.

Firm's response in April 21, 2015 amendment (Sequence 012): CCI testing has implemented at the (b) (4) month time point in the stability protocol and an updated the protocol is provided with this response.

Satisfactory

Reviewer's comments: The remaining sections of the post-approval stability protocol should be reviewed by OBP.

Stability data

Stability data from process validation lots manufactured at both (b) (4) and Lilly are provided. All lots were sterile and endotoxin levels were within specification (< (b) (4) EU/mg) for the tested time points. Sterility and endotoxin met their acceptance criteria

Reviewer's comments: Stability data other than sterility and endotoxin should be reviewed by OBP.

Satisfactory

3.2.A.1 FACILITIES AND EQUIPMENT

Necitumumab drug product is manufactured (b) (4) facility located at Indianapolis, IN (b) (4)

(b) (4)

(b) (4)

3.2.R.3 REGIONAL INFORMATION

Addition of a New Product into a Commercial Multi-Product Facility (Eli Lilly and Company)

Necitumumab is manufactured in a multi-product facility (b) (4)

Protocol for new product introduction

The protocols for introduction of new commercial or new clinical products into the facility are described in section 3.2.R.3.1. Before a new product is manufactured for the first time, a risk assessment will be performed. The risk assessment will consider the potential for cross-contamination, the potential for mix-ups, an evaluation of process steps to ensure that all risk elements are included. The risk assessment will include calculations for cleaning based on toxicology assessment of the new product.

Cleaning limits will be established from the worst-case of the following values: the maximum of the allowable daily intake of the product appearing in the normal maximum daily dosage level of the next product manufactured; (b) (4) ppm of the active ingredient appearing in the next product manufactured; or a maximum of (b) (4) micrograms active drug per swab area (b) (4) n^2). If the current cleaning and changeover procedures are not adequate, new procedures will be implemented before the new product is manufactured.

After the first instance of manufacture of a new product in the commercial necitumumab Drug Product facility, if new cleaning validation studies are not required, swab samples will be taken during manufacture of the new product to confirm that predetermined acceptance criteria for cleaning shared equipment are met. EM data (non-viable) will be assessed to verify that the facility remains in a state of control

Reporting Category

New product introduction into commercial necitumumab Drug Product facility at Lilly will be reported in the BLA annual report if:

- no changes to cleaning or change-over procedures are required.
- changes to the cleaning calculation strategy or protocol

If necitumumab cleaning or change-over procedures are modified to accommodate the new product, a CBE-30 will be submitted with the following information: risk assessment results, evaluation and update of cleaning and/or change-over procedures and new cleaning procedures data supporting the introduction of the new product.

High risk products (e.g., beta-lactams including cephalosporins and penicillins, potent hormones, pesticides, or other potentially hazardous materials) will not be added to Necitumumab Drug Product commercial facilities without prior approval.

Reviewer's comments: (b) (4) *The strategy for new product introduction at the Eli Lilly site appears to be appropriate.*

Satisfactory

cGMP Status

Please see Panorama

Conclusion

I. The drug product section of this BLA, was reviewed from a product quality microbiology perspective and is recommended for approval with the following PMC:

Qualification of the endotoxin and sterility test methods was performed with two nonclinical demonstration/engineering batches of drug product. As a post-marketing commitment, perform the endotoxin and sterility test method qualification studies with two additional drug product batches and submit the information and summary data in the first annual report.

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

III. The inspection of the drug product manufacturing site, Eli Lilly, Indianapolis, IN (FEI# 1819470) was performed by the district from July 27 - August 04, 2015.

Lakshmi Narasimhan -A
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CMC Microbiology Deficiencies for STN 125547/0 necitumumab
Information Requests sent

April 14, 2015

Labeling

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

Container closure integrity test

2. *Please clarify if negative controls are included in the dye ingress test and if they are exposed to the test conditions.*
3. *You have provided the CCI dye ingress test results for batches manufactured at both [(b) (4)] and Lilly sites. Please clarify if the challenge conditions, positive control preparation, sensitivity of the method (LOD) are the same for both sites.*

Necitumumab drug product manufacturing process and process controls

4. *Please specify [(b) (4)] during the commercial manufacturing process.*
5. *Please revise the Table 3.2.P.3.4.1, [(b) (4)]*
6. *A sample volume [(b) (4)] is used for the endotoxin testing of the formulation [(b) (4)] and formulated bulk drug product. Please provide justification.*

Process Validation

7. *The acceptance criteria and results for the [(b) (4)] test are listed [(b) (4)] in the Section 3.2.P.3.5. Please provide the actual values for the acceptance criteria and results for the [(b) (4)] test. Also, clarify if the testing was performed with drug product [(b) (4)]*
8. *It is not clear from the submission [(b) (4)] Please indicate [(b) (4)] 3.2.P.3.5.2.2.2.1, 3.2.P.3.5.2.2.2.2, and 3.2.P.3.5.2.2.2.3. In addition, clarify [(b) (4)]*
9. *You have provided the recent requalification summary results [(b) (4)] Please provide qualification reports, including summary [(b) (4)]*

10. [redacted]

11. Please provide information and summary data [redacted]

12. Please provide validation information and summary data [redacted] *under worst case conditions. In your response,*

i. Describe [redacted]

ii. Include [redacted]

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

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

i. The media fill durations

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

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

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

15. Please clarify [redacted] *t.*

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

Analytical procedures

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

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

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

Container Closure system

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

Stability

21. Implement CCI testing at [redacted] *month time point in the stability protocol.*

Endotoxin Specification

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

July 28, 2015

I. [redacted]

II. *Validation of Analytical procedures*

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

III. *Endotoxin Hold Time Study for Necitumumab drug product*

a *Please clarify and confirm if the endotoxin hold time study was performed* (b) (4)

b *The endotoxin hold time studies performed* (b) (4) *You have stated in your response dated April 21, 2015 that* (b) (4) *will be proposed* (b) (4) *Please submit your proposal* (b) (4)

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

BLA/NDA Number: **STN125547**
Applicant: Eli Lilly
Stamp Date: 10/22/2014

Established/Proper Name: **Necitumumab/ Portrazza**
BLA/NDA Type: **Priority/Standard**

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 ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	N	*Not required*
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	

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	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
Companion application received if a shared or divided manufacturing arrangement	Y N	*Not applicable*

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	*Not required*
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 N	*Defer to OBP*
❑ Novel Excipients	Y N	*Defer to OBP*
❑ Executed Batch Records	Y N	*Defer to OBP*
❑ Method Validation Package	Y	*Provided in 3.2.R*
❑ Comparability Protocols	N	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
characterization, and testing		
❑ control of critical steps and intermediates o justification of specifications o stability	Y	
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance	Y	
❑ control of drug substance o specifications o justification of specs. o analytical procedures o analytical method validation o batch analyses	Y	
❑ reference standards	Y N	*Defer to OBP*
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval o protocol o results o method validation	Y	
Drug Product [3.2.P] [Dosage Form]		*Sterile solution in vials for intravenous infusion*
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	N	*Not applicable*
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	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	
❑ controls of critical steps and intermediates	Y	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)	Y	 *Provided in Section 3.2.A.1* *NA*
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	*Defer to OBP*
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	*Method validation for bioburden will be requested*
❑ reference standards or materials	Y N	*Defer to OBP*
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y Y Y Y N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of diluent ❑ pharmaceutical development o preservative effectiveness o container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved)	 Y N Y N Y N Y N Y N	*Not applicable*

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

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ batch formula		
❑ 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	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program		
o Lyophilizer sterilization validation	Y N Y N	
o Other needed validation data (hold times)		
❑ 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		
o specifications (vial, elastomer, drawings)	Y N Y N	
o availability of DMF & LOAs		
❑ stability		
❑ summary		
❑ post-approval protocol and commitment	Y N	
❑ pre-approval		
o protocol		
o results		

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	*Not applicable.*
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y Y N Y N	 *Defer to OBP* *Not applicable*
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y Y N	 *Defer to OBP* *Validation for micro assays provided in 3.2.P.5.* *Defer to OBP*
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	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	*NA*
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	*In the Form 356h*
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 N	*Defer to OBP*
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 N Y Y N Y	 *Defer to OBP*
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.

Not applicable

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

Not applicable

Lakshmi Narasimhan -A

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Candace Y. Gomez-broughton -S

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Patricia F. Hughestroost -S

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