

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125554Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



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

Date: 12/05/2014
To: Administrative File, STN 125554/0
From: Steven Fong, Ph.D., Reviewer, CDER/OC/OMPQ/BMAB
Endorsement: Patricia Hughes, Ph.D. Team Leader, CDER/OC/OMPQ/BMAB
Subject: Original BLA
US License: 1713
Applicant: Bristol-Myers Squibb
Facility: Bristol-Myers Squibb Holdings Pharma, Ltd, Manati, Puerto Rico
FEI 2650089
Product: Nivolumab (Opdivo)
Dosage: 3 mg/kg administered intravenously over 60 minutes every two weeks. Provided in vials containing 40 mg/4 mL and 100 mg/10 mL of DP.
Indication: Treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.
Due date: PDUFA goal date: 03/08/2015

Recommendation on Approvability – The BLA, as amended, is recommended for approval from a product quality microbiology perspective.

Drug Product Review: Nivolumab DP Manufacture at Bristol-Myer Squibb Holdings Pharma, Ltd., Manati, Puerto Rico

Summary

The subject BLA proposes marketing of Nivolumab DP as a treatment for unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status. The Nivolumab API is a (b) (4) expressed, human monoclonal IgG4 antibody whose therapeutic activity is based on its ability to act as a highly specific programmed death immune checkpoint inhibitor. Nivolumab DP manufacture will be conducted at Bristol-Myers Squibb Holdings Pharma, Ltd., in Manati, Puerto Rico (BMS-Manati). Following formulation, the bulk DP is (b) (4) in 4.0 mL or 10.0 mL volumes into (b) (4) vials. The filled vials are stoppered (b) (4) sealed with aluminum crimp seals, and inspected. A LOA dated 07/03/2013 to review DMF (b) (4) was provided with the BLA submission. The current Review considers DP microbiology quality information provided in the submissions listed below in Table 1.

STN 125554 Bristol Myers Squibb Nivolumab

TABLE 1. Summary of Submissions reviewed in Current DP Microbiology Quality Review

eCTD Sequence Number	Support Document Number (SDN)	Receipt Date	IR Being Responded to	Comments
0000	1	07/30/2014	N/A	Original BLA
0008	9	10/06/2014	IR-1 submitted 09/26/2014	eCDT seq. 0008 contained rabbit pyrogen data and filter validation information.
0020	22	11/14/2014	IR-2 submitted 11/06/2014	eCTD seq. 0020 contained responses to microbiology quality questions regarding (b) (4) equipment requalification, shipping validation, the rabbit pyrogen test, and stability testing.
See footnote*	See footnote*	12/04/2014	IR-3 submitted 12/3/2014	The SDN received 12/04/2014 contained responses to questions regarding stopper bioburden limit and (b) (4) specificity.

*eCTD and SDN numbers had not yet been assigned to the 12/04/2014 response to IR-3 at the time of Review submission.

P DRUG PRODUCT:

P.1 Description of the Composition of the Drug Product

Descriptions of the Nivolumab DP and Nivolumab DP composition were presented, respectively, in Modules 3.2.P.1.1 and 3.2.P.1.2. Descriptions of the Nivolumab container closure system (CCS) were presented in Modules 3.2.P.1.4 and 3.2.P.7.1.

- **Description of drug product** – Nivolumab Injection DP is a sterile, single-use, preservative-free, isotonic aqueous solution for intravenous administration. The solution is clear to opalescent with a colorless to pale yellow tint, and contains Nivolumab API, sodium citrate, sodium chloride, mannitol, pentetic acid, polysorbate 80, HCl, NaOH, and WFI. The DP is provided in 40 mg/4 mL and 100 mg/10 mL formats, each of which is filled into 10 mL Type 1 (b) (4) glass vials. The vials are stoppered (b) (4), and sealed with 20 mm aluminum crimp seals with dark blue flip-off seals. Nivolumab DP may be administered undiluted at a concentration of 10 mg/mL, or further diluted with 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP to concentrations as low as 1 mg/mL.
- **Drug product composition** – The compositions of the 40 mg/4 mL and 100 mg/10 mL presentations of Nivolumab DP are presented below in Table 2. For both formats a (b) (4) (b) (4) is utilized to accommodate vial, needle, and syringe (b) (4).

TABLE 2. Compositions of Nivolumab 40 mg/4 mL and 100 mg/10 mL DP Presentations^{1,2}

Component	Quality Standard	Function	Quantity per Vial ³ for 40 mg/4 mL Format	Quantity per Vial ³ for 100 mg/10 mL Format
Nivolumab (BMS 936558)	BMS Specification ⁴	API	(b) (4)	(b) (4)
Sodium Citrate Dihydrate	USP, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	USP, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Mannitol	USP, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)
Pentetic Acid ⁵	USP	(b) (4)	(b) (4)	(b) (4)
Polysorbate 80	NF, Ph. Eur.	(b) (4)	(b) (4)	(b) (4)

STN 125554 Bristol Myers Squibb Nivolumab

Hydrochloric Acid ⁶	NF, Ph. Eur.	pH adjustment	q.s. to pH 6.0	q.s. to pH 6.0
Sodium Hydroxide ⁶	NF	pH adjustment	q.s. to pH 6.0	q.s. to pH 6.0
WFI	USP, Ph. Eur.	(b) (4)		
(b) (4)	NF, Ph. Eur.			

¹ The information in this table for the 40 mg/4 mL and 100 mg/10 mL presentations were taken, respectively, from sections in Module 3.2.P.1 entitled “Description and Composition of the Drug Product 40 mg/vial,” and “Description and Composition of the Drug Product 100 mg/vial.”

² Abbreviations: USP = United States Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; NF = National Formulary; q.s. = quantity sufficient; NA = Not Applicable.

³ Both the 40 mg and 100 mg formats contain a (b) (4) overfill to accommodate vial, needle, and syringe (b) (4) of the DP.

⁴ The BMS specifications for Nivolumab API were provided in Module 3.2.S.4.1, “Specifications”.

⁵ Pentetic acid is also known as diethylenetriaminepentaacetic acid (DTPA).

⁶ Diluted hydrochloric acid and sodium hydroxide may be used for pH adjustment.

(b) (4)

- Description of container closure system (CCS)** – The Nivolumab CCS was described in Modules 3.2.P.1.2.4 and 3.2.P.7. The primary packaging components are listed below in Table 3 and illustrated below in Figure 1 (Review Page 4). The components consist of a 10 mL, 20 mm (b) (4) type I (b) (4) vial, a (b) (4) stopper (b) (4), and a (b) (4) 20 mm aluminum seal with plastic flip-off cap. (b) (4)

TABLE 3. Nivolumab DP CCS Components*

CCS Component	Manufacturer	DMF	Description	Dimensions
10 mL Vial	(b) (4)			
20 mm (b) (4) Stopper				
20 mm aluminum crimp seal				

* The information in this table was taken from submission Module 3.2.P.7.

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- Acceptance Criteria and Results. The acceptance criteria for validation were based on the requirements in *Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E*, and *Guidance for Industry: ICH Q1A (R2) Stability Testing of New Drug Substances and Products, Section 2.2.7*. As per the guidances, the criteria required that no more than 0.5 log increases in growth occur relative to the previously measured values. The results for the 3 Nivolumab-containing infusion solutions and 2 control infusion solutions lacking DP are presented below in Table 30. These results were presented in graph format in submission Figures 3.2.P.2.5.2-1 through 3.2.P.2.5.2-7. For all solutions and test microorganisms the criteria were achieved: no species exhibited a more than 0.5 log increase in growth relative to the previously measured value. In some cases there was no increase at all or a decline in population. Some test microorganisms (b) (4) exhibited no viability by the end of the study.

cGMP Status

Please see the TB-EER assessment.

Conclusion

- I. The BLA, as amended, is recommended for approval from a sterility assurance and microbiology quality standpoint.
- II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.
- III. No inspectional follow-up items were identified.

Cc: Meredith Libeg, Joel Welch, Laurie Graham, Bo Chi, Zhihao Peter Qiu

Steven Fong -S

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ou=FDA, ou=People, cn=Steven Fong -S,
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File Name: 125554.rev.mem.BLA.DP.12.05.2014.Final

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

Date: 12/2/2014
To: Administrative File, STN 125554/0
From: Bo Chi, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Applications (BLA)
Applicant: Bristol-Myers Squibb Company
US License: 1713
Facility: Lonza Biologics, Incorporated
Portsmouth, NH
FEI: 3001451441
Product: Opdivo (Nivolumab)
Dosage: 100 mg/10 mL and 40 mg/4 mL, Intravenous Infusion
Indication: Melanoma
PDUFA date: March 30, 2015

Recommendation: The drug substance part of this BLA, as amended, is recommended for approval from product quality microbiology perspective with the following post-market commitment:

Re-evaluate and tighten the endotoxin limits [REDACTED] (b) (4)

[REDACTED]
Re-evaluate and tighten the endotoxin limits for the following additional samples: [REDACTED] (b) (4)

Review Summary

Bristol-Myers Squibb (BMS) submitted this Biologics License Application (BLA) for nivolumab for melanoma treatment. The drug substance (DS) is manufactured at Lonza, Portsmouth, NH. The drug product (DP) is manufactured at BMS, Manati, PR. The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of nivolumab drug substance from microbiology perspective.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Nivolumab is a human monoclonal antibody to programmed death-1 (PD-1) receptor. PD-1 receptor has important T-cell regulatory functions and mediates tumor-specific inhibition of T-cell responses in tumors. Nivolumab blocks the interaction of PD-1 ligands to the PD-1 receptor and restores T-cell immune response to tumor cells. Nivolumab drug substance contains (b) (4) nivolumab, (b) (4) Sodium Citrate, (b) (4) Sodium Chloride, (b) (4) Mannitol, (b) (4) Pentetic Acid, (b) (4) Polysorbate 80, pH 6.0. Nivolumab is produced in (b) (4)

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Drug substance manufacture and storage, drug substance release and stability testing

Lonza Biologics, Incorporated
101 International Drive
Portsmouth, New Hampshire 03801
FEI: 3001451441

Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps (3.2.S.2.4)

(b) (4)

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Environmental Assessment:

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.15(d) and 25.31(c) was provided by the sponsor.

cGMP Status:

A pre-license inspection was conducted at the Lonza facility on 9/29/2014—10/3/2014. A 4-item Form FDA 483 was issued at the end of the inspection. See TB-EER for GMP status of the facility.

Conclusion

I. The drug substance part of this BLA, as amended, is recommended for approval from product quality microbiology perspective with the following post-market commitment:

Re-evaluate and tighten the endotoxin limits (b) (4)

(b) (4)

(b) (4) Re-evaluate and tighten the endotoxin limits for the following additional samples: (b) (4)

(b) (4)

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the DMA reviewer.

III. A pre-license inspection was conducted at the Lonza facility on (b) (4) A 4-item Form FDA 483 was issued at the end of the inspection. See TB-EER for GMP status of the facility.

Cc: Chi
Hughes
Libeg

Primary reviewer signature

Bo Chi -
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ou=HHS, ou=FDA, ou=People,
cn=Bo Chi -A,
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Secondary reviewer signature

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

BLA/NDA Number: STN125554 **Applicant:** Bristol-Myers Squibb **Stamp Date:**

Established/Proper Name: Nivolumab **BLA/NDA Type:** Priority

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 <input type="checkbox"/> including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y N	N/A
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	Defer to OND and 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: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> compatible file formats <input type="checkbox"/> navigable hyper-links <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y Y	
Companion application received if a	Y N	N/A

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

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

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

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> ○ justification of specifications ○ stability 	Y	
<input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions)	Y	
<input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	Defer to OBP
<input type="checkbox"/> characterization of drug substance	Y N	Defer to OBP
<input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specifications <ul style="list-style-type: none"> ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses 	Y Y Y Y Y	
<input type="checkbox"/> reference standards	Y N	Defer to OBP
<input type="checkbox"/> container closure system	Y	
<input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	Y Y	
Drug Product [3.2.P] [Dosage Form]		
<input type="checkbox"/> description and composition	Y	
<input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity 	Y N	N/A (no preservative) (b) (4) method sensitivity not provided. Will request during review.
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> batch formula	Y	
<input type="checkbox"/> 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	
<input type="checkbox"/> controls of critical steps and intermediates	Y	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:		

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ Filter validation 	Y	Filter validation report will be requested in 74 day letter.
<ul style="list-style-type: none"> ○ Component, container, closure depyrogenation and sterilization validation 	Y	
<ul style="list-style-type: none"> ○ Validation of aseptic processing (media simulations) 	Y	
<ul style="list-style-type: none"> ○ Environmental Monitoring Program 	Y	
<ul style="list-style-type: none"> ○ Lyophilizer validation ○ Other needed validation data (hold times) 	Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	Defer to OBP.
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	Information and data regarding low endotoxin recovery provided in Module 3.2.P.5.3 reports entitled "Validation of Endotoxin", "Validation Report of Endotoxin", and "Endotoxin LER Protocol".
<input type="checkbox"/> reference standards or materials	Y N	Defer to OBP.
<input type="checkbox"/> container closure system [3.2.P.7]	Y	LOAs were provided for DMF (b) (4) [REDACTED] DMF (b) (4) [REDACTED], and DMF (b) (4)
<ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) 	Y	
<ul style="list-style-type: none"> ○ availability of DMF & LOAs 	Y	
<ul style="list-style-type: none"> ○ administration device(s) 	Y N	
<input type="checkbox"/> stability	Y	
<input type="checkbox"/> summary	Y	
<input type="checkbox"/> post-approval protocol and commitment	Y	
<input type="checkbox"/> pre-approval	Y	
<ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	Y	
Diluent (vials or filled syringes) [3.2P']	Y N	N/A. DP is provided in liquid format and does not require a diluent.
<input type="checkbox"/> description and composition of diluent	Y N	
<input type="checkbox"/> pharmaceutical development	Y N	
<ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity 		

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

CTD Module 3 Contents	Present?		If not, justification, action & status
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
<input type="checkbox"/> batch formula	Y	N	
<input type="checkbox"/> 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	
<input type="checkbox"/> controls of critical steps and intermediates	Y	N	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y	N	
<input type="checkbox"/> Filter validation	Y	N	
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y	N	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y	N	
<input type="checkbox"/> Environmental Monitoring Program	Y	N	
<input type="checkbox"/> Lyophilizer sterilization validation	Y	N	
<input type="checkbox"/> Other needed validation data (hold times)	Y		
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y	N	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y	N	
<input type="checkbox"/> reference standards	Y	N	
<input type="checkbox"/> container closure system	Y	N	
<input type="checkbox"/> specifications (vial, elastomer, drawings)	Y	N	
<input type="checkbox"/> availability of DMF & LOAs	Y	N	
<input type="checkbox"/> stability	Y	N	
<input type="checkbox"/> summary	Y	N	
<input type="checkbox"/> post-approval protocol and	Y	N	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 	Y N	
Other components to be marketed (full description and supporting data, as listed above): <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit)	Y N Y N	This section is not applicable.
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	Y Y N Y N	Other products made at the DP site are not listed. Will request. Defer to OBP. Defer to OBP.
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols	Y N Y Y N	Defer to OBP. Micro tests provided in 3.2.S and 3.2.P. Other tests to be reviewed by OBP. Not applicable.
Literature references and copies [3.3]	Y N	Defer to OBP.

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	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes data demonstrating consistency of manufacture	Y N	Defer to OBP
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP.
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP.
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	Defer to OBP.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y Y N Y	Defer to OBP.
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
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	

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

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.

BLA is fileable from a microbiology quality standpoint.

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

Data for the rabbit pyrogen test were provided in the IND but not the BLA. The data will be requested in the 74 day letter. In the letter the Applicant will also be requested to provide the filter validation report and data supporting the hold time for the (b) (4) bulk drug product.

{See appended electronic signature page}

Bo Chi, Ph.D. Drug Substance Microbiology Reviewer OC/OMPQ/DGMPA/BMAB	Date
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{See appended electronic signature page}

Steven Fong, Ph.D. Drug Product Microbiology Reviewer OC/OMPQ/DGMPA/BMAB	Date
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{See appended electronic signature page}

Patricia Hughes, Ph.D. Team Leader OC/OMPQ/DGMPA/BMAB	Date
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/s/

STEVEN FONG

09/10/2014

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