CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: 28 July, 2014

To: Administrative File, STN 125514/0

From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB

Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB

Subject: New Biologic License Application (BLA)

US License: 0002

Applicant: Merck Sharp & Dohme Corp.

Facilities: (b) (4)

MedImmune, LLC; Frederick Manufacturing Center (FMC), 633/636/660 Research Court, Frederick, MD 21703-8619, USA (FEI: 3002617711)

Product: Keytruda (pembrolizumab, MK-3475)

Dosage: Sterile lyophilized powder in single-use 15-ml vials for reconstitution with SWFI to 50 mg/vial and further dilution with 0.9% sodium chloride for injection prior to IV administration.

Indication: Breakthrough therapy for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab; orphan drug for the treatment of Stage IIB – IV malignant melanoma

Due date: 28 October 2014

Recommendation for Approvability: The drug substance part of BLA 125514 is recommended for approval from a microbial control and microbiology product quality perspective .

Review Summary

Merck Sharp & Dohme Corporation has submitted BLA 125514 to license pembrolizumab drug substance and drug product.

BLA 125514 was submitted in eCTD as a rolling BLA; the original application was submitted on November 22, 2013 and contained modules 1, 2, and 4; module 3 was submitted on December 20, 2013 in amendment 0001; amendment 0003 was submitted on January 30, 2014 with information regarding drug substance shipping validation in section 3.2.S.2.5 and 3.2.P.3.5. Amendment 0005 was submitted on February 27, 2014 and included the last portion of the BLA. Two different 3.2.S sections were provided to cover the drug substance manufacturing process in (b) (4)

88 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

---

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

/s/

REYES CANDAU-CHACON
07/28/2014

PATRICIA F HUGHES TROOST
07/28/2014

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

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

BLA	125514/0
APPLICANT	Merck Sharp & Dohme Corp.
US LICENSE NUMBER	0002
SUBMISSION REVIEWED	Original BLA
PRODUCT	KEYTRUDA™ (pembrolizumab, MK-3475)
MANUFACTURING FACILITY	**Drug Substance:** [redacted] (b) (4) [redacted] (b) (4) [redacted] MedImmune, LLC, Frederick Manufacturing Center, (FMC), 633/636/660 Research Court, Frederick, MD 21703-8619, USA (FEI No. 3002617711) **Drug Product:** Schering Plough Brinny Co., Ballinacurra Road, Innishannon, County Cork, Ireland FEI No. 3002808087
INDICATION	Treatment of unresectable or metastatic melanoma patients who have been previously treated with ipilimumab.
DOSAGE FORM	Powder for Solution for Infusion (50 mg)
ROUTE OF ADMINISTRATION	Intravenous
SUPPORTING DOCUMENTS	IND 110080, DMF [redacted] (b) (4), DMF [redacted] (b) (4), DMF [redacted] (b) (4), DMF [redacted] (b) (4), DMF [redacted] (b) (4)
CDER RECEIPT DATE	October 24, 2013
REVIEW ASSIGN DATE	October 31, 2013
REVIEW COMPLETE DATE	July 24, 2014
GRMP GOAL DATE	August 31, 2014
PDUFA GOAL DATE	October 24, 2014
PROJECT MANAGER	Sickafuse, Sharon
DIVISION	Division of Oncology Products 2
TO	S:\archive\BLA\125514\STN125514.rev.mem.BLA.07-24-2014.doc

1. PRODUCT QUALITY MICROBIOLOGY SUMMARY

I. EXECUTIVE SUMMARY

The subject of this BLA is KEYTRUDA™ (pembrolizumab, MK-3475), a recombinant human IgG4 antibody that binds to the human programmed cell death 1 (PD-1) receptor and blocks the interaction between the PD-1 receptor and its ligands (PD-LI and PD-L2). This blockage facilitates tumor regression. The proposed indication for KEYTRUDA™ is treatment of unresectable or metastatic melanoma that is refractory to ipilimumab treatment. Manufacture of pembrolizumab involves [redacted] (b) (4) MK-3475 drug substance is manufactured in two locations:

- [redacted] (b) (4)

- Frederick Manufacturing Center (FMC; Frederick, MD) of MedImmune, LLC; Drug Substance produced using FMC manufacturing proces [redacted] (b) (4)

MK-3475 Powder for Solution for Infusion (50 mg/vial) is a preservative-free, non-pyrogenic, lyophilized formulation for single-use. The proposed shelf-life for drug product is [redacted] (b) (4) at 2-8°C. After reconstitution with sterile water for injection to 25 mg/mL MK-3475, it is further diluted with 0.9% Sodium Chloride Injection, USP (normal saline) in an intravenous (IV) bag and the admixture is administered intravenously. This review covers assessment of microbial controls of the drug product manufacturing process and sterility assurance of drug product described in the original BLA and amendments [eCTD sequence numbers 0002 (Proprietary Name), 0003 (shipping), 0032 (labeling), 0036 (quality micro IR response), 0042 (quality micro IR response), and 0050 (microbial data to support storage of diluted drug product and LER studies and commitments)]. For a review of the microbial controls in drug substance manufacture, please see the review by Dr. Marie Candauchacon.

The drug product is manufactured at Schering Plough Brinny Co., located at Ballinacurra Road, Innishannon, Cork, Ireland. FEI No. 3002808087. The pre-license inspection of this site was waived. The site has under gone surveillance inspection and has an acceptable compliance status.

II. Recommendation and Conclusion on Approvability

Section 3.2.P of the BLA pertaining to product quality microbiology of the drug product manufacturing process was reviewed. The BLA, as amended, is recommended for approval from a product quality microbiology perspective pending proposed labeling changes (see section on LABELING) and with the following post-marketing commitment.

PMC: To conduct a study to assess the endotoxin recovery at various time-points from 3 drug product lots spiked with Control Standard Endotoxin (7.5 EU/mL and 10 EU/mL) in vials using the Kinetic Turbidometric Assay. The study protocol and report with data should be submitted by (date to be provided by applicant).

The drug product manufacturing site, Schering Plough Brinny Co., located at Ballinacurra Road, Innishannon, Cork, Ireland (FEI No. 3002808087) was inspected January 27-Februaury 4, 2014 and covered the profiles (b) (4). The inspection was classified as NAI.

70 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

CGMP STATUS:

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

CONCLUSION:

I. Section 3.2.P of the BLA pertaining to product quality microbiology of the drug product manufacturing process was reviewed. The BLA, as amended, is recommended for approval from a product quality microbiology perspective pending proposed labeling changes (see section on LABELING) and with the following post-marketing commitment.

   PMC: To conduct a study to assess the endotoxin recovery at various time-points from 3 drug product lots spiked with Control Standard Endotoxin (7.5 EU/mL and 10 EU/mL) in vials using the Kinetic Turbidometric Assay. The study protocol and report with data should be submitted by (date to be provided by applicant).

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

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

STN 125514, Merck Sharp & Dohme Corp

SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Kalavati Suvarna, Ph.D. Date:

Concurring BMAB Team Leader: Patricia. F. Hughes, Ph.D. Date:

cc:

OND/OHOP/DOP II RPM/Sickafuse, Sharon

OC/OMPQ/BMAB TL/Hughes, Patricia

OND/OHOP/DOP II MO/Chuk, Meredith

OND/OHOP/DOP II CDTL /Theoret, Marc

3 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

---

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

/s/

KALAVATI C SUVARNA
07/24/2014

PATRICIA F HUGHES TROOST
07/25/2014

Determining When Pre-License / Pre-Approval Inspections are Necessary

Inspection Waiver Memorandum

Date: 30 May 2014
From: Kalavati Suvarna, Ph.D., CDER/OC/OMPQ/BMAB
Deborah Schmiel, Ph.D., OPS/OBP/DMA
Rashmi Rawat, Ph.D., OPS/OBP/DMA
To: BLA File – STN 125514/0
Subject: Recommendation to waive a pre-approval inspection
Sponsor: Merck Sharp & Dohme Corp
Manufacturing Facility: Schering Plough Brinny Co., Ballinacurra Road, Innishannon, Cork, Ireland (FEI: 3002808087).
Product: Proposed name KEYTRUDA (pembrolizumab, MK-3475)
Indication: Treatment of unresectable or metastatic melanoma patients who have been previously treated with ipilimumab
Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/BMAB

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that Schering Plough Brinny Company has been approved to manufacture multiple CDER products using the same manufacturing process, we recommend that the pre-approval inspection of the Schering Plough Brinny Company drug product manufacturing facility in Cork, Ireland (FEI: 3002808087) be waived for STN 125514/0.

Clearance Routing

{See appended electronic signature page}

_____

Zhihao Peter Qiu, Ph.D.
Acting Director, Division of Manufacturing and Product Quality, Office of Compliance, CDER

{See appended electronic signature page}

_____

Kathleen Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER

3 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

---

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

/s/

KALAVATI C SUVARNA
06/05/2014

PATRICIA F HUGHES TROOST
06/05/2014

DEBORAH H SCHMIEL
06/05/2014

RASHMI RAWAT
06/06/2014

KATHLEEN A CLOUSE STREBEL
06/06/2014

ZHIHAO PETER QIU
06/09/2014

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

BLA/NDA Number:	Applicant:	Stamp Date:
125514/0	Merck Sharp & Dohme Corp	2/27/2014

Established/Proper Name: Keytruda (pembrolizumab)
BLA/NDA Type: Original

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y	
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 Y Y Y N Y N Y N Y N Y N Y N Y N	Defer to OBP

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 shared or divided manufacturing arrangement	Y N	Not applicable

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info	Y	Defer to OBP
○ nomenclature		
○ structure (e.g. sequence, glycosylation sites)		
○ properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	OBP has the lead; BMAB reviews bioburden and endotoxin.
○ batch numbering and pooling scheme	Y	
○ cell culture and harvest	Y	
○ purification	Y	
○ filling, storage and shipping	Y	
❑ control of materials	Y	Defer to OBP
○ raw materials and reagents		
○ biological source and starting materials		
○ cell substrate: source, history, and generation		
○ cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	OBP has the lead; BMAB reviews [redacted] (b) (4)
○ justification of specifications	Y	Justification for microbial quality [redacted] (b) (4) [redacted] (b) (4) will be asked during the review cycle
○ stability	Y N	Defer to OBP

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

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	OBP has the lead; BMAB reviews validation data, microbial control strategy, process hold times, (b) (4) Some microbial quality (b) (4) results missing for the process validation batches at the (b) (4) facility.
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	Defer to OBP
❑ characterization of drug substance	Y	Defer to OBP
❑ control of drug substance	Y	OBP has the lead; bioburden & endotoxin evaluation in BMAB review
○ specifications	Y	
○ justification of specs.	Y	
○ analytical procedures	Y	
○ analytical method validation	Y	
○ batch analyses	Y	
❑ reference standards	Y	Defer to OBP
❑ container closure system	Y	
❑ stability	Y	OBP has the lead; bioburden and endotoxin tested only for the (b) (4) drug substance because FMC drug substance is (b) (4).
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval		
○ protocol	Y	
○ results	Y	
○ method validation	Y N	
Drug Product [3.2.P] [Dosage Form]		Vial presentation – lyophilized drug product 50 mg
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	Y N	No preservative
○ container-closure integrity		
❑ 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	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y	
○ Filter validation	Y	Study protocol and report not included for (b)(4) validation. Only summary is provided.
○ Component, container, closure depyrogenation and sterilization validation	Y Y	
○ Validation of aseptic processing (media simulations)	Y Y	
○ Environmental Monitoring Program	Y	
○ Lyophilizer validation	Y	
○ Other needed validation data (hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	OBP Lead
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	Sterility and endotoxin acceptance criteria included
❑ reference standards or materials	Y N	OBP Lead
❑ container closure system [3.2.P.7]	Y	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF & LOAs		
○ administration device(s)		
❑ stability	Y	OBP Lead
❑ 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 responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y N	
○ Validation of aseptic processing (media simulations)	Y N	
○ Environmental Monitoring Program		
○ Lyophilizer sterilization validation	Y N Y N	
○ 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		
○ specifications (vial, elastomer, drawings)	Y N Y N	
○ availability of DMF & LOAs		
❑ stability		
❑ summary		
❑ post-approval protocol and commitment	Y N	
❑ pre-approval		
○ protocol		
○ results		
Other components to be marketed (full description and supporting data, as listed above):		Not applicable.

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

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients	 Y Y N Y N	 OBP Lead OBP Lead
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y Y	 OBP Lead OBP Lead
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	OBP Lead
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	OBP Lead
Data demonstrating comparability of product to be marketed to that used in	Y	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
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 results for 3 drug product lots included. Endotoxin detection is by Kinetic turbidometric method. (b) (4) in-process control test
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	OBP Lead
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.

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

Reyes Candau-Chacon, Ph.D. (Drug Substance) 3/31/2014
Kalavati Suvarna, Ph.D. (Drug Product) 3/31/2014

Product Quality Reviewer(s) Date

Patricia Hughes, Ph.D.	3/31/2014
Team Leader	Date

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

/s/

KALAVATI C SUVARNA
03/31/2014

REYES CANDAU-CHACON
03/31/2014

PATRICIA F HUGHES TROOST
04/01/2014