CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761038Orig1s000

CHEMISTRY REVIEW(S)

BLA 761038: Priority Review
Recommendation: Approval

BLA761038
Addendum-1
September 28, 2016

Quality Review Data Sheet

(Includes only information updated since the initial OPQ-IQA-Memo Dated July 29, 2016)

1. **BLA#:** STN 761038

2. **Review #:** 2 (Addendum-1)

3. **Review Date:** September 27, 2016

4. **Reviewers:** Natalia Pripuzova, PhD, primary reviewer, DMA
   Colleen Thomas, PhD, Quality Assessment Lead, DMA
   Rashmi Rawat, Ph.D., Application Team Lead, OBP/OPQ/CDER

5. **Through:** Juhong Liu, Ph.D., Acting Review Chief, OBP/OPQ/CDER

6. Communications with the sponsor and supporting documents since the finalization of the initial IQA Memo

Sequence Number	Date	Description
0050	06-27-2016	Response to IR/updated (b) (4)
0060	08-18-2016	Response to IR

Recommendations

A Recommendation and Conclusion on Approvability

a. Recommendation

A final recommendation from the Office of Pharmaceutical Quality, CDER, recommends approval of STN 761038 for LARTRUVO™ (olaratumab) manufactured by Eli Lilly and Company. The data submitted in this application support the conclusion that the manufacture of LARTRUVO™ is well controlled and produces 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.

b. Approval Action Letter Language

- Manufacturing location
  - Drug Substance: (b) (4)
  - Drug Product: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN

- Fill Size and Dosage Form
  500 mg/50 mL in single dose vial, Injection

- Dating Period:
  - Drug Product: 24 months; 2-8 °C
  - Drug substance: (b) (4) months; (b) (4) °C
  - Stability Option
    - For Stability Protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

- Exempt From Lot Release
  - Yes
  - Rationale for exemption: Specified Product (note: we exempt specified products according to CFR 601.2a)

There are some minor product quality issues identified during the BLA review, which do not preclude approval of the BLA and will be addressed as post marketing commitments.

B Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements (OBP)

- Conduct a study to re-assess drug substance and drug product specifications based on additional clinical experience with materials manufactured using the commercial process and/or additional characterization data on product quality attributes. The corresponding data, the analysis and statistical method used to evaluate the specifications, and any proposed changes to the specifications will be provided.

Review Summary

Based on the communication and the information obtained after the submission of the initial OPQ-IQA memo the following changes to the BLA and to PMC recommendations are made:

- (b) (4)
- Additionally, on August 18, 2106 Lilly proposed cancelation of the following post-marketing commitment (b) (4)

(b) (4)

(b) (4)

The Agency agreed with Lilly's proposal. The PMC has been canceled.

Review recommendation and Conclusion

The PMC proposed by the Division of Microbiology Assessment is cancelled. The (b) (4)

Colleen Thomas

Digitally signed by Colleen Thomas
Date: 9/28/2016 12:13:36PM
GUID: 50757caa000038fe1c8b291b2af190fd

Rashmi Rawat

Digitally signed by Rashmi Rawat
Date: 9/28/2016 11:25:35AM
GUID: 508da6d8000263c147354329386d4f19

Juhong Liu

Digitally signed by Juhong Liu
Date: 9/28/2016 11:43:01AM
GUID: 508da6da000265f64de5224635a510aa

Natalia Pripuzova

Digitally signed by Natalia Pripuzova
Date: 9/28/2016 11:22:03AM
GUID: 5565e2a10014242a6a2653c966bf9552

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

Date:	26 September, 2016
To:	BLA 761038
From:	Natalia Pripuzova, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/ Branch IV
Endorsement:	Colleen Thomas, Ph.D., QAL, CDER/OPQ/OPF/DMA/Branch IV
Applicant:	Eli Lilly and Company
US License Number:	1891
Submission Reviewed:	Original BLA
Product:	Olaratumab (500 mg/50 ml)
Indication:	Advanced Soft Tissue Sarcoma
Dosage Form:	10 mg/mL, solution for intravenous infusion
Manufacturing Sites:	Lilly Corporate Center, Indianapolis, IN, 46285, USA (FEI: 1819470)
FDA Receipt Date:	24 February 2016
Action Date:	24 October 2016

Approvability Recommendation: This is an addendum to the primary review. The BLA, as amended, was reviewed from drug product quality microbiology prospective and is recommended for approval. The PMC #1 (for CMC) is no longer required as it is part of the BLA approval.

Summary: BLA761038 was submitted as a rolling submission in electronic format on 24-February-2015 to license olaratumab for the use in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy. This memo is an addendum to the product quality microbiology review for the drug product (DP) dated July 28, 2016. This memo covers (b) (4)

(b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0050	27 June 2016	Response to IR/Update (b) (4)
0060	18 August 2016	Response to IR

Module 3.2.

(b) (4)

SATISFACTORY

Conclusion

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

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

III. No inspection follow up items were identified.

Archived File: 761038.rev.mem.addendum.BLA.09-26-2016.doc

NATALIA PRIPUZOVA
(REVIEWER)
09/26/2016

COLLEEN THOMAS (QUALITY ASSESMENT LEAD)
09/26/2016

Colleen Thomas

Digitally signed by Colleen Thomas
Date: 9/26/2016 01:37:29PM
GUID: 50757caa000038fe1c8b291b2af190fd

Natalia Pripuzova

Digitally signed by Natalia Pripuzova
Date: 9/26/2016 01:34:31PM
GUID: 5565e2a10014242a6a2653c966bf9552

BLA 761038: Priority Review

Recommendation: Approval

BLA761038
Review
July 29, 2016

Drug Name/Dosage Form	LARTRUVO™ (olaratumab)/ Injection
Strength/Potency	500mg/50 mL (10mg/mL) Injection, in a single-dose vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Indication	LARTRUVO™ is indicated, in combination with doxorubicin, for the treatment of advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy and surgery
Applicant/Sponsor	Eli Lilly and Company
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Product Quality and Immunogenicity	Chikako Torigoe	Division of Biotechnology Review Research II
Manufacturing Facilities	Ruth Moore	Division of Inspectional Assessment
Microbiology Quality Assessment	Monica Markovski Natalia Pripuzova	Division of Microbiology Assessment
Business Regulatory Process Manager	Melinda Bauerlien	OPRO/OPQ
Application Technical Lead and Product Quality Team Leader	Rashmi Rawat	Division of Biotechnology Review Research II

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Leah Her	OND/OHOP/DOPII
Cross-disciplinary Team Lead	Marc Theoret	OND/OHOP/DOPII
Clinical	Meredith Chuk, Leslie Doros	OND/OHOP/DOPII
Non-Clinical	Emily Wearne	OND/OHOP/DOPII
Clinical Pharmacology	Fang Li, Ruby Leong	OND/OHOP/DOPII
Biometrics	Kun He	OTS/OB/DBV

Quality Review Team – Signature Page

DISCIPLINE	REVIEWER	DIVISION/OFFICE	e-SIGNATURE
Microbiology Quality Assessment (Team Leader)	Colleen Thomas	DMA/OPF/OPQ	Colleen Thomas -S Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas -S, 0.9.2342.19200300.100.1.1=2000334597 Date: 2016.07.29 14:43:52 -04'00'
Manufacturing Facilities (Branch Chief)	Zhihao Qiu	DIA/OPF/OPQ	Zhihao Qiu -S Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274 Date: 2016.07.31 08:46:36 -04'00'
Product Quality Application Technical Lead and Team Leader	Rashmi Rawat	DBRRII/OBP/OPQ	Rashmi Rawat -S Digitally signed by Rashmi Rawat -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rashmi Rawat -S, 0.9.2342.19200300.100.1.1=2001437532 Date: 2016.07.29 14:34:29 -04'00'
Product Quality Acting Review Chief	Joel Welch	DBRRII/OBP/OPQ	Joel T. Welch -S Digitally signed by Joel T. Welch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch -S, 0.9.2342.19200300.100.1.1=2000403745 Date: 2016.07.29 15:22:24 -04'00'

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. Submission Reviewed:

Submission	Date Received	Review Completed (Yes/No)
STN 761038/1	12/10/2015	Yes
STN 761038/4	1/27/2016	Yes
STN 761038/5	2/11/2016	Yes
STN 761038/8	2/24/2016	Yes
STN 761038/42	6/7/2016	Yes
STN 761038/48	6/27/2016	Yes
STN 761038/54	7/20/2016	Yes
STN 761038/57	7/27/2016	Yes

B. DMFs

	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b) (4)		
21219	Eli Lilly and Company		Yes	No review required as all the relevant information is provided in the BLA.

(b) (4)	Yes	No review required as all the relevant information related to compatibility with the product is in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
	Yes	No review required as the relevant information was in the BLA
	Yes	No review required as the relevant information was provided in the BLA
	Yes	No review required because all the relevant information related to compatibility with the product is in the BLA, and the (b) (4) data had already been reviewed for another application and deemed adequate.
	Yes	No review required as all the relevant information was provided in the BLA

3. CONSULTS: *None*

Executive Summary

I. Recommendations

A Recommendation and Conclusion on Approvability

a. Recommendation

A final recommendation from the Office of Pharmaceutical Quality, CDER, recommends approval of STN 761038 for LARTRUVO™ (olaratumab) manufactured by Eli Lilly and Company. The data submitted in this application support the conclusion that the manufacture of LARTRUVO™ is well controlled and produces 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.

b. Approval Action Letter Language

- Manufacturing location
  - Drug Substance: (b) (4)
  - Drug Product: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN

- Fill Size and Dosage Form
  500 mg/50 mL in single dose vial, Injection

- Dating Period:
  - Drug Product: 24 months; 2-8 °C
  - Drug substance: (b) (4) months; (b) (4) °C
  - Stability Option
    - For Stability Protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

- Exempt From Lot Release
  - Yes

- Rationale for exemption: Specified Product (note: we exempt specified products according to CFR 601.2a)

There are some minor product quality issues identified during the BLA review, which do not preclude approval of the BLA and will be addressed as post marketing commitments.

B Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Product Quality (OBP)

Conduct a study to re-assess drug substance and drug product specifications based on additional clinical experience with materials manufactured using the commercial process and/or additional characterization data on product quality attributes. The corresponding data, the analysis and statistical method used to evaluate the specifications, and any proposed changes to the specifications will be provided.

Product Quality Microbiology (DMA)

(b) (4)

II. Summary of Quality Assessments

A. Product Overview

Olaratumab is a human monoclonal antibody of IgG1/kappa isotype. It binds to human platelet-derived growth factor receptor alpha (PDGF-R-α). Binding of olaratumab to PDGF-R-α blocks the interaction of PDGF-R-α with PDGF-AA, -BB and –CC ligands, thereby preventing the PDGF ligand-induced receptor activation and subsequent downstream PDGF-R-α signaling pathway.

a. Names:

i. **Proprietary Name:** LARTRUVO™
ii. **Trade Name:** LARTRUVO™
iii. **Non-Proprietary/USAN:** Olaratumab
iv. **CAS name:** 1024603-93-7
v. **Common Name:** LY3012207, IMC-3G3 and IMC3G3
vi. **INN Name:** Olaratumab
vii. **OBP systematic name:** MAB HUMAN (IGG1) ANTI P16234 (PGFRA_HUMAN)[LY3012207]

b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody (IgG1), anti-(human alpha-type platelet-derived growth factor receptor (PDGF-R-α)

B. Drug Substance [olaratumab] Quality Assessment

a. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below provides a summary of product-related critical quality attributes that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management. For additional information see ***Appendix A*** for the OBP product quality review and ***Appendix B*** for the product quality microbiology review.

18 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix-A

Product Quality Review

DBRR II / OBP /OPQ

BLA 761038

Olaratumab

Eli Lilly and Company

Primary reviewer: Chikako Torigoe, PhD
Team Leader: Rashmi Rawat, PhD

DBRRII, Office of Biotechnology Products,

Office of Pharmaceutical Quality, CDER

OBP CMC Review Data Sheet

1. **BLA#:** STN 761038

2. **REVIEW DATE:** 7/28/2016

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Meredith Chuk, Leslie Doros
Pharm/Tox: Emily Wearne
Product Quality Team: Chikako Torigoe, Rashmi Rawat (TL)
Product Quality Microbiology: Monica Markovski, Natalia Pripuzova
Manufacturing Facility: Ruth Moore
Clinical Pharmacology: Fang Li, Ruby Leong
Statistics: Kun He
OBP Labeling: Jibril Abdus-Samad
RBPM: Leah Her, Melinda Bauerlien

4. **MAJOR GRMP DEADLINES**
Filing Meeting: 3/23/2016
Mid-Cycle Meeting: 5/20/2016
Wrap-Up Meeting: 7/25/2016
Primary Review Due: 7/28/2016
Secondary Review Due: 8/1/2016
CDTL Memo Due: 10/3/2016
PDUFA Action Date: 10/24/2016

5. **COMMUNICATIONS WITH SPONSOR**

Communication/Document	Date
CMC Pre-BLA Meeting	10/6/2015
Information Request #1	5/18/2016
Information Request #2	6/16/2016
Information Request #3	7/14/2016
t-con	7/18/2016
Information Request #4	7/20/2016

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 761038/1	12/10/2015	Yes
STN 761038/4	1/27/2016	Yes
STN 761038/5	2/11/2016	Yes
STN 761038/8	2/24/2016	Yes
STN 761038/42	6/7/2016	Yes
STN 761038/48	6/27/2016	Yes
STN 761038/54	7/20/2016	Yes
STN 761038/57	7/27/2016	Yes

7. DRUG PRODUCT NAME/CODE/TYPE

a. Proprietary Name: Lartruvo
b. Trade Name: Olaratumab
c. Non-Proprietary/USAN: Olaratumab
d. CAS name: 1024603-93-7
e. INN Name: Olaratumab
f. OBP systematic name: MAB HUMAN (IGG1) ANTI P16234 (PGFRA_HUMAN)[LY3012207]
g. Other Names: IMC-3G3, IMC3G3, LY3012207

8. PHARMACOLOGICAL CATEGORY: Platelet-derived growth factor receptor α-binding human monoclonal antibody

9. DOSAGE FORM: Injection

10. STRENGTH/POTENCY:

(i) The concentration/strength of the Drug Product: 500 mg/50 mL (10 mg/mL)

(ii) Type of potency assay: A cell proliferation assay to evaluate the inhibitory activity of olaratumab for ligand-dependent cell proliferation

11. ROUTE OF ADMINISTRATION: Intravenous infusion

12. REFERENCED MASTER FILES

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
21219	Eli Lilly and Company	(b) (4)	Yes	No review required as all the relevant information is provided in the BLA.
		(b) (4)	Yes	No review required as all the relevant information related to compatibility with the product is in the BLA.
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA

13. INSPECTIONAL ACTIVITIES

The inspection of the manufacturing and testing facility of olaratumab drug substance was conducted from (b) (4) at (b) (4) The FDA participants were Patricia Hughes (OPF/DMA), Monica Markovski (OPF/DMA), Chikako Torigoe (OBP) and Ruth Moore (OPF/DIA). The facility was found to be acceptable from a cGMP perspective and the inspection was classified as NAI .

14. CONSULTS REQUESTED BY OBP

N/A

15. QUALITY BY DESIGN ELEMENTS

Design Space	No
Design of Experiments	Yes
Risk Assessment / Risk Management	Yes
Multivariate Statistical Process Control	Yes
Process Analytical Technology	No

16. PRECEDENTS

There are no precedents set by the review of this application.

17. ADMINISTRATIVE

A. Signature Block

Title and Name	Signature and Date
Team Leader, OBP/DBRRII Rashmi Rawat	Rashmi Rawat -S Digitally signed by Rashmi Rawat -S DN c US,o U.S. Government, ou HHS, ou FDA, ou People, cn Rashmi Rawat -S, 0.9.2342.19200300.100.1.1 0014137532 Date 2016.07.28 14:04:58 -04'00'
Primary Reviewer, OBP/DBRRII Chikako Torigoe	Chikako Torigoe -A Digitally signed by Chikako Torigoe -A DN c US,o U.S. Government, ou HHS,ou FDA, ou People, 0.9.2342.19200300.100.1.1 1300430897, cn Chikako Torigoe -A Date 2016.07.28 14:02:30 -04'00'

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of Lartruvo™ (olaratumab) is well controlled, and leads to a product that is pure and potent. The product is free from 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 the multiple production runs presented. It is recommended that Lartruvo™ (olaratumab) be approved for human use (under conditions specified in the package insert).

I recommend an expiry of (b) (4) months for olaratumab drug substance when stored at (b) (4) °C.

I recommend an expiry of 24 months for olaratumab drug product when stored at 2-8°C.

The post-approval stability protocols are acceptable.

II. List of Deficiencies To Be Communicated

There are no CMC deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments/Requirement

Conduct a study to reevaluate olaratumab drug substance and drug product (b) (4) specifications (b) (4) The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided.

IV. Review of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The sponsor requested a categorical exclusion from the environmental assessment requirement pursuant to 21 CFR 25.15 (d) based on the exclusion allowed by 21 CFR 25.31 (b and c) and the request is acceptable.

V. Primary Container Labeling Review

Labeling review was performed by Jibril Abdus-Samad and the review is on file.

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 immunogenicity assays is provided at the end of this review. The screening, confirmatory and neutralizing anti-olaratumab antibody assays are acceptable.

Table of Contents

In this review, tables and figures were directly copied from the submission, unless otherwise stated.

3.2.S. DRUG SUBSTANCE

3.2.S.1. General Information

3.2.S.1.2 Structure

Olaratumab is a human IgG1with two heavy chains each consisting of 457 amino acid residues and two light chains (κ) with 214 amino acid residues. The structure and amino acid sequence of the light and heavy chains of olaratumab are provided below.

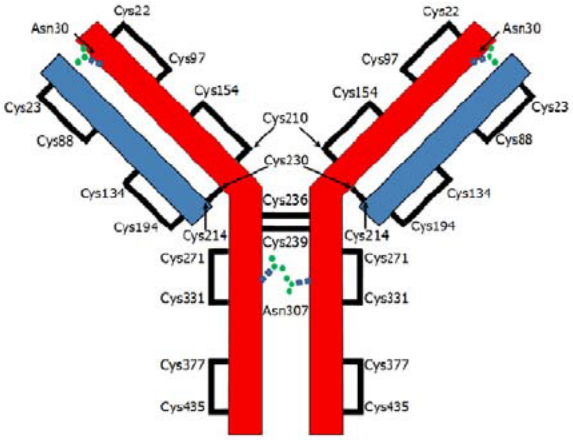

Figure 3.2.S.1.2-3 Schematic of Olaratumab with Confirmed Disulfide Bonds (N-linked Glycosylation Sites Depicted at Asn[30] and Asn[307])

```
        10         20         30         40         50         60
EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA

        70         80         90        100        110        120
RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPAFGQ GTKVEIKRTV AAPSVFIFPP

       130        140        150        160        170        180
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT

       190        200        210
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
```

Sequence of variable region is shown in blue, Complementarity Determining Regions (CDR) in red, and constant region in black.

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

```
        10         20         30         40         50         60
QLQLQESGPG LVKPSETLSL TCTVSGGSIN SSSYYWGWLR QSPGKGLEWI GSFFYTGSTY

        70         80         90        100        110        120
YNPSLRSRLT ISVDTSKNQF SLMLSSVTAA DTAVYYCARQ STYYYGSGNY YGWFDRWDQG

       130        140        150        160        170        180
TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF

       190        200        210        220        230        240
PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKRVEPKSC DKTHTCPPCP

       250        260        270        280        290        300
APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK

       310        320        330        340        350        360
PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT

       370        380        390        400        410        420
LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL

       430        440        450
TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
```

Sequence of variable region is shown in blue, CDR in red, and constant region in black.

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

3.2.S.1.3 General Properties

Olaratumab is a recombinant human IgG1 produced in NS0 cells. Olaratumab binds to the platelet-derived growth factor receptor α (PDGFRα) that is expressed on the surface of tumor cells. Olaratumab blocks the binding of PDGF-AA, -BB and -CC ligands to PDGFRα, and inhibits the activation of PDGFRα. The potency assay used for release and stability testing measures the inhibition of PDGF-AA-dependent growth of cells that express PDGFRα. Olaratumab drug substance is formulated at (b) (4) . The storage temperature is (b) (4) °C.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

The manufacture and the testing sites for the olaratumab drug substance are listed in the table below.

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

Manufacturing Facility	The drug substance is manufactured in accordance with current Good Manufacturing Practices at the following facility: (b) (4)
Storage Facility	Storage facilities for drug substance, Master and Working Cell Banks: (b) (4)
Control Facilities	(b) (4)

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

[a] The manufacturing site (b) (4) is referred to as "(b) (4)" throughout this submission.

Reviewer's Note: *All above facilities are correctly listed in the Form 356h.*

3.2.S.2.2 Description of Manufacturing Process and Process Controls
3.2.S.2.2.1 Overview of Drug Substance Manufacturing Process

164 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix-B

Product Quality Microbiology Review

DMA / PDF /OPQ

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date:	28 July 2016
To:	Administrative File, **BLA 761038**
From:	Monica Markovski, Ph.D., CDER/OPQ/OPF/DMA/BIV
Through:	Colleen Thomas, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV
Subject:	New Biologics License Application
Applicant:	Eli Lilly and Company
US License:	1891
Product:	Olaratumab (Compound LY3012207; Proposed name: Lartruvo)
Indication:	Advanced soft tissue sarcoma
Dosage Form:	Injection, Solution for Intravenous Infusion
Facility:	(b) (4) (Drug substance manufacturing facility) (b) (4) FEI: (b) (4)
Receipt Date:	24 February 2016
Action Date:	24 October 2016

Recommendation: The drug substance section of BLA 761038 is recommended for approval, as amended, from a product quality microbiology perspective.

Review Summary

Eli Lilly has submitted this Biologics License Application (BLA) for olaratumab to be used in combination with doxorubicin to treat advanced soft tissue sarcoma in patients who are not amenable to surgery or radiotherapy. The drug substance (DS) is manufactured at the (b) (4) (FEI: (b) (4)). The drug product (DP) is manufactured in the Lilly Corporate Center located in Indianapolis, Indiana (FEI: 1819470).

BLA 761038 (olaratumab) was initially submitted as a rolling BLA on 10 December 2015 with partial modules 1, 2, 4, and 5. Partial module 3 was added on 17 December 2015, with additional submissions on 19 January 2016 and 27 January2016. Module 3 was completed on 27 January 2016. The remainder of the BLA was submitted on 24 February 2016. The application contains CMC information in an eCTD format.

Drug Substance and Drug Product Quality Microbiology Information Reviewed

Document Type	eCTD Sequence	Date
Quality submission	0003	27 January 2016
Information Request #1 Responses	0028	10 May 2016
Information Request #2 Responses	0054	11 July 2016

This review contains the assessment of the manufacturing process for olaratumab drug substance from a product quality microbiology perspective. Full responses to FDA Information Requests are provided at the end of this review memo.

Product Quality Microbiology Assessment: Drug Substance

MODULE 3.2.S DRUG SUBSTANCE

S.1 General Information

Olaratumab is a recombinant human-derived monoclonal antibody of the IgG_1 subclass that acts as a platelet-derived growth factor receptor alpha (PDGFR-α) antagonist. By binding PDGFR-α, Olaratumab blocks PDGF-AA, -BB, and –CC binding and receptor activation domains. The molecule consists of 2 heavy chain molecule fragments (457 residues each) and 2 light chain fragments (214 residues each). Olaratumab is produced in murine myeloma GS-NS0 cell line. (b) (4)

The description is satisfactory.

S.2 Manufacture

S.2.1 Manufacturers (3.2.S.2.1)

DS manufacturing facility	Tests performed at DS facility
(b) (4)	• Drug substance manufacturing • Drug substance/Master and Work Cell Bank storage • (b) (4) drug substance release and stability testing • (b) (4) viral testing and characterization • Drug substance release and stability tests • Working Cell Bank sterility testing

Reviewer's comments: *The* (b) (4) *facility manufactures olaratumab DS* (b) (4)

(b) (4)

The description is satisfactory.

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

29 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Reviewer comments: *The remainder of this section is deferred to OBP.*

Conclusion

I. This BLA was reviewed from a product quality microbiology perspective, and it is recommended for approval as amended.

II. A pre-license inspection was conducted at (b) (4), on (b) (4) – (b) (4). A Form FDA 483 was not issued at the end of the inspection.
   a. No additional inspection follow-up items were identified.

III. Information and data related to areas outside of microbial control of the drug substance is not reviewed here and noted in the review.

24 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

SIGNATURES

Monica Markovski, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV
July 28, 2016

Colleen Thomas, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/BIV
July 28, 2016

Archived file: BLA761038.rev.memo.DS.DMAFinal.pdf

Colleen Thomas

Digitally signed by Colleen Thomas
Date: 7/28/2016 11:37:14AM
GUID: 50757caa000038fe1c8b291b2af190fd

Monica Markovski

Digitally signed by Monica Markovski
Date: 7/28/2016 11:33:52AM
GUID: 56c21fb00023a450a9d1733bdf21bc80
Comments: Digital signatures can be viewed once the document is downloaded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Natalia Pripuzova, Ph.D.
QUALITY ASSESSMENT LEAD: Colleen Thomas, Ph.D.

Date:	July 28, 2016
BLA:	761038
Applicant:	Eli Lilly and Company
US License Number:	1891
Submission Reviewed:	Original BLA (Breakthrough Therapy Designation)
Product:	Olaratumab, rHuman MAb to PDGFR-alpha; IMC-3G3
Indication:	Advanced Soft Tissue Sarcoma
Dosage Form:	10 mg/mL, solution for intravenous infusion
Manufacturing Sites:	Lilly Corporate Center, Indianapolis, IN, 46285, USA (FEI: 1819470)
FDA Receipt Date:	24 February 2016
PDUFA Date:	24 October 2016

Approvability Recommendation: The Drug Product section of the BLA was reviewed from product quality microbiology prospective. The BLA as amended is recommended for approval.

Summary: BLA761038 was submitted as a rolling submission in electronic format on 24-February-2015 to license olaratumab for the use in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy. Olaratumab is a targeted recombinant human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that specifically binds PDGFR-α, blocking PDGF AA, -

BB, and -CC binding and receptor activation. Olaratumab Injection, Solution for Intravenous Infusion, 10 mg/mL, is a sterile solution, intended for single use, presented as 500 mg in 50 mL vial. The drug product (DP) is diluted with 0.9% Sodium Chloride Injection (normal saline) prior to administration by intravenous infusion. The drug substance (DS) is manufactured at the (b) (4). The DP is manufactured and QC tested at the Lilly Corporate, Indianapolis, IN, USA.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0003	27 January 2016	Original BLA
0007	24 February 2016	Original BLA
0023	9 May 2016	Response to IR
0048	15 June 2016	Response to IR
0052	28 June 2016	Response to IR

Drug Product Review

Module 3.2

P.1 Description and Composition of the Drug Product

The unit formula for Olaratumab DP is provided in Table 3.2.P.1-1, copied below from the submission.

Table 3.2.P.1-1 Unit Formula for Olaratumab Drug Product, 500 mg/50 mL

Ingredient	Quantity (mg/mL)	Quantity (mg/50 mL vial) [a]	Function	Reference to Standards
Active Ingredient:				
Olaratumab	10	500	Active Ingredient	In-house
Other Ingredients:				
L-Histidine	0.3	14.9	(b) (4)	USP, Ph. Eur., JP
L-Histidine Monohydrochloride	1.7	84.8		Ph. Eur., JP
Glycine	7.5	375.4		USP, Ph. Eur., JP
Sodium Chloride	2.9	146.1		USP-NF, Ph. Eur., JP
Mannitol	13.7	683.2		USP, Ph. Eur., JP
Polysorbate 20	0.2	10.0		USP-NF, Ph. Eur., JPE
Water for Injection	(b) (4)			USP-NF, Ph. Eur., JP

q.s = quantity sufficient.
[a] Value is determined by calculation using the full precision quantity (mg/mL) number.

***Reviewer's comment**: This information is provided in this review memo for reference.*

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)

47 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Conclusion

I. The Drug Product section of the BLA as amended was reviewed from a product quality microbiology perspective and is recommended for approval.

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

III. No inspection follow-up items were identified.

DP Quality Microbiology Information Requests Sent

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Archived File: 761038.rev.mem.BLA.07-28-2016.doc

NATALIA PRIPUZOVA
(REVIEWER)
07/28/2016

COLLEEN THOMAS (QUALITY ASSESMENT LEAD)
07/28/2016

Colleen Thomas

Digitally signed by Colleen Thomas
Date: 7/28/2016 09:15:36AM
GUID: 50757caa000038fe1c8b291b2af190fd

Natalia Pripuzova

Digitally signed by Natalia Pripuzova
Date: 7/28/2016 08:40:19AM
GUID: 5565e2a10014242a6a2653c966bf9552

Appendix-C

Manufacturing Facility Review

DIA/OPF/OPQ

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51,10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 6/23/2016
To: Administrative File, STN 761038/0
From: Ruth Moore, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA B1
Subject: Original BLA
US License: 1891
Applicant: Eli Lilly Company
Mfg Facility: Drug Substance: (b) (4)

Drug Product: Eli Lilly and Company, Indianapolis, IN 46221
FEI 1819470
Product: Olaratumab Injection, Solution for Intravenous Infusion, 10 mg/mL
Dosage: 10 mg/mL provided as a 500 mg/50mL presentation for intravenous infusion.
Indication: Treatment of advanced/metastatic soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery
Due Date: 11/02/2016

RECOMMENDATION: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of Olaratumab drug substance (DS) and drug product (DP), respectively, at (b) (4) (FEI (b) (4)), and Eli Lilly and Company, Indianapolis, IN (FEI 1819470). (b) (4) will perform release and stability tests for DS and DP, sterility testing for the working cell bank (WCB), viral testing and characterization (b) (4) and will store the master and working cell banks. (b) (4) will perform control testing functions including viral testing, mycoplasma testing, MCB and WCB qualification and release testing. Eli Lilly and Company, Indianapolis will manufacture, package, label, and perform release and stability testing, except cell based potency testing, for the drug product.

Olaratumab is a humanized IgG1 monoclonal antibody produced in NSO cells. It is proposed for the treatment of patients with advanced/metastatic soft tissue sarcoma. Olaratumab drug product

is manufactured as a sterile solution for infusion, 10 mg/mL, provided as a 500 mg/50mL presentation.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for Olaratumab DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Olaratumab DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
(b) (4)			Olaratumab DS manufacture, packaging, release testing and stability testing; storage of master and working cell bank; viral testing and characterization (b) (4)
			viral testing and characterization (b) (4)
			Qualification testing of the MCB and WCB
			Qualification testing of the MCB and WCB
			Qualification testing of the MCB and WCB

***Reviewer Comment 1**: The facilities for manufacture of Olaratumab DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

DRUG PRODUCT FACILITIES

- **3.2.P.3.1. DP Manufacturers.**
  The sites proposed for Olaratumab DP manufacture, testing, packaging, and labeling are presented below in Table 3.

TABLE 3. Sites Proposed for Olaratumab Drug Product Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
Eli Lilly and Company	Lilly Corporate Center Indianapolis, Indiana USA 46285	1819470	Olaratumab DP manufacture; release testing and stability testing secondary packaging and labeling
[redacted] (b) (4)			Olaratumab DP release and stability testing

- **Prior Inspection History for DP Manufacturing and Testing Sites**
  - Eli Lilly and Company (FEI 1819470) Olaratumab DP Manufacturing, Testing, Packaging and Labeling Site.
    - Inspection Conducted 07/27/2015 to 08/04/2015 by DET-DO. Inspection coverage was given in accordance with CP 7346.832, Pre-Approval Inspections, CP #7356.002, Drug Process Inspection, CP #7356.002A, Sterile Drug Process Inspection – Small Volume Parenteral. The inspection was classified NAI, and included coverage of profiles SVL and SVS. The PAI was conducted for [redacted] (b) (4) which is manufactured in [redacted] (b) (4) Manufacturing area.
    - Inspection Conducted 07/21/2014 to 07/25/2014. This was a PLI conducted in support of [redacted] (b) (4) prefilled syringe manufacture in [redacted] (b) (4). The inspection was classified NAI and the application was recommended for approval.
    - Inspection Conducted 12/02/2013 to 12/06/2013 by DET-DO. Inspection included pre-approval coverage of operations related to the production and control of [redacted] (b) (4). A two-item form FDA-483 was issued at the conclusion of the inspection; the inspection was classified VAI.

  - [redacted] (b) (4) (FEI) Olaratumab DP Testing Site (Release and Stability Testing)
    Refer to Drug Substance section above for the compliance history of the facility.

- **Current Prior Approval Inspection Decisions**
  A PLI waiver was recommended for the Eli Lilly Manufacturing Facility for BLA 761038/0. The approved inspection waver memo is on file.

  The Olaratumab drug product will be manufactured in the [redacted] (b) (4) facility at Eli Lilly. [redacted] (b) (4) The facility was

inspected by DET-DO from 07/27/2015 to 08/04/2015, and classified NAI. PAI coverage for (b) (4) and CGMP coverage for SVS and SVL profiles were provided during the inspection. There were no concerns related to manufacture of sterile product (b) (4) at the facility. Facility design, utilities, equipment, cleaning, sanitization, sterilization and other procedures for prevention of contamination and cross-contamination during manufacture of Olaratumab DP described in the submission were reviewed and found to be adequate.

Reviewer Comment 11. *The production and testing facilities associated with the manufacture of Olaratumab DP are acceptable from a facilities assessment standpoint.*

- **3.2.P.3. Overview of Olaratumab DP Manufacturing Operations Conducted at Eli Lilly, Indianapolis**.

The drug product manufacturing process for Olaratumab consists of (b) (4) A flow diagram of the manufacturing process with critical process parameters and in-process controls was presented in Figure 3.2.P.3.3.1-1 of Module 3.2.P.3.3.

- **3.2.A.1. Eli Lilly Facility Design, Floor Plans and Room Classifications for Olaratumab Manufacture**

(b) (4)

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for [redacted] (b) (4). (FEI [redacted] (b) (4)) and Eli Lilly (FEI 1819470) proposed for Olaratumab DS and DP manufacture. All proposed manufacturing and testing sites for BLA 761038/0 are recommended for approval from a facilities assessment standpoint.

_____

Ruth Moore Ph.D.
Chemist/ Quality Assessment Lead (Ag.)
OPF Division of Inspectional Assessment
Branch 1

_____

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: 6/14/2016

From: Ruth Moore, Ph.D., OPQ/OPF/DIA
Chikako Torigoe, Ph.D., OPQ/OBP/DBRRII
Natalia Pripuzova, Ph.D., OPQ/OPF/DMA

To: BLA File, STN 761038/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of Olaratumab drug product at the Eli Lilly facility in Indianapolis IN

Applicant: Eli Lilly Co.

Facility: Eli Lilly Co.
Lilly Corporate Center
Indianapolis
Indiana, 46285 USA
FEI #1819470

Product: Olaratumab Injection, Solution for Intravenous Infusion

Dosage: 10 mg/mL provided as a 500 mg/50mL presentation for intravenous infusion

Indication: Treatment of advanced/metastatic soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery

Waiver Recommendation

The Olaratumab drug product will be manufactured in (b) (4) at Eli Lilly Indianapolis. The proposed commercial manufacturing scheme for Olaratumab is similar to the approved processes for other sterile aseptically-filled products manufactured at Eli Lilly. (b) (4) The facility was inspected by DET-DO and CDER-OC from 5/05/2014–5/16/2014, and classified NAI. CGMP coverage was provided for SVS and SVL profiles during the inspection, and there were no concerns related to manufacture of sterile product (b) (4) at the facility. Based on the firm's compliance history and current acceptable GMP status, and the fact that the facility, similar processes, and the equipment at Eli Lilly (b) (4) proposed for Olaratumab manufacture are currently approved for manufacture of (b) (4) we recommend that inspection of The Eli Lilly Indianapolis facility be waived for STN 761038/0.

Summary

BLA STN 761038/0 was submitted by Eli Lilly Co. and provided information and data to support manufacture of Olaratumab Injection for infusion, 10 mg/mL in a 500 mg/50 mL vial presentation. The manufacture of Olaratumab drug substance is performed at [redacted] FEI [redacted]), and Olaratumab drug product is manufactured at Eli Lilly, Indianapolis (FEI 1819470). The current waiver recommendation is in regards to drug product manufacture at Eli Lilly, Indianapolis IN.

Facility Information

[redacted]. The drug product manufacturing process for Olaratumab consists of [redacted]

[redacted]

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

   The Eli Lilly site is a multi-product facility that has already been approved for commercial manufacture of [redacted]

(b) (4) The site also manufactures several other commercial sterile products.

2. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The facility was inspected by DET-DO from 07/27/2015 to 08/04/2015. Inspection coverage was given in accordance with CP #7356.002, Drug Process Inspection, CP #7356.002A, Sterile Drug Process Inspection – Small Volume Parenteral, and CP 7346.832, Pre-Approval Inspections. The inspection on 07/27/2015 – 08/04/2015 was classified NAI, and included coverage of profiles SVS and SVL.

3. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.*

The same areas and equipment at Eli Lilly (b) (4) approved for (b) (4) manufacture are proposed for Olaratumab manufacture.

4. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The proposed manufacturing scheme for Olaratumab is similar to the approved processes for other sterile, (b) (4), injectable products manufactured at Eli Lilly Indianapolis, , including (b) (4)

Signed:

Ruth Moore, Ph.D., DIA/OPF Reviewer Ruth A. Moore -S Digitally signed by Ruth A. Moore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890 Date: 2016.06.16 15:36:25 -04'00' DATE _____

Chikako Torigoe, Ph.D., DBRR/OBP Reviewer Chikako Torigoe -A Digitally signed by Chikako Torigoe -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300430897, cn=Chikako Torigoe -A Date: 2016.06.16 16:00:37 -04'00' DATE _____

Natalia Pripuzova, Ph.D., DMA/OPF Reviewer Natalia S. Pripuzova -S (Affiliate) Digitally signed by Natalia S. Pripuzova -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000351935, cn=Natalia S. Pripuzova -S (Affiliate) Date: 2016.06.16 16:30:42 -04'00' DATE _____

Rashmi Rawat, Ph.D., DBRRII /OBP ATL Rashmi Rawat -S Digitally signed by Rashmi Rawat -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rashmi Rawat -S, 0.9.2342.19200300.100.1.1=2001413732 Date: 2016.06.16 15:57:18 -04'00' DATE _____

Colleen Thomas, Ph.D., DMA/OPF QAL Colleen Thomas -S Digitally signed by Colleen Thomas -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas -S, 0.9.2342.19200300.100.1.1=2000334597 Date: 2016.06.16 16:03:33 -04'00' DATE _____

Zhihao Qiu, Ph.D., DIA/OPF Branch Chief Zhihao Qiu -S Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274 Date: 2016.06.23 09:30:20 -04'00' DATE _____

David Frucht, M.D. David M. Frucht -S Digitally signed by David M. Frucht -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300168604, cn=David M. Frucht -S Date: 2016.06.22 [illegible] CONCUR DO NOT CONCUR DATE
Director, Division of Biotechnology Review and Research II
Office of Biotechnology Products, Office of Pharmaceutical Quality, CDER

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51,10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 6/13/2016
To: Administrative File, STN 761038/0
From: Ruth Moore, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA B1
Subject: Original BLA
US License: 1891
Applicant: Eli Lilly Company
Mfg Facility: Drug Substance: [redacted (b) (4)]
FEI [redacted (b) (4)]
Drug Product: Eli Lilly and Company, Indianapolis, IN 46221
FEI 1819470
Product: Olaratumab Injection, Solution for Intravenous Infusion, 10 mg/mL
Dosage: 10 mg/mL provided as a 500 mg/50mL presentation for intravenous infusion.
Indication: Treatment of advanced/metastatic soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery
Due Date: 11/02/2016

RECOMMENDATION: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of Olaratumab drug substance (DS) and drug product (DP), respectively, at [redacted (b) (4)] (FEI [redacted (b) (4)]), and Eli Lilly and Company, Indianapolis, IN (FEI 1819470). [redacted (b) (4)] will perform release and stability tests for DS and DP, sterility testing for the working cell bank (WCB), viral testing and characterization [redacted (b) (4)], and will store the master and working cell banks. [redacted (b) (4)] will perform control testing functions including viral testing, mycoplasma testing, MCB and WCB qualification and release testing. Eli Lilly and Company, Indianapolis will manufacture, package, label, and perform release and stability testing, except cell based potency testing, for the drug product.

Olaratumab is a humanized IgG1 monoclonal antibody produced in NSO cells. It is proposed for the treatment of patients with advanced/metastatic soft tissue sarcoma. Olaratumab drug product

is manufactured as a sterile solution for infusion, 10 mg/mL, provided as a 500 mg/50mL presentation.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for Olaratumab DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for Olaratumab DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
(b) (4)			Olaratumab DS manufacture, packaging, release testing and stability testing; storage of master and working cell bank; viral testing and characterization (b) (4) (b) (4)
			viral testing and characterization (b) (4) (b) (4) Qualification testing of the MCB and WCB
			Qualification testing of the MCB and WCB
			Qualification testing of the MCB and WCB

***Reviewer Comment 1**: The facilities for manufacture of Olaratumab DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**

(b) (4)

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

DRUG PRODUCT FACILITIES

- **3.2.P.3.1. DP Manufacturers.**
  The sites proposed for Olaratumab DP manufacture, testing, packaging, and labeling are presented below in Table 3.

TABLE 3. Sites Proposed for Olaratumab Drug Product Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
Eli Lilly and Company	Lilly Corporate Center Indianapolis, Indiana USA 46285	1819470	Olaratumab DP manufacture; release testing and stability testing secondary packaging and labeling
(b) (4)			Olaratumab DP release and stability testing

- **Prior Inspection History for DP Manufacturing and Testing Sites**
  - Eli Lilly and Company (FEI 1819470) Olaratumab DP Manufacturing, Testing, Packaging and Labeling Site.
    - Inspection Conducted 07/27/2015 to 08/04/2015 by DET-DO. Inspection coverage was given in accordance with CP 7346.832, Pre-Approval Inspections, CP #7356.002, Drug Process Inspection, CP #7356.002A, Sterile Drug Process Inspection – Small Volume Parenteral. The inspection was classified NAI, and included coverage of profiles SVL and SVS. The PAI was conducted for (b) (4) which is manufactured in (b) (4) Manufacturing area.
    - Inspection Conducted 07/21/2014 to 07/25/2014. This was a PLI conducted in support of (b) (4) prefilled syringe manufacture in (b) (4). The inspection was classified NAI and the application was recommended for approval.
    - Inspection Conducted 12/02/2013 to 12/06/2013 by DET-DO. Inspection included pre-approval coverage of operations related to the production and control of (b) (4) . A two-item form FDA-483 was issued at the conclusion of the inspection; the inspection was classified VAI.

  - (b) (4) Olaratumab DP Testing Site (Release and Stability Testing)
    Refer to Drug Substance section above for the compliance history of the facility.

- **Current Prior Approval Inspection Decisions**
  A PLI waiver was recommended for the Eli Lilly Manufacturing Facility for BLA 761038/0. The approved inspection waver memo is on file.

  The Olaratumab drug product will be manufactured in the (b) (4) facility at Eli Lilly. The proposed commercial manufacturing scheme for Olaratumab is similar to that for other approved monoclonal antibody products, (b) (4) manufactured at Eli Lilly. The facility was

inspected by DET-DO from 07/27/2015 to 08/04/2015, and classified NAI. PAI coverage for (b) (4) and CGMP coverage for SVS and SVL profiles were provided during the inspection. There were no concerns related to manufacture of sterile product (b) (4) at the facility. Facility design, utilities, equipment, cleaning, sanitization, sterilization and other procedures for prevention of contamination and cross-contamination during manufacture of Olaratumab DP described in the submission were reviewed and found to be adequate.

Reviewer Comment 11. *The production and testing facilities associated with the manufacture of Olaratumab DP are acceptable from a facilities assessment standpoint.*

- **3.2.P.3. Overview of Olaratumab DP Manufacturing Operations Conducted at Eli Lilly, Indianapolis.**

The drug product manufacturing process for Olaratumab consists of (b) (4) A flow diagram of the manufacturing process with critical process parameters and in-process controls was presented in Figure 3.2.P.3.3.1-1 of Module 3.2.P.3.3.

- **3.2.A.1. Eli Lilly Facility Design, Floor Plans and Room Classifications for Olaratumab Manufacture**

(b) (4)

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for [redacted] (b) (4) (FEI [redacted] (b) (4)) and Eli Lilly (FEI 1819470) proposed for Olaratumab DS and DP manufacture. All proposed manufacturing and testing sites for BLA 761038/0 are recommended for approval from a facilities assessment standpoint.

Ruth A. Moore -S

Digitally signed by Ruth A. Moore -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890
Date: 2016.06.13 15:34:38 -04'00'

Ruth Moore Ph.D.
Chemist/ Quality Assessment Lead (Ag.)
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274
Date: 2016.06.13 15:39:48 -04'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 761038	**Submission Type: Original**	**Established/Proper Name: olaratumab**
Applicant: Eli Lilly and Company	**Letter Date: 04/04/2016**	**Dosage Form: Injection, solution**
Chemical Type: Biologic	**Stamp Date: 2/24/2016**	**Strength: 10 mg/mL**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		x	

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☒	☐	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other_____	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	Olaratumab
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☒	☐	
25.	Other_____		☐	☒	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☒	☐	Container closure integrity test for stability samples
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☒	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product	☒ Y	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	Y			
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒ Y Y Y Y Y	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒ ✓ ✓	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance	☒	☐	☐	

C. FILING CONSIDERATIONS					
	manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes 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				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes 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 ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies*)	☐	☐	☒	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☒	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the 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	☒	☐	☐	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	x			(b) (4) [redacted]

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

/s/

CHIKAKO TORIGOE
04/05/2016

RASHMI RAWAT
04/05/2016