CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125547Orig1s000

CHEMISTRY REVIEW(S)

The Quality Team Leader's Executive Summary

From: **Chana Fuchs, Ph.D., Team Lead**
DBRRIV, OPB/OPQ/CDER/FDA

Chana Fuchs -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chana Fuchs -S, 0.9.2342.19200300.100.1.1=2000601863
Date: 2015.11.19 13:24:05 -05'00'

Through: **Michele Dougherty, Ph.D., Acting Review Chief**
DBRRIV, OPB/OPQ/CDER/FDA

Michele Dougherty -S
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Date: 2015.11.19 14:25:02 -05'00'

BLA Number: 125547

Product: **Portrazza (necitumumab)**

Sponsor: **Eli Lilly and Company**

First Approval for Indication

LEGAL BASIS FOR SUBMISSION: 351(a)

Drug Name/Dosage Form	**Portrazza (necitumumab) solution for injection**
Strength/Potency	**16 mg/ml**
Route of Administration	**Intravenous**
Rx/OTC Dispensed	**Rx**
Indication	**First-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin**
Applicant/Sponsor	**Eli Lilly and Company**
US agent, if applicable	**NA**

Quality Team Leader Review

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILLITY

The Office of Biotechnology Products, OPQ/CDER, recommends approval of BLA STN 125547 for Portrazza (necitumumab) manufactured by Ely Lilly and Co. The data submitted in this application are adequate to support the conclusion that the manufacture of Portrazza (necitumumab) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

Benefit/Risk Considerations:
Portrazza is proposed to be used as first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin. Based on assessment of the manufacturing process and controls, and GMP compliance of the manufacturing facilities, the drug substance and drug product manufacturing processes are well controlled and should consistently deliver drug product of desired quality.

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture the necitumumab drug substance at ImClone Systems LLC , (b) (4) in Branchburg, NJ.

Necitumumab (Portrazza) vialed drug product will be filled, labeled, and packaged at Eli Lilly and Company in Indianapolis, IN (Lilly) and tested for release at Lilly and at ImClone Systems LLC, Branchburg, NJ, USA.

The dating period for necitumumab drug product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.
The dating period for necitumumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

You may label your product with the proprietary name, PORTRAZZA™, and will market it as an 800 mg/50 mL injection in a single-dose vial.

The dating period for PORTRAZZA™ shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

The dating period for necitumumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the annual stabilitiy protocols in your license application for the

purpose [redacted] (b) (4)
[redacted] under 21 CFR 601.12

III. POST MARKETING COMMITMENTS

PMC #1 - To re-evaluate all necitumumab drug substance lot release and stability data after availability of IEC and CE-SDS release data from 30 lots of drug substance manufactured by [redacted] (b) (4) To submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC #2 - To re-evaluate all necitumumab drug product lot release and stability data after availability of IEC and CE-SDS release data from at least 20 lots of drug product manufactured by the commercial manufacturing process. To submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications based on the available drug substance and drug product data.

PMC #3 - To further characterize the molecular changes that are associated with changes in ADCC activity of necitumumab, and update the necitumumab control strategy accordingly.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

V. EXECUTIVE SUMMARY

A. Description of necitumumab (Portrazza) drug substance and drug product

Product Overview

Portrazza (necitumumab) is a humanized IgG1 monoclonal antibody produced in NS0 cells. Necitumumab binds to the extracellular domain of the epidermal growth factor receptor (EGFR), thereby inhibiting the binding of the EGFR to its ligands and its subsequent activation. EGFR is over-expressed in squamous non-small cell lung cancer (NSCLC) and is thought to contribute to cancer invasion, metastasis, and proliferation. Portrazza is proposed to be used in combination with gemcitabine and cisplatin as first line treatment in patients with locally advanced or metastatic NSCLC. The drug product is supplied as an 800mg/50mL sterile solution in a 50mL type I glass vial intended for single use. Necitumumab is formulated in an aqueous [redacted] (b) (4) solution at pH 6.0, containing [redacted] (b) (4) 40mM sodium chloride, 133mM glycine, 50mM mannitol, and 0.01% w/v polysorbate 80. The drug product is to be diluted in 0.9% sodium chloride injection USP in an infusion container prior to administration by intravenous infusion. 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.

A. Drug Substance: Necitumumab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management:
Drug substance critical quality attributes and their control strategy are identified with a superscript "a" in table 1 below. For more detailed information about the CQA analysis see the OBP quality review (DS section) and the DMA DP microbiology review.

Necitumumab is a full length recombinant human IgG1, κ monoclonal antibody (IMC-11F8, LY3012211) that is directed to the extracellular domain of the human Epidermal Growth Factor Receptor (EGFR).

Necitumumab is expressed in the NS0 mouse myeloma cell line and is comprised of (b) (4)

DS formulation:
The drug substance (DS) is formulated (b) (4) containing (b) (4) 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol and 0.01% (w/v) polysorbate 80, pH 6.0. Theoretical extinction coefficient of (b) (4) mg $mL^{-1}cm^{-1}$ has been used to determine necitumumab protein concentration. The experimentally determined extinction coefficient is (b) (4) mg $mL^{-1}cm^{-1}$. The necitumumab drug substance can be stored at (b) (4) °C for up to (b) (4) month (b) (4)

Mechanism of action:
Necitumumab binds the ligand binding region on the extracellular domain of the epidermal growth factor receptor (EGFR) and blocks ligand stimulated EGFR activation. Dysregulation of EGFR activation of has been implicated in malignant progression, induction of angiogenesis, and inhibition of apoptosis or cell death.

Potency Assay:
The potency of necitumumab is determined based on its mechanism of action by a cell-based potency assay. In the assay, the potency of necimumumab is demonstrated (b) (4) Potency is defined as the percent activity relative to necitumumab reference standard.

Reference material(s):
A two tiered reference standard system was developed consistent with ICHQ6B recommendations. The primary reference standard was qualified against an earlier reference standard derived from a drug substance lot used in the phase 3 clinical trial. Primary reference standard is used to qualify new working reference standards and requalify current working reference standard. The working reference standard is used for routine testing. The primary and working reference standards were derived from a DS lot

that was manufactured by (b) (4) and were rigorously characterized by both release testing and additional biochemical characterization. The reference standards are suitable for their intended uses in necitnmumab testing.

Manufacturing process summary:

(b) (4)

(b) (4)

Necitumumab drug substance is formulated in (b) (4) 40mM sodium chloride, 50mM mannitol, 133mM glycine, and 0.01% (w/v) polysorbate 80, pH 6.0.
The overall control strategy combines control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The combined control strategies with in-process and release testing ensure process consistency and a drug substance with appropriate quality attributes that is free of adventitious agents.

DS Container closure system:
The container closure system used for necitumumab drug substance is (b) (4) designed specifically for storage, transfer, and transport of biopharmaceutical fluids. The portion of the container closure system that comes into contact with drug substance is comprised of (b) (4) The closure portion of the system is comprised of (b) (4) The container closure systems are suitable for necitumumab drug substance based on stability data, maintain integrity for bioburden control, and prevent leaching.

Dating period and storage conditions:
The sponsor conducted real time, accelerated, and stressed stability studies to support a dating period of (b) (4) months when stored at (b) (4) °C. (b) (4) The end of shelf-life quality is controlled by the end of shelf-life specification. At least one DS batch will be placed on routine stability evaluation in a calendar year and a post-approval stability protocol was included.

B. Drug Product Quality Summary

A summary of the the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes are identified with a superscript "b" in table 1 below. For more detailed

information on CQA analysis see the OBP quality review and the Division of Microbiology Assessment DP review.

Potency and Strength:
Potency is defined as the percent activity relative to necitumumab reference standard. The potency assays for DP are the same as those described in the DS section of this memo. Portrazza will be available at a strength of 16 mg/mL.

Summary of Product Design:
Necitumumab will be available in single-dose vials for intravenous infusion following dilution. Each vial contains 800 mg PORTRAZZA in 50 mL (16 mg/mL).

Excipients:
Citric acid anhydrous, glycine, mannitol, polysorbate 80, sodium chloride, sodium citrate dehydrate. The excipients used in manufacturing are compendial quality grade and acceptable for use. None of the excipients are of human or animal origin and therefore are of little risk for viral or TSE contamination. The drug product is preservative free.

Reference material(s)
There is no drug product specific reference material. The primary and working reference materials are drug substance.

Manufacturing Process:
The drug product manufacturing process starts with (b) (4) The comerical batch size is approximately (b) (4) L. drug product batch sizes may vary (b) (4)

The control strategy includes in-process testing of critical and non-critical parameters and release testing of final vialed DP. Critical parameters selected for routine monitoring relate to (b) (4)
Process validation studies included manufacture of three commercial scale lots ranging in lot size from minimum ((b) (4) L) to maximum ((b) (4) L) and in DS origin from a single DS lot to manufacture one lot of DP.

Sterility is measured (b) (4) and sterility assurance is maintained (b) (4) The integrity of the container closure system was assessed as part of validation by using both dye ingress and microbial ingress test methods, and is included in the DP stability program.

Container Closure System:
The primary container closure system for Portrazza is a single-use 50 mL type I tubing glass vial stoppered with a 20mm (b) (4) stopper and sealed with a 20mm aluminum two piece flip-top seal.

The drug product container closure system components are suitable for parenteral products

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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				of manfuacturing and use.	
CQA	**Type**	**Risk**	**Origin**	**Control Strategy**	**Other**

[a] CQAs for DS
[b] CQAs for DP

C. Novel Approaches/Precedents

N/A

D. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C
Do note freeze
Protect from light

E. Establishment Information

Table 2 – establishment information

FUNCTION	SITE INFORMATIO	DUNS/FEI	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS
• Cell Bank Storage • Cell bank release Testing • Cell Bank Stability Testing • Raw Material Release Testing • Manufacture of DS • IPC Testing • DS Release and Stability Testing	ImClone Systems LLC 33 ImClone Drive Branchburg, NJ, USA.	3002889358	PLI Inspection Required	The ImClone Systems LLC facility was inspected on March 6-9, 2015 by Peter Qiu, Ph.D., OPQ/OPF/DIA and Audrey Jia, Ph.D., OPQ/OBP/DBRRIV. 483 observations: - Lack of validation in (b) (4) - Insufficient data to support storage (b) (4)
Cell Bank Storage	Eli Lilly and Company Indianapolis, ndiana	1819470	Inspection can be deferred based on Facility profile	

(b) (4)			Inspection can be deferred based on Facility profile	N/A
			Inspections can be deferred based on Facility profile	N/A
			Inspections can be deferred based on Facility profile	N/A
			nspections can be deferred based on Facility profile	
• DP manufacture • DP release testing (except for cell based potency) • DP stability testing(except for cell based potency) • DP labeling • Secondary packaging •	Eli Lilly and Company Lilly corporate center Indianapolis, IN, USA.	1819470	PLI Inspection Required	

• DP release testing (except for sterility and volume in container) • DP stability testing(except for container closure integrity and sterility)	ImClone Systems LLC 33 ImClone Drive Branchburg, NJ, USA.	3002889358	PLI Inspection Required	The ImClone Systems LLC facility was inspected on March 6-9, 2015 by Peter Qiu, Ph.D., OPQ/OPF/DIA and Audrey Jia, Ph.D., OPQ/OBP/DBRRIV.

F. Facilities

The pre-license inspection of the drug substance manufacturing facility at ImClone Systems, LLC, Branchburg, NJ was conducted on March 2-6, 2015 by Audrey Jia, OBP/OPQ and Peter Qiu, DIA/OPQ. The inspection covered the manufacturing of drug substance in the (b) (4) manufacturing areas, (b) (4) (warehouse and QC inspection), (b) (4) (cell bank suite and QC labs), and (b) (4) (cell bank suite and QC labs). The inspection covered Quality systems, production, laboratory controls, materials control, facilities and equipment systems. A 2-item FDA form 483 was issued for lack of validation of necitumumab manufacturing (b) (4) and insufficient validation of storage conditions (b) (4) It was recommended that the inspection be classified as Voluntary Action Indicated.

The pre-license inspection of the drug product manufacturing facility at Eli Lilly and company, Indianapolis, IN, was conducted on July 27 – August 4, 2015 by the ORA Detroit district personnel. No form 483 was issued and the inspector recommended that the inspection be classified as no action indicated.

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Table 3: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product			
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	

10.	New Molecular Entity		X		
11.	PEPFAR Drug			X	
12.	PET Drug			X	
13.	Sterile Drug Product		X		
14.	Other_____				
	Regulatory				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____				
	Quality				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other			
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				

BLA STN 125547

Portrazza™ (necitumumab)

Eli Lilly and Company

Ying-Xin Fan, Ph.D., Reviewer
Yan Wang, Ph.D. , Reviewer
Ralph M. Bernstein, Ph.D., Reviewer
Chana Fuchs, Ph.D., Team Lead

CDER/OPQ/OBP/DBRRIV

OBP CMC Review Data Sheet

1. **BLA#:** STN 125547

2. **REVIEW DATE:** 11/18/2015

3. **PRIMARY REVIEW TEAM:**

   Medical Officer: Lee Pai-Scherf

   Pharm/Tox: Margaret E. Brower

   Product Quality Team: Ying-Xin Fan (Drug Substance), Yan Wang (Drug Product); Ralph Bernstein (method validation and immunogenicity validation), Candace Gomez-Broughton (Drug Substance Microbiology), Lakshmi Narasimhan (Drub Product Microbiology)

   Clinical Pharmacology: Safaa Burns

   Statistics: Lijun Zhang

   OBP Labeling: Jibril Abdus-Samad

   RPM: Missiratch Biable

4. **MAJOR GRMP DEADLINES**

   Filing Meeting: 1/23/2015

   Mid-Cycle Meeting: 4/24/2015

   Wrap-Up Meeting:

   Primary Review Due: 8/8/2015

   Secondary Review Due: 8/15/2015

   CDTL Memo Due: 10/21/2015

   PDUFA Action Date:12/2/2015

5. **COMMUNICATIONS WITH SPONSOR**

Communication/Document	Date
Information request #1	January 30, 2015
Information request #2	April 14, 2015
Information request #3	14 August 2015
Tcon with Sponsor	12 August 2015
Information request #4	October 6, 2015
Information request #5	October 1, 2015,
Information request #6	October 23, 2015
Email correspondence	October 29, 2015
Tcons with sponsor	October 29, 2015
Information request #7	November 6, 2015

Information request #8	November 16, 2015
Information request #9	November 16, 2015
Email correspondence	November 17, 2015
Tcon with Sponsor	November 17, 2015

6. **SUBMISSION(S) REVIEWED:**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	Review Completed
STN 125547/0002	12/02/2015	yes
STN 125547/0006	02/06/2015	Yes
STN 125547/0012	04/21/2015	yes
STN 125547/0028	08/03/2015	yes
STN 125547/0030	08/13/2015	yes
STN 125547/0031	08/19/2015	yes
STN 125547/0032	08/31/2015	yes
STN 125547/0033	08/31/2015	yes
STN 125547/0035	09/08/2015	yes
STN 125547/0037	09/11/2015	yes
STN 125547/0034	09/17/2015	yes
STN 125547/0038	10/08/2015	yes
STN 125547/0039	10/08/2015	yes
STN 125547/0040	10/13/2015	yes
STN 125547/0041	10/13/2015	yes
STN 125547/0043	10/30/2015	yes
STN 125547/0047	11/10/2015	yes
STN125547/0048	11/12/2015	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Portrazza
   b. Trade Name: Portrazza
   c. Non-Proprietary/USAN: Necitumumab
   d. CAS name: 906805-06-9
   e. Common name: IgG1κ, anti-(human epidermal growth factor receptor (EGFR)
   f. INN Name: Necitumumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMAN (IGG1) (b) (4) (EGFR_HUMAN)[LY3012211]
   i. Other Names: IMC-11F8, LY3012211

8. **PHARMACOLOGICAL CATEGORY:** Therapeutic monoclonal antibody to the human Epidermal Growth Factor Receptor (EGFR)

9. **DOSAGE FORM:** injection

10. **STRENGTH/POTENCY:**

- **a.** The concentration of Portrazza drug product is 16 mg/mL in a 50 mL vial presentation.
- **b.** Potency is determined by a cell based proliferation assay. The potency assay acceptance criterion is (b) (4) % relative to the reference standard.
- **c.** The dating period for vialed drug product is 24 months when stored at 2-8°C.

11. **ROUTE OF ADMINISTRATION:** intravenous infusion

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	Letter of Cross-Reference	COMMENTS
(b) (4)			3	N/A	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA. (b) (4)
			3	N/A	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA

(b) (4)			3	N/A	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			3	N/A	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			3	N/A	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			3	N/A	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
21219	Eli Lilly and Company, IN	(b) (4) manufacturing process	3	N/A	Yes	To be assessed by DMA reviewer

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available;6 – Other (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

13. INSPECTIONAL ACTIVITIES

The pre-license inspection of the drug substance manufacturing facility at ImClone Systems, LLC, Branchburg, NJ was conducted on March 2-6, 2015 by Audrey Jia, OBP/OPQ and Peter Qiu, DIA/OPQ. The inspection covered the manufacturing of drug substance in the (b) (4) manufacturing areas, (b) (4) (warehouse and QC inspection), (b) (4) (cell bank suite and QC labs), and (b) (4) (cell bank suite and QC labs). The inspection covered Quality systems, production, laboratory controls, materials control, facilities and equipment systems. A 2-item FDA form 483 was issued for lack of validation of necitumumab manufacturing (b) (4) and insufficient validation of storage conditions (b) (4) It was recommended that the inspection be classified as Voluntary Action Indicated.

The pre-license inspection of the drug product manufacturing facility at Eli Lilly and company, Indianapolis, IN, was conducted on July 27 – August 4, 2015 by the ORA Detroit district personnel. No form 483 was issued and the inspector recommended that the inspection be classified as no action indicated.

14. CONSULTS REQUESTED BY OBP - None

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Risk assessments to identify critical quality attributes of necitumumab and to identify process parameters for assessment in process characterization studies were performed according to methods described in the submission and review of Module 3.
A design of experiments (DoE) approach was utilized to generate process understanding. Results from DoE experiments were used to support the overall control strategy proposed for necitumumab drug substance and drug product. The sponsor does not claim a design space.

17. PRECEDENTS- None

18. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Ying-Xin Fan, Ph.D. Product Quality Reviewer Divisions of Biotechnology Review and Research IV, OBP, OPQ, CDER	Ying Xin Fan -S Digitally signed by Ying Xin Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ying Xin Fan -S, 0.9.2342.19200300.100.1.1=2000604371 Date: 2015.11.18 20:06:27 -05'00'
Yan Wang, Ph.D. Product Quality Reviewer Divisions of Biotechnology Review and Research IV, OBP, OPQ, CDER	Yan Wang -S Digitally signed by Yan Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yan Wang -S, 0.9.2342.19200300.100.1.1=0011514221 Date: 2015.11.18 20:00:03 -05'00'
Ralph M. Bernstein, Ph.D. Product Quality Reviewer Divisions of Biotechnology Review and Research IV, OBP, OPQ, CDER	Ralph M. Bernstein -S Digitally signed by Ralph M. Bernstein -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605501, cn=Ralph M. Bernstein -S Date: 2015.11.18 19:32:42 -05'00'
Chana Fuchs, Ph.D. Product Quality Team Lead Divisions of Biotechnology Review and Research IV, OBP, OPQ, CDER	Chana Fuchs -S Digitally signed by Chana Fuchs -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chana Fuchs -S, 0.9.2342.19200300.100.1.1=2000601863 Date: 2015.11.18 19:49:47 -05'00'

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of Portrazza (necitumumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that Portrazza (necitumumab) be approved for human use under conditions specified in the package insert.

We recommend an expiration dating period of (b) (4) months for necitumumab drug substance when stored at (b) (4) °C.

We recommend an expiration dating period of 24 months for necitumumab drug product when stored at 2-8°C.

We recommend approval of the proposed release and shelf-life specifications for necitumumab drug substance and drug product.

II. List Of Deficiencies To Be Communicated

There are no CMC deficiencies precluding approval of this BLA.

III. List Of Post-Marketing Commitments :

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

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

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

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental

assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

V. Primary Container Labeling Review

The review of the drug product label was performed by Jibril Abdus-Samad under separate cover.

VI. Review Of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

A review of the product immunogenicity assays is included at the end of the primary review document.

TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

3. Quality

3.2. S. DRUG substance

(This section was reviewed by Ying-Xin Fan)

3.2. S.1 General information

3.2. S.1.1 Nomenclature

International Non-proprietary Name (INN) and Non-proprietary Name (USAN) is Necitumumab. Two chemical names were given in the submission:

1. Immunoglobulin G1, anti-(human epidermal growth factor receptor) (human monoclonal IMC-11F8 γ1-chain), disulfide with human monoclonal IMC-11F8 κ-chain, dimer
2. Immunoglobulin G1, anti-(human endothelial growth factor receptor (receptor tyrosineproteinkinase ErbB1, EC 2.7.10.1)); human monoclonal IMC-11F8 γ1 heavy chain (224-214')-disulfide with human monoclonal IMC-11F8 κ light chain dimer (230-230":233-233")-bisdisulfide

The Lilly compound number is LY3012211.

The Chemical Abstracts Number (CAS) is 906805-06-9

3.2. S.1.2 Structure

Necitumumab is a recombinant human IgG1 monoclonal antibody composed of (b) (4) The sponsor provided the amino acid sequence of the HC and LC in Figures 3.2.S.1.2-1 and 3.2.S.1.2-2 as follows:

(b) (4)

Figure 3.2.S.1.2-1 Light Chain Amino Acid Sequence of Necitumumab

Figure 3.2.S.1.2-2 Heavy Chain Amino Acid Sequence of Necitumumab

The sponsor depicted the structure of necitumumab in Figure 3.2.S.1.2-3 below.

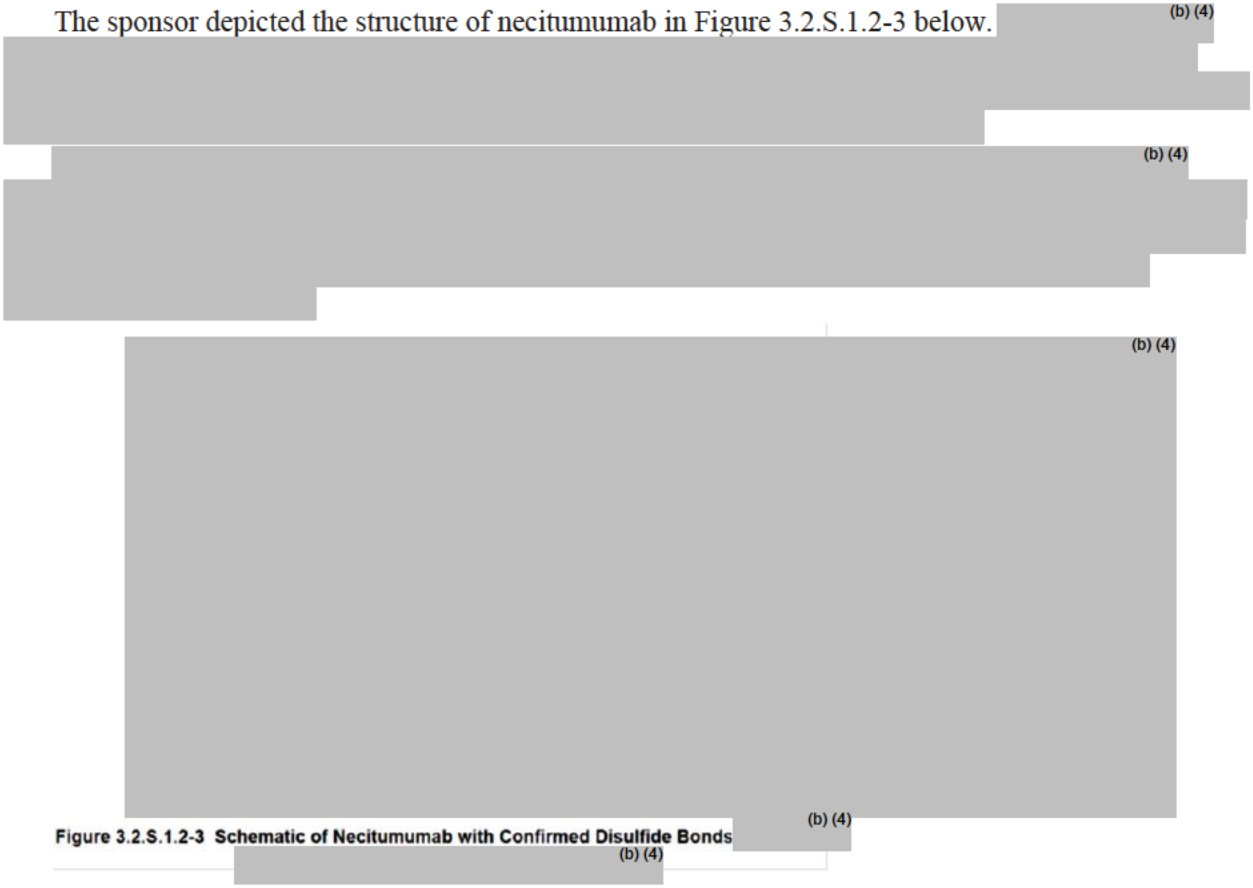

Figure 3.2.S.1.2-3 Schematic of Necitumumab with Confirmed Disulfide Bonds

3.2. S.1.3 General Properties

Necitumumab binds to the ligand binding region of the epidermal growth factor receptor (EGFR). The drug substance (DS) is formulated [redacted] containing [redacted] 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol and 0.01% (w/v) polysorbate 80, pH 6.0. Theoretical extinction coefficient is [redacted] mg $mL^{-1}cm^{-1}$.

Reviewer's comment: [redacted]

3.2. S.2 Manufacture

3.2. S.2.1 Manufacturer(s)

The sponsor listed the manufacturing, storage and control facilities in Table 3.2.S.2.1-1below:

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

Manufacturing Facility	The drug substance is manufactured in accordance with current Good Manufacturing Practices at the following facility: ImClone Systems LLC [redacted] 33 ImClone Drive Branchburg, New Jersey 08876 USA Establishment Identification Number: 3002889358
Storage Facility	Storage facilities for drug substance, Master and Working Cell Banks: ImClone Systems LLC 33 ImClone Drive Branchburg, New Jersey 08876 USA Back up storage facility for Master and Working Cell Banks: Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285 USA Establishment Identification Number: 1819470
Control Facilities	Release and stability testing for bulk drug substance and sterility testing for the Working Cell Bank are performed at: ImClone Systems LLC 33 ImClone Drive Branchburg, New Jersey 08876 USA Establishment Identification Number: 3002889358 [redacted]

(Table continued)

Table 3.2.S.2.1-1 (continued) Manufacture and Control Facilities for Necitumumab Drug Substance

Control Facilities (continued)	(b) (4)
Control Facilities (continued)	

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(b) (4)

3.2.P. DRUG PRODUCT

(This section was reviewed by Yan Wang)

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

Necitumumab drug product (DP) is formulated in an aqueous (b) (4) solution at pH 6.0, containing (b) (4) 40mM sodium chloride, 133mM glycine, 50mM mannitol, and 0.01% w/v polysorbate 80 (b) (4) sterile presentation is manufactured as 800 mg/50 ml (16mg/mL). The composition of necitumumab DP is provided 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

3.2.P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

3.2.P.8.3 Stability Data

The quality attributes used to determine the stability of necitumumab DP in the primary stability studies are listed in the above stability protocol. In addition, osmolality, SDS-PAGE, IEF, Endotoxin and potency by binding (Biacore) data are also collected.

The following is the summarized results by the reviewer based on the data from the primary stability studies provided by the sponsor.

i. CQAs meet USP/ph.Eur requirements under all the tested conditions: Visual Appearance, Color, Clarity, Endotoxin, Sterility, and Container Closure Integrity.

ii. CQAs are with no trend under all the tested conditions:

Tests	Proposed AC (Shelf-life)	Results
Osmolality (mOsm/kg):	(b) (4)	
pH:		
Protein Concentration (mg/ml):		

Cell-Based Potency Assay (%):
Particulate Matter: ≥ (b)(4) µm in size
≥ (b)(4) µm in size
IEF: Relative concentration ≥ (b)(4) %
PI

Potency by Binding (Biacore) (%):

(b) (4)

Reviewer comment

i. The amount of change expected to occur for stability indicating CQAs were calculated by the reviewer based on the data from the primary stability studies updated on August 31, 2015 and listed below:

(b) (4)

*ii. Since the proposed AC of the DP lot release for purity and heterogeneity (*charge variants*) needs to be* (b) (4) *based on the reviewer's analysis, the AC for the end of shelf life also need to be revised. The IR regarding the revised specification for the DP stability was sent to Lilly on 10/23/2015. Lilly responded to the IR on 10/30/2015 (SN0043) and agreed to the proposed AC, which can be found in the review of 3.2.P.5. Therefore, the proposed AC for lot release and shelf-life listed above was revised to be consistent with the Agency request.*

iii. All other proposed AC are acceptable.

iv. The stability data from the lots manufactured in Lilly under the commercial manufacturing process should be provided once they are available. On August 14, 2015, an IR was sent out requesting the submission of any additional stability data. The sponsor updated the stability data on August 31, 2015.

iii. Comparison of the "commercial manufacturing process" at (b) (4) *and commercial manufacturing process at Lilly: Comparing to* (b) (4) *manufacturing process,* (b) (4) *were implemented at Lilly .*

a. (b) (4)

[redacted]

b. The filling process technology can impact product quality by introducing physical stresses such as shear, friction, and cavitation. [redacted] *Therefore the fill technology implemented at the Lilly site is unlikely to impact product quality of necitumumab.*

c. In addition, the lots manufactured using the commercial manufacturing process at Lilly are comparable with lots manufactured at [redacted]

d. The same commercial container closure systems were used for the lots manufactured at both [redacted] *and Lilly using the similar "commercial manufacturing process".*

e. All above analyses suggested that the "commercial manufacturing process "at [redacted] *is sufficiently similar to the commercial manufacturing process at Lilly such that the stability samples manufactured at* [redacted] *may be representative of the product made at Lilly for the purposes of supporting expiration dating.*

iv. Analysis of the data from the primary stability data updated on August 31, 2015:

a. All the quality attributes remain stable and met the revised AC for 36, 18 and 15 months for the registration lots, [redacted] *PV lots and Lilly PV lots respectively when the drug produces were stored at the recommended storage condition at 2 - 8°C .*

b. The trend rate calculated by the reviewer of all stability indicating quality attributes [redacted] *are similar for* [redacted] *months for the registration lots,* [redacted] *PV lots and Lilly PV lots respectively when the drug produces were stored at the stressed condition* [redacted]

c. The trend rate calculated by the reviewer of all stability indicating quality attributes [redacted] *) are similar for* [redacted] *months for the registration lots,* [redacted] *PV lots and Lilly PV lots respectively when the drug produces were stored at the accelerated condition* [redacted]

d. The 12 month time point on accelerated stability [redacted] *shows a consistent and reproducible difference for the attributes* [redacted] *between the 3 DP lots manufactured at Lilly and all the DP lots manufactured at* [redacted]*. This difference might be a result of differences in manufacturing between Lilly and* [redacted] *An IR was sent on 11/6/2015 requesting Lilly to provide data from any investigation that was done regarding this difference and if any clear cause was identified. Lilly submitted the response in amendment SN0048 on 11/12/2015. Lilly stated that the perceived difference was the result of* [redacted]

[redacted] *Regarding the differences in the way the data are integrated at different location, the methods were not being performed in a similar manner for testing the* [redacted] *and the Lilly lots. It is unclear as to whether this is due to* [redacted] *Since data highlighting this issue was submitted after the PAI had been performed, the performance of the method at difference sites should be assessed at the next GMP inspection.*

v. Recommendation for the DP shelf life:

a. Since the "commercial manufacturing process "at [redacted] *is similar to the commercial manufacturing process at Lilly as well as all the quality attributes remain stable for the registration lots,* [redacted] *PV lots and Lilly PV lots respectively when the drug produces were stored at the recommended storage condition at 2 - 8°C, the proposed 24 months shelf-life for the necitumumab stored at 2-8°C is acceptable.*

b. Due to the difference initially noted in the accelerated stability data [redacted] he Lilly lots and this was relayed in the *IR sent on 11/6/2015. In the submitted response in amendment SN0048 on 11/12/2015, Lilly updated the post-approval stability protocol stating that* [redacted] *and this information has been updated to reflect this commitment in Section 3.2.P.8.1.*

Photostability testing was conducted on one DP lot (C1200158, registration lot) according to ICH Q1B and as outlined in the following table provided by the sponsor:

Table 3.2.P.8.3.3.1-1 Drug Product Photostability Study Design

(b) (4)

(b) (4)

Reviewer comment

The results of photostability testing (b) (4) *demonstrated the sensitivity of necitumumab to ICH light conditions. However, the secondary package provides necitumumab DP adequate protection from light.*

Stability of DP having undergone Multiple Freeze/Thaw Cycles was performed on one stability registration lot (C1200159). Vials from this lot were pulled from the recommended storage condition (2 - 8°C) between 6 - 9 months of DP age. (b) (4) The analytical properties used to determine the stability of necitumumab DP post-freeze/thaw cycling were visual appearance, osmolality, pH, protein concentration, charge variants by ion-exchange chromatography and isoelectric focusing, purity by SE-

HPLC and SDS-PAGE (reduced and non-reduced), potency by binding (Biacore), cell based potency and particulate matter.

Reviewer comment

The data up to 24 month were available at the original submission. In the amendment SN0032 submitted on August 31, 2015, the data up to (b) (4) months were provided. All the tested attributes were within the proposed AC including the proposed AC for DP lot release by the reviewer for SE-HPLC and IEC. The results indicated that temperature cycling did not adversely affect DP stability up to (b) (4) months.

3.2. A Appendices

(b) (4)

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(b) (4)

Assessment of necitumumab immunogenicity:

The Sponsor has provided the assessment of anti necitumumab antibody occurrence from 6 studies, "comprising 981 patients, of which 814 patients had samples collected and analyzed after the start of necitumumab treatment (post-treatment immunogenicity evaluations). Seventy-one patients (8.7%) had samples positive for anti-drug antibody (ADA) (post-treatment ADA positive). Treatment-emergent ADA were observed for 33 patients (4.1%). Neutralizing antibodies were observed in
11 patients (1.4%)." The tabular immunogenicity data are below, in Table 2.7.2.6

Table 2.7.2.6. Immunogenicity Results for Necitumumab-Treated Patients

Abbreviated Study Code	Immunogenicity Evaluations Any Time (including baseline)				Post-Treatment Immunogenicity Evaluations			
	Patients Analyzed (N_{IK})	ADA-positive Patients	TE ADA-positive Patients	Neutralizing Antibody-positive Patients	Patients Analyzed with Post-treatment Samples Available	Post-Treatment ADA-positive Patients (%)[a]	TE ADA-positive Patients (%)[a]	Neutralizing Antibody-positive Patients (%)[a]
I4X-IE-JFCC [IMCL CP11-0806] SQUIRE	528	81 (15.3)	15 (2.8)	5 (0.9)	448	39 (8.7)	15 (3.3)	1 (0.2)
I4X-IE-JFCB [IMCL CP11-0805] INSPIRE	301	37 (12.3)	9 (3.0)	18 (6.0)	229	13 (5.7)	9 (3.9)	6 (2.6)
I4X-IE-JFCE [IMCL CP11-0401]	60	12 (20.0)	4 (6.7)	4 (6.7)	48	11 (22.9)	4 (8.3)	3 (6.3)
I4X-IE-JFCD [IMCL CP11-0602]	42	6 (14.3)	4 (9.5)	1 (2.4)	40	5 (12.5)	4 (10.0)	1 (2.5)
14X-IE-JFCJ [IMCL CP11-1115]	35	3 (8.6)	1 (2.9)	0 (0)	34	3 (8.8)	1 (2.9)	0 (0)
I4X-IE-JFCA [IMCL CP11-0907]	15	2 (13.3)	0 (0)	0 (0)	15	0 (0)	0 (0)	0 (0)
Total	**981**	**141 (14.4)**	**33 (3.4)**	**28 (2.9)**	**814**	**71 (8.7)**	**33 (4.1)**	**11 (1.4)**

Abbreviations: ADA= anti-drug antibodies; N_{IK} = number of patients with immunogenicity data available; TE ADA = treatment-emergent anti-drug antibodies.

[a] Percentages were calculated using the number of patients with post-treatment immunogenicity samples as the denominator.

Reviewer comment: *the immunogenicity rate for necitumumab is acceptably low. While it is not clear why so many patients had pre existing binding antibodies to necitumumab, the over all neutralizing rate is very low. The preexisting versus post treatment antibody rate is an interesting outcome that I have not observed before.*

Labeling: The following is the Immunogenicity, section 6.2, labeling that is found in the necitumumab label.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, treatment-emergent anti-necitumumab antibodies (ADA) were detected in 4.1% (33/814) of patients using an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 1.4% (11/814) of patients post exposure to PORTRAZZA. No relationship was found between the presence of ADA and incidence of infusion-related reactions. The impact of ADA on efficacy (overall survival) could not be assessed due to the limited number of patients with treatment-emergent ADA. In Study 1, the exposure to necitumumab was lower in patients with ADA post-treatment than in patients without detectable ADA *[see Clinical Pharmacology (12.3)]*.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to PORTRAZZA with the incidences of antibodies to other products may be misleading.

Reviewer comment: *The Clinical team has condensed the immunogenicity labeling down to the most basic results for patients. The* (b) (4) *section has been removed. This is acceptable for increased clarity. The Immunogenicity label is acceptable.*

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary Task Details Issues Updates **Inspection Management Form**

Inspection Management Form As of 4:17 PM

Inspection Management Form

BLA 125547-Orig1-New/BLA(3)

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

ELI LILLY AND COMPANY | 1819470 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

IMCLONE SYSTEMS LLC | 3002889358 | CBI BIOTECHNOLOGY DERIVED API (STERILE (b) (4) | Approve Facility

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility

Overall Manufacturing Inspection Recommendation

Approve
Withhold

Cancel

Assigned To

OPF Reviewer

Michael Shanks
Biologist

Edit Assignment

This was done on
Oct 22, 2015
(32 days ago)

Status
Complete

This task is waiting on
2 Tasks

Last Update
Oct 22, 2015

Submitted On
Nov 27, 2014

Reference Number
3404158

APPEARS THIS WAY ON ORIGINAL

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	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation including aseptic processing & sterility assurance:	Y	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation		
○ Validation of aseptic processing (media simulations)		
○ Environmental Monitoring Program		*Provided in Section 3.2.A.1*
○ Lyophilizer validation		*NA*
○ Other needed validation data (hold times)		
❑ 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]	Y	
○ specifications (vial, elastomer, drawings)	Y	
○ availability of DMF & LOAs	Y	
○ administration device(s)	Y N	
❑ stability	Y	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Diluent (vials or filled syringes) [3.2P′]		*Not applicable*
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity		
❑ manufacturers (names, locations, and	Y N	
responsibilities of all sites involved)	Y N	

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

Digitally signed by Lakshmi Narasimhan -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640223, cn=Lakshmi Narasimhan -A
Date: 2015.02.13 08:12:30 -05'00'

Candace Y. Gomez-broughton -S

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Date: 2015.02.13 09:58:00 -05'00'

Patricia F. Hughestroost -S

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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: 2015.02.13 11:02:07 -05'00'

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

BLA/NDA Number: 125547 **Applicant:** Eli Lilly and Company **Stamp Date:** December 2, 2014

Established/Proper Name:
Necitumumab /Portrazza (proposed)

BLA/NDA Type: Standard review

EDR:
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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	N	Not required.
❑ Patient Insert	N	Not required.
❑ package and container	Y	
❑ diluent	N	Not applicable
❑ other components	N	Not applicable
❑ 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	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a	N	Not applicable

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Examples of Filing Issues	Yes?	If not, justification, action & status
shared or divided manufacturing arrangement		

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	N	No novel excipients are used.
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	N	No Comparability protocols were submitted in the BLA for the purposes of post-marketing manufacturing changes and reduction in submission category.

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

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CTD Module 3 Contents	Present?	If not, justification, action & status
❑ control of critical steps and intermediates o justification of specifications o stability	Y	In process specification and critical controls/non critical controls for each unit operation are provided. (b) (4)
❑ 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	Y	
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation	Y	
o batch analyses	Y	
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol	Y	
o results	Y	
o method validation	Y	
Drug Product [3.2.P] [Dosage Form]		
❑ 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	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation		(b) (4) validation is deferred to micro/DMA reviewer for assessment
o Component, container,		

CTD Module 3 Contents	Present?	If not, justification, action & status
closure depyrogenation and sterilization validation		.
○ Validation of aseptic processing (media simulations)		
○ Environmental Monitoring Program		
○ Lyophilizer validation		Lyo not applicable. The drug product is a solution for injection.
○ Other needed validation data (e.g. hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	N	Ref. std. is same as described for drug substance in 3.2.S.5
❑ container closure system [3.2.P.7]	Y	
○ specifications (vial, elastomer, drawings)	Y	
○ availability of DMF & LOAs	Y	
○ administration device(s)	N	Administration device - Not applicable.
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
○ protocol	Y	
○ results	Y	
○ method validation	Y	
Diluent (vials or filled syringes) [3.2P′]	N	Not applicable. The sponsor does not have a diluent that is co-packaged.

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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)	 N 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 Y Y Y Y Y Y Y Y Y Y Y Y	 No novel excipients were used.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y N	 No new comparability study was proposed.
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	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
of manufacture		
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	
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	
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	
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	Rabbit pyrogen test is provided. Endotoxin test conforms to USP <85>, and the sterility test conforms to USP <71>. Mycoplasma tests conforms to USP <63>.
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	
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	

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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.

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

Yunhua Jia -S

Digitally signed by Yunhua Jia -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yunhua Jia -S, 0.9.2342.19200300.100.1.1=2000377236
Date: 2015.01.23 14:31:49 -05'00'

Product Quality Reviewer(s) Date

Chana Fuchs -S

Digita ly signed by Chana Fuchs S
DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Chana Fuchs S 0 9 2342 19200300 100 1 1=2000601863
Date: 2015 01 23 14:47:12 05 00

Branch Chief/Team Leader/Supervisor Date

Division Director Date

APPEARS THIS WAY ON ORIGINAL