CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: BLA125514/000

Stamp Date: 18-NOV-2013

Regulatory: 28-OCT-2014

Applicant: (b) (4)

, ,

Priority: 1

Org. Code: 106

Action Goal:

District Goal:

Brand Name: UNKNOWN

Estab. Name:

Generic Name:

Product Number; Dosage Form; Ingredient; Strengths

001; POWDER, FOR SOLUTION; PEMBROLIZUMAB; 50MG

Application Comment: BLA 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 (on 10-MAR-2014 by T. WILSON () 2404024226)

FDA Contacts:				
	K. SUVARNA	Facility Reviewer	(HFD-520)	3017960821
	D. SCHMIEL	Prod Qual Reviewer		2404024126
	R. CANDAU-CHACON	Micro Reviewer	(HFD-320)	3017960488
	M. PACIGA	Product Quality PM	(HFD-123)	3017961660
	S. SICKAFUSE	Regulatory Project Mgr	(HFD-107)	3017961462

Overall Recommendation:					
	ACCEPTABLE	on 29-AUG-2014	by R. PRABHAKARA	()	3017964668
	PENDING	on 29-AUG-2014	by EES_PROD		
	ACCEPTABLE	on 29-AUG-2014	by R. PRABHAKARA	()	3017964668
	ACCEPTABLE	on 29-AUG-2014	by R. PRABHAKARA	()	3017964668
	PENDING	on 29-AUG-2014	by EES_PROD		
	PENDING	on 29-AUG-2014	by EES_PROD		
	PENDING	on 19-MAR-2014	by EES_PROD		
	PENDING	on 10-MAR-2014	by EES_PROD		
	PENDING	on 10-MAR-2014	by EES_PROD		

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: RELEASE AND STABILITY TESTING FOR ID BY COMPETITIVE BINDING ELISA (on 06-AUG-2014 by T. WILSON () 2404024226)

RELEASE AND STABILITY TESTING FOR ID BY COMPETITIVE BINDING ELISA - FMC DRUG SUBSTANCE AND (b) (4) DRUG PRODUCT (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-MAR-2014				WILSONT
OC RECOMMENDATION	07-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO DO	29-AUG-2014	10-Day Letter			PRABHAKARAR
SITE HAS AN INITIAL CLASSIFICATION OF NAI.					
DO RECOMMENDATION	29-AUG-2014			ACCEPTABLE	MROSE
SEE EXPEDITED REVEIW IN CMS WORK #78260					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND INITIALLY CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE PER DO REVIEW (CMS #78260)					

FDA CDER EES
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Establishment: **CFN:** **FEI:** 3002617771

MEDIMMUNE LLC

633 RESEARCH COURT
FREDERICK, MD 21703

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE OTHER TESTER

Establishment Comment: DS MANUFACTURE, RELEASE AND STABILITY TESTING (on 10-MAR-2014 by T. WILSON () 2404024226)

DS MANUFACTURE (FMC), RELEASE AND STABILITY TESTING (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

Profile: BIOTECHNOLOGY DERIVED API (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-MAR-2014				WILSONT
INSPECTION PERFORMED	25-APR-2014		25-APR-2014		PRABHAKARAR
SUBMITTED TO BMR	19-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY BLT-DO FROM SEPTEMBER 17-21, 2012 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SUEVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE MANUFACTURING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA.					
ASSIGNED INSPECTION TO BMR	10-JUL-2014	Product Specific and GMP Inspection			PRABHAKARAR
BLA PILOT - BMAB WILL PERFORM A PLI IN SUPPORT OF THIS ORIGINAL BLA.					
INSPECTION SCHEDULED	10-JUL-2014		25-APR-2014		PRABHAKARAR
EIR RECEIVED BY OC	26-AUG-2014				PRABHAKARAR
BMR RECOMMENDATION	28-AUG-2014			ACCEPTABLE	PRABHAKARAR
BMAB HAS INDICATED THAT THIS SITE IS ACCEPTABLE FOR THE MANUFACTURING OPERATIONS LISTED IN BLA 125514/0. THE EIR SHOULD BE REVIEWED AND FACTS CLOSED OUT BY A COMPLIANCE OFFICER IN DGMPA BEFORE A FINAL OC REC IS ENTERED INTO EES.					
OC RECOMMENDATION	28-AUG-2014			ACCEPTABLE	CAPACCIDANIC
SEE CMS CASE #78163 THIS SITE WAS INSPECTED BY CDER-OMPQ FROM 4/21/2014 - 4/25/2014 AND CLASSIFIED VAI. THIS WAS A PRE-LICENSE INSPECTION COVERING PEMBROLIZUMAB DRUG SUBSTANCE MANUFACTURING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.					

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1036761 **FEI:** 1036761

MERCK SHARP & DOHME, WILSON FACILITY

4633 MERCK RD W
WILSON, NC 278939613

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE PACKAGER

Establishment Comment: PACKAGING AND LABELING AND FINAL DRUG PRODUCT RELEASE SITE - (b) (4) DRUG PRODUCT (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)
PACKAGING AND LABELING AND FINAL DRUG PRODUCT RELEASE SITE - (b) (4) DRUG PRODUCT (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)
PACKAGING AND LABELING AND FINAL DRUG PRODUCT RELEASE SITE (on 08-APR-2014 by T. WILSON () 2404024226)
PACKAGING AND LABELING AND FINAL DRUG PRODUCT RELEASE SITE (on 12-MAR-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

(b) (4), LYOPHILIZED NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	08-APR-2014				WILSONT
OC RECOMMENDATION	16-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY ATL-DO FROM JUNE 25 ¿ 28, 2013 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING, PACKAGING AND LABELING OPERATIONS. THE CTX AND (b) (4) (b) (4)) PROFILES WERE UPDATED AND ARE ACCEPTABLE.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY ATL-DO FROM JUNE 25-28, 2013 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING, PACKAGING AND LABELING OPERATIONS. THE CTX AND (b) (4) (b) (4) PROFILES WERE UPDATED AND ARE ACCEPTABLE.					
SUBMITTED TO OC	19-MAR-2014				WILSONT
OC RECOMMENDATION	16-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY ATL-DO FROM JUNE 25 ¿ 28, 2013 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING, PACKAGING AND LABELING OPERATIONS. THE CTX AND (b) (4) (b) (4) PROFILES WERE UPDATED AND ARE ACCEPTABLE.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY ATL-DO FROM JUNE 25-28, 2013 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING, PACKAGING AND LABELING OPERATIONS. THE CTX AND (b) (4) (b) (4) PROFILES WERE UPDATED AND ARE ACCEPTABLE.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
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Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: RELEASE AND STABILITY TEST EXCEPT FOR BIOBURDEN AND ENDOTOXIN
RELEASE AND STABILITY TESTING FOR DRUG PRODUCT (b) (4) (on 12-MAR-2014 by T. WILSON () 2404024226)
RELEASE AND STABILITY TEST EXCEPT FOR BIOBURDEN AND ENDOTOXIN
RELEASE AND STABILITY TESTING FOR DRUG PRODUCT (b) (4) - (b) (4) DRUG PRODUCT (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-MAR-2014				WILSONT
OC RECOMMENDATION	07-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE. ALTHOUGH THIS SITE IS NOT PROFILED AS CTL, FACTS INDICATES THAT LABS WERE COVERED DURING THE LAST CGMP INSPECTION OF THIS FIRM.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE. ALTHOUGH THIS SITE IS NOT PROFILED AS CTL, FACTS INDICATES THAT LABS WERE COVERED DURING THIS INSPECTION.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: CONTAINER CLOSURE INTEGRITY TESTING (on 12-MAR-2014 by T. WILSON () 2404024226)

CONTAINER CLOSURE INTEGRITY TESTING - (b) (4) DRUG PRODUCT (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	19-MAR-2014				WILSONT
SUBMITTED TO DO	07-APR-2014	10-Day Letter			PRABHAKARAR
BLA PILOT - SITE HAS AN INITIAL GMP STATUS.					
DO RECOMMENDATION	11-APR-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	16-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND INITIALLY CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND HAS AN INITIAL STATUS OF ACCEPTABLE. PLEASE RESUBMIT THIS TBEER 15-30 DAYS PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION OF THIS SITE.					
SUBMITTED TO DO	29-AUG-2014	10-Day Letter			PRABHAKARAR
SITE HAS AN INITIAL CGMP STATUS					
DO RECOMMENDATION	29-AUG-2014			ACCEPTABLE	MROSE
EXPEDITED REVEIW BASED ON CMS WORK #78263					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND INITIALLY CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE BASED UPON AN EXPEDITED REVIEW PERFORMED BY OMPQ/DIDQ (SEE CMS WORK ACTIVITY #78263).					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9616653 **FEI:** 3002808087

SCHERING-PLOUGH (BRINNY) CO.

INNESHANNON
CO. CORK, CORK, IRELAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, RELEASE AND STABILITY TESTING, BULK DRUG PRODUCT RELEASE (on 12-MAR-2014 by T. WILSON () 2404024226)

DRUG PRODUCT MANUFACTURING, RELEASE AND STABILITY TESTING, BULK DRUG PRODUCT RELEASE - (b) (4) DRUG PRODUCT (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

Profile: (b) (4) LYOPHILIZED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	19-MAR-2014				WILSONT
SUBMITTED TO BMR	19-JUN-2014	Request BMR Evaluation			PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM JANUARY 27 - FEBRUARY 4, 2014 AND IS NOT YET CLASSIFIED. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND HAS AN INITIAL STATUS OF ACCEPTABLE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA.					
RESUBMISSION FROM BMR	10-JUL-2014	Waive Inspection			PRABHAKARAR
BLA PILOT - PETER QIU (BMAB) INDICATED IN AN EMAIL DATED 6/23/2014 THAT THIS FIRM WILL NOT REQUIRE A PLI BEFORE APPROVAL OF BLA 125514/000.					
SUBMITTED TO DO	10-JUL-2014	10-Day Letter			PRABHAKARAR
BLA PILOT - THIS SITE IS A FD MANUFACTURER WITH AN INITIAL GMP STATUS.					
UNDER REVIEW	01-AUG-2014				MROSE
DO RECOMMENDATION	29-AUG-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	CAPACCIDANIC
BLA PILOT - THIS SITE WAS INSPECTED BY IOG FROM 1/27/2014 - 2/4/2014 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) (4) AND (b) (4) PROFILES WERE UPDATED AND ARE ACCEPTABLE.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: BIOBURDEN TESTING OF (b) (4) (on 10-MAR-2014 by T. WILSON () 2404024226)

BIOBURDEN TESTING OF (b) (4) - FMC DRUG SUBSTANCE ONLY (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-MAR-2014				WILSONT
OC RECOMMENDATION	07-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) ON (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY (b) (4) FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4) - FMC DRUG SUBSTANCE ONLY (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)

(b) (4) (on 10-MAR-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-MAR-2014				WILSONT
OC RECOMMENDATION	07-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY (b) (4) FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4) TESTING: (b) (4) - FMC DRUG SUBSTANCE ONLY (on 29-AUG-2014 by R. PRABHAKARA () 3017964668)
(b) (4) TESTING (b) (4) (on 10-MAR-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	10-MAR-2014				WILSONT
SUBMITTED TO DO	07-APR-2014	10-Day Letter			PRABHAKARAR
BLA PILOT - SITE HAS AN INITIAL GMP STATUS.					
DO RECOMMENDATION	07-APR-2014			ACCEPTABLE	VMATUSOV
PREVIOUS GMP EI UNDER PAC 56002M DATED (b) (4) IS CLASSIFIED AS NAI. PROFILE CTX IS LISTED AS ACCEPTABLE. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.					
OC RECOMMENDATION	09-APR-2014			ACCEPTABLE	PRABHAKARAR
BLA PILOT - THIS SITE WAS INSPECTED BY (b) (4) FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY (b) (4) FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.					

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

/s/

RANJANI PRABHAKARA
08/29/2014

BLA STN 125514

Pembrolizumab

Manufacturer: Merck

Team Leader: Rashmi Rawat, Ph.D.

Division of Monoclonal Antibodies
Office of Biotechnology Product

Product Quality Review Data Sheet

(Includes only information updated since the initial review finalized on Aug. 1, 2014)

1. **BLA#** STN 125514-0

2. **REVIEW #:** 2 (Addendum 1)

3. **REVIEW DATE:** August 29, 2014

4. **REVIEWER(s):** Rashmi Rawat, Ph.D., Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS SINCE THE FINALIZATION OF THE INITIAL REVIEW:**

Communication/Documents	Date
Information Request-5	07-31-2014
Information Request-6	08-15-2014
Teleconference	08-26-2014

6. **SUBMISSION(S) REVIEWED UNDER THIS ADDENDUM:**

Submission(s) Reviewed	Document Date
STN 125514, eCTD#076	08-05-2014
STN 125514, eCTD#084	08-19-2014
STN 125514, eCTD#088	08-27-2014
STN 125514, eCTD#091	08-28-2014

17. **ADMINISTRATIVE**

Signature Block
Rashmi Rawat, Ph.D., Team Leader, Division of Monoclonal Antibodies

Sarah Kennett, Ph.D., Review Chief, Division of Monoclonal Antibodies

I. Recommendation

The data submitted in this Biologics License Application (BLA) support the conclusion that the manufacture of Keytruda (pembrolizumab; MK-3475) 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 multiple production runs at both manufacturing sites presented. It is recommended that Keytruda (pembrolizumab) be approved for human use (under conditions specified in the package insert).

I recommend an expiry period of (b) (4) month for FMC MK-3475 drug substance when stored at (b) (4)

The stability protocols are acceptable and the updated stability data will be reported to the BLA in the Annual Report.

I recommend an approval of the proposed release specifications for pembrolizumab drug product and drug substance

II. List of Deficiencies To Be Communicated

There are no CMC-related deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments

Same as listed in the primary review dated 08/01/14.

(b) (4)

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

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

/s/

RASHMI RAWAT
08/29/2014

SARAH B KENNETT
08/29/2014

First Approval for Indication
Breakthrough and Priority Review

Recommendation: Approval

BLA 125514
Review # 01
Review Date August 8, 2014

Drug Name/Dosage Form	**Keytruda/For Injection**
Strength/Potency	**50 mg**
Route of Administration	**Intravenous**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of unresectable or metastatic melanoma in patients whose disease has progressed after treatment with ipilimumab, and a BRAF (b) (4) inhibitor (b) (4) (b) (4)**
Applicant/Sponsor	**Merck**

Communication/Document	Date
Information Request #01(IR#01)	May 14, 2014
Information Request #02 (IR#02)	July 11, 2014
Information Request #03 (IR#03)	July 24, 2014
Information Request #04 (IR#04)	July 29, 2014
Information Request #05 (IR#05)	July 30, 2014

Submission	Date Received	Review Completed (Yes/No)
Response to FDA IR#01 (eCTD seq. #0036)	May 30, 2014	Yes
Response to FDA IR#02 (eCTD seq. #0057)	July 21, 2014	Yes
Response to FDA IR#02 (stability update) eCTD seq.#0060)	July 22, 2014	Yes
Amendments and Commitments made in previous responses to IR's (eCTD seq. #0062)	July 24, 2014	Yes
Additional Information / Corrections (eCTD #0063)	July 24, 2014	Yes
Response to FDA IR#03 (eCTD seq. #0069)	July 29, 203014	Yes
Response to Issues in FDA IR#04 (e-mail communication)	July 31, 2014	Yes
Response to Issues Related to DS, DP release and stability specifications (e-mail communication)	August 1, 2014	Yes

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Mark Paciga	DMA/OBP/OPS
Drug Product	Deborah Schmiel	DMA OBP/OPS
Immunogenicity	Deborah Schmiel	DMA OBP/OPS
Biologics Manufacturing and Assessment Branch	Kalavati C. Suvarna (DP) Reyes Candau-Chacon (DS)	OC/OMPQ/DGMPA/BMAB
Labeling	Jibril Abdus-Samad	OBP/OPS
Labeling	Otto L. Townsend	OPE/DMEPA
Secondary Reviewer	Rashmi Rawat	OBP/DMA
Tertiary Reviewer	Sarah Kennett	OBP/DMA

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Sharon Sickafuse	DOPII/OHOP/CDER
Cross-disciplinary Team Lead	Marc Theoret	DOPII/OHOP/CDER
Medical Officer	Meredith K. Chuk, Jennie T. Chang	DOPII/OHOP/CDER
Pharm/Tox	Shawna L. Weis	CDER/OCP/PS
Clinical Pharmacology	Runyan Jin, Hongshan Li	CDER/OCP/
Biometrics	Emmanuel Sampene	CDER/OB/DBV

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)		Type V (b) (4)	Provided in BLA	Cross referenced by BLA (b) (4) Review in DARTS 6/18/2014 found no CMC issues at this facility. No further review required as sufficient information was provided in BLA.
		Type III (b) (4)	Provided in BLA	Review in DARRTS 1/25/2013 adequate to support NDA (b) (4). No further review required as sufficient information was provided in BLA.
		Type III (b) (4)	Provided in BLA	Review in DARRTS 1/24/2014 adequate to support NDA (b) (4) No further review required as sufficient information was provided in BLA.
		Type III (b) (4)	Provided in BLA	Review in DARRTS 2/11/2014 adequate to support NDA (b) (4) No further review required as sufficient information was provided in BLA.

B. Other Documents: *None*

3. CONSULTS: *None*

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125514 for Keytruda manufactured by Merck pending acceptable compliance checks and resolution of the issues regarding the primary and secondary reference standard (RS) qualification and primary RS requalification. The data submitted in this application are adequate to support the conclusion that the manufacture of Keytruda 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 the conditions specified in the package insert.

b. Action letter language

- Manufacturing location:
  - Drug substance
    (i) (b) (4)
    (ii) MedImmune, LLC, Frederick Manufacturing Center Frederick, MD (FMC)
  - Drug product
    Schering Plough Brinny Co., County Cork, Ireland

- Fill sized and dosage form – 50 mg single dose vial
- Dating period:
  - Drug product: 18 months; 2-8 ºC
  - Drug substance: For (b) (4) drug substance: (b) (4)
    For FMC drug substance: (b) (4)
  - 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 if exempted – specified product
    - Note: We exempt specified products according to 601.2a

c. Benefit/Risk Considerations

The current pembrolizumab release specifications include a commercial host cell protein (HCP) ELISA method for evaluating HCP levels in drug substance (DS). This method detects various proteins from the pembrolizumab-producing (b) (4) cell line. However, this method is not optimal for the detection of proteins from the pembrolizumab producing (b) (4) cell line. As a PMC, the sponsor was asked to develop a process-specific HCP-antiserum for use in HCP ELISA that would be able to detect a wider range of pembrolizumab process-specific host cell proteins and thereby increase the sensitivity of the HCP ELISA method to detect HCP in DS. The DS release specifications approved under the BLA are sufficient to ensure adequate

quality and safety of pembrolizumab for the initial marketed product. The improvement and implementation of a process-specific HCP assay will provide better control of HCP levels in DS.

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

1. To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the pembrolizumab drug substance release program. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.

2. To re-evaluate pembrolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

3. To re-evaluate pembrolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

The table below provides a summary of product related critical quality attributes and are relevant to both drug substance and drug product. The table includes the identification of the various attributes along with their risk management.

Identification of other CQAs associated with just drug substance (e.g., process related impurities, adventitious agents, pH, appearance, etc.) or drug product are described in separate risk tables in section B, Drug Substance Quality Summary and section C, Drug Product Quality Summary.

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Introduction	Control Strategy	Other
(b) (4)				

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/s/

RASHMI RAWAT
08/08/2014

SARAH B KENNETT
08/08/2014

KATHLEEN A CLOUSE STREBEL
08/08/2014

BLA STN 125514

Pembrolizumab (MK-3475)

Merck Sharp and Dohme Corp.

Reviewer: Mark Paciga, Ph.D.
Reviewer: Deborah Schmiel, Ph.D.
LC/TL Reviewer: Rashmi Rawat, Ph.D.
Division of Monoclonal Antibodies

OBP CMC Review Data Sheet

1. **BLA#:** STN 125514

2. **REVIEW DATE:** August 1, 2014

3. **PRIMARY REVIEW TEAM:**
Biometrics: Emmanuel Sampene
Clinical: Meredith K. Chuk, Jennie T. Chang
Non-Clinical: Shawna L. Weis
Product Quality Team: Mark Paciga, Deborah Schmiel, Rashmi Rawat
BMT or Facilities: Kalavati C. Suvarna, Reyes Candau-Chacon
Clinical Pharmacology: Runyan Jin, Hongshan Li
Labelling: Otto L. Townsend, Sharon R. Mills
OBP Labeling: Jibril Abdus-Samad
Marketing and Advertising Reviewer: Carole C. Broadnax, Olga Salis
RPM: Sharon Sickafuse

4. **MAJOR 21st Century Review DEADLINES**
Filing Meeting: April 10, 2014
Mid-Cycle Meeting: June 26, 2014
Wrap-Up Meeting: September 18, 2014
Primary Review Due: August 1, 2014
Secondary Review Due: August 5, 2014
CDTL Memo Due: September 30, 2014
PDUFA Action Date: October 28, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information Request #01(IR#01)	May 14, 2014
Information Request #02 (IR#02)	July 11, 2014
Information Request #03 (IR#03)	July 24, 2014
Information Request #04 (IR#04)	July 29, 2014
Information Request #05 (IR#05)	July 30, 2014

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

Submission	Date Received	Review Completed (Yes/No)
Response to FDA IR#01 (eCTD seq. #0036)	May 30, 2014	Yes
Response to FDA IR#02 (eCTD seq. #0057)	July 21, 2014	Yes
Response to FDA IR#02 (stability update) eCTD seq.#0060)	July 22, 2014	Yes

Amendments and Commitments made in previous responses to IR's (eCTD seq. #0062)	July 24, 2014	Yes
Additional Information / Corrections (eCTD #0063)	July 24, 2014	Yes
Response to FDA IR# (eCTD seq. #0069)	July 29, 203014	Yes
Response to Issues in FDA IR#04 (e-mail communication)	July 31, 2014	Yes
Response to Issues Related to DS, DP release and stability specifications (e-mail communication)	August 1, 2014	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Keytruda
   b. Trade Name: Keytruda
   c. Non-Proprietary/USAN: Pembrolizumab
   d. CAS name: Anti-(human protein PDCD1 (programmed cell death 1) immunoglobulin G4 (b) (4)
   e. Common name: MK-3475, SCH900475
   f. INN Name: Pembrolizumab
   g. Compendial Name: N/A
   h. OBP systematic name: Humanized anti-PD-1_mAb (H409A11) IgG4
   i. Other Names: MK-3475, SCH900475

8. **PHARMACOLOGICAL CATEGORY:** humanized IgG4 monoclonal antibody against (programmed cell death 1) PD-1
9. **DOSAGE FORM:** lyophilized powder
10. **STRENGTH/POTENCY:**
The drug product is a lyophilized powder intended for single-use. MK-3475 powder for solution for infusion, single-use 50 mg/vial is reconstituted with sterile water for injection and further diluted with normal saline prior to intravenous administration.

Potency is determined by a competitive binding ELISA that measures the ability of MK-3475 to compete with PD-L1 for binding to PD-1-Fc immobilized on an ELISA plate. The potency percentage is based on a comparison to a reference standard.

Dating period for the vialed drug product is 18 months when stored at 5 $\pm$3 °C.

11. **ROUTE OF ADMINISTRATION:** intravenous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	Type V (b) (4)	Provided in BLA	Cross referenced by BLA (b) (4) Review in DARTS 6/18/2014 found no CMC issues at this facility. No further review required as sufficient information was provided in BLA.
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13. INSPECTIONAL ACTIVITIES

FMC

A pre-licensure inspection (PLI) of the FMC drug substance manufacturing facility was conducted following a request by the Office of Manufacturing and Product Quality, Office of Compliance, CDER, under FEI No. 3002617771. The inspection covered the manufacturing operations for BLA STN 125514 for pembrolizumab drug substance at MedImmune LLC Frederick Manufacturing Center, Frederick, MD, USA. The inspection was conducted on April 21-25, 2014 by BMAB reviewers, Patricia F. Hughes and Reyes Candau-Chacon as well as product reviewers Subramanian Muthukkumar and Mark Paciga in accordance with applicable section of CP 7356.002M, Inspection of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of pembrolizumab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

Two 483 observations were identified by the BMAB and product quality team during the PLI. 1) Procedures are not designed to ensure that correct labels are used. For example, both manufacturing personnel and QA failed to compare the accuracy of the printed label with the instructions in the MPR. In another case drug substance bathes were not labeled with the lot number of the product. Several other labeling deviations were also noted. 2) In several instances written procedures were not followed. These discrepancies were attributed to human error or unclear instructions. Examples included, but were not limited to an operator (b) (4) (b) (4) using in incorrect version of the MPR and several instances where SOP was not followed and incorrect expiry dates were assigned to (b) (4).

(b) (4)

[redacted]

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
X	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS: NONE

17. ADMINISTRATIVE

A. Signature Block

Primary Reviewers: Mark Paciga, Ph.D.
Deborah Schmiel, Ph.D.
OBP/Division of Monoclonal Antibodies

Team Leader: Rashmi Rawat, Ph.D.
OBP/Division of Monoclonal Antibodies

Review Chief: Sarah Kennett, Ph.D.
OBP/Division of Monoclonal Antibodies

B. CC Block: Sharon Sickafuse
DOP II BLA RPM

(b) (4)

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/s/

MARK PACIGA
08/01/2014

DEBORAH H SCHMIEL
08/01/2014

RASHMI RAWAT
08/01/2014

SARAH B KENNETT
08/01/2014

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: Pembrolizumab (Keytruda™)

BLA/NDA Type: Original BLA

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
❑ including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
❑ PI –non-annotated	Y	
❑ PI –annotated	Y	
❑ PI (electronic)	Y	
❑ Medication Guide	Y	
❑ Patient Insert	Y	
❑ package and container	Y	
❑ diluent	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 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]	N	
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	Not applicable
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y	
❑ Comparability Protocols	N	No comparability protocols are proposed

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	
Drug Substance [3.2.S]		
❑ general info	Y	
○ 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	
○ batch numbering and pooling scheme		
○ cell culture and harvest		
○ purification		
○ filling, storage and shipping		
❑ control of materials	Y	
○ 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	
○ justification of specifications	Y	
○ stability	Y	
❑ process validation (prospective plan,	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
results, analysis, and conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance	Y	
❑ control of drug substance	Y	
○ specifications	Y	
○ justification of specs.		
○ analytical procedures	Y	
○ analytical method validation	Y	
○ batch analyses	Y	
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability	Y	
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	N	Not applicable
○ 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	
○ Filter validation	Y	
○ Component, container, closure depyrogenation and sterilization validation	Y	
○ Validation of aseptic processing (media simulations)	Y	
○ Environmental Monitoring	Y	

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

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 sterilization validation ○ Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	N N N N N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	N	No other components are included
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	Y N	Defer to BMAB

CTD Module 3 Contents	Present?	If not, justification, action & status
prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	Y	
❑ novel excipients	N	Not applicable
USA Regional Information [3.2.R]		
❑ executed batch records	Y	
❑ method validation package	Y	
❑ comparability protocols	N	No comparability protocols are 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 of manufacture	Y	
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 N	Defer to BMAB
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	Y N	Defer to BMAB

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

Examples of Filing Issues	Yes?	If not, justification, action & status
alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	 Y N Y N Y N	
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	Not applicable
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	Defer to BMAB
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	Defer to BMAB

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.

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

Mark Paciga, Drug Substance and Deborah Schmiel, Drug Product	4/23/2014
Product Quality Reviewer(s)	Date
Branch Chief/Team Leader/Supervisor	Date
Division Director	Date

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/s/

DEBORAH H SCHMIEL
04/24/2014

MARK PACIGA
04/24/2014

RASHMI RAWAT
04/25/2014

KATHLEEN A CLOUSE STREBEL
04/25/2014