

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125554Orig1s000**

**CHEMISTRY REVIEW(S)**

**First Approval for Indication  
Expedited and Breakthrough Review**

**Recommendation: Approval**

**BLA 125554  
Review # 1  
Review Date December 8, 2014**

<b>Drug Name/Dosage Form</b>	<b>Opdivo for injection</b>
<b>Strength/Potency</b>	<b>100 mg/10 mL and 40 mg/4 mL</b>
<b>Route of Administration</b>	<b>Intravenous infusion</b>
<b>Rx/OTC Dispensed</b>	<b>Rx</b>
<b>Indication</b>	<b>Treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status</b>
<b>Applicant/Sponsor</b>	<b>Bristol-Myers Squibb Company</b>
<b>US agent, if applicable</b>	<b>Not applicable</b>

<b>COMMUNICATIONS WITH SPONSOR and OND</b>	<b>Date</b>
CMC Only Pre-BLA Meeting	April 18, 2014
Pre-BLA Meeting	April 28, 2014
Sponsor Telecon	September 15, 2014
Information Request #1	October 28, 2014
Midcycle Meeting	November 3, 2014
Information Request #2	November 20, 2014
Information Request #3	November 24, 2014
Information Request #4	December 5, 2014
Late Cycle Meeting	December 12, 2014

<b>SUBMISSIONS REVIEWED</b>	<b>Date Received</b>	<b>Review Completed (Yes/No)</b>
125554/0	July 30, 2014	Yes
125554/0.05	September 26, 2014	Yes
125554/0.12	October 12, 2014	Yes
125554/0.17 (Response to IR 1)	November 10, 2014	Yes
125554/0.22	November 19, 2014	Yes
125554/0.25 (Response to IR 2)	December 1, 2014	Yes
125554/0.30 (Response to IR 3)	December 3, 2014	Yes
125554/0.34 (Response to IR 4 and teleconference)	December 8, 2014	Yes

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
<b>Drug Substance</b>	Joel Welch	OBP/DMA
<b>Drug Product</b>	Joel Welch	OBP/DMA
<b>Immunogenicity Assay</b>	Joel Welch	OBP/DMA
<b>OBP Labeling</b>	Jibril Adbus-Samad	OBP
<b>Facility and Microbiology</b>	Bo Chi for Drug Substance Steve Fong for Drug Product Patricia Hughes TL	BMAB
<b>Team Lead for OBP</b>	Laurie Graham	OBP/DMA
<b>Tertiary Reviewer for OBP</b>	Sarah Kennett	OBP/DMA

**Multidisciplinary Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>OFFICE/DIVISION</b>
<b>RPM</b>	Meredith Libeg	OHOP/DOP2
<b>Cross-disciplinary Team Lead</b>	Marc Theoret	OHOP/DOP2
<b>Medical Officer</b>	Meredith Chuk Maitreyee Hazarika	OHOP/DOP2
<b>Pharm/Tox</b>	Shawna Weis Whitney Helms TL	OHOP/DOP2
<b>Clinical Pharmacology</b>	XianHua Cao Stacy Shord TL	OTS/OCF
<b>Statistics</b>	Sirisha Mushti Kun He TL	OTS/OB

*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)			Yes	Adequate Leachables /Extractables information provided. Reviewed by BMAB. No review required.
			Yes	Adequate Leachables /Extractables information provided. Reviewed by BMAB. No review required.
			Yes	Adequate Leachables /Extractables information provided. No review required.
			Yes	Deferred to BMAB
			Yes	Adequate Leachables /Extractables information provided. No review required.

**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 125554 for OPDIVO manufactured by Bristol-Myers Squibb Company pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of OPDIVO is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

##### b. Approval action letter language.

- Manufacturing location:
  - Drug substance: Lonza Biologics, Incorporated (FEI 3001451441)  
Portsmouth, New Hampshire
  - Drug product: Bristol-Myers Squibb Holdings Pharma, Ltd (FEI 2650089)  
Manati, Puerto Rico
- Fill size and dosage form: 100 mg/10 mL and 40 mg/4 mL
- Dating period:
  - Drug product: 24 months; 2-8 °C
  - Drug substance: (b) (4)
- Exempt from lot release
  - Yes
  - Rationale if exempted – Exempt per 601.2a (specified product)

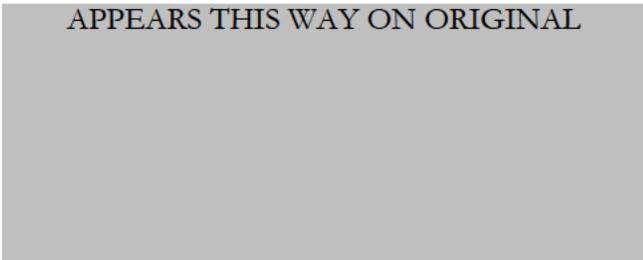
##### c. Benefit/Risk Considerations –

OPDIVO (nivolumab) is for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

The current nivolumab drug substance release specifications include a commercial host cell protein (HCP) ELISA method for evaluating HCP levels. While this method can detect various proteins from the nivolumab-producing (b) (4) cell line, it is not optimal. In order to detect a wider range of nivolumab process specific host cell proteins in drug substance, the sponsor was asked, as a PMC, to develop a process-specific HCP-antiserum for use in the HCP ELISA. It should be noted that the DS release specifications approved under the BLA are sufficient to ensure adequate quality and safety of nivolumab for the initial marketed product. The improvement and implementation of a process-specific HCP assay will provide better control of HCP levels in DS.

The current nivolumab drug substance and drug product release and stability specifications include a non-reduced CE-SDS based method for evaluating nivolumab purity. However, this method demonstrates unusually high run to run variability. While the current assay is sufficient to ensure adequate control and safety of nivolumab for the initial marketed product, an improved assay would provide more accurate control of purity in both drug substance and drug product. The sponsor was, therefore, asked as a PMC to optimize and revalidate the non-reduced CE-SDS method to improve reproducibility.

APPEARS THIS WAY ON ORIGINAL



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

We recommend the following four post-marketing commitments

- 1) To re-evaluate nivolumab 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.
- 2) To re-evaluate nivolumab 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.
- 3) 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 nivolumab drug substance release program. The analytical procedure, validation report, proposed specification acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.
- 4) To optimize and re-validate an improved non-reduced CE-SDS method which has improved reproducibility. The analytical procedure, validation report, any proposed specification acceptance criterion change and data used to establish the proposed acceptance criterion will be provided in the final study report.

**II. Summary of Quality Assessments**

The control strategy for nivolumab is based upon multiple factors including identification of critical quality attributes (CQAs), manufacturing and clinical experience, characterization data, process understanding, stability data, and analytical understanding.

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: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Introduction	Control Strategy	Other
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Immediately Following this Page

a. Names

- I. Proprietary Name: Opdivo
- II. Trade Name: Opdivo
- III. Non-Proprietary/USAN: Nivolumab
- IV. CAS name: 946414-94-4
- V. Common name: BMS-936558
- VI. INN Name: Nivolumab

VII. Compendial Name: N/A

VIII. OBP systematic name: MAB HUMAN (IGG4) ANTI Q15116  
(PD1\_HUMAN) [BMS936558].

b. Pharmacologic category

Human IgG4 monoclonal antibody against (programmed cell death 1) PD-1 receptor.

c. Description

Nivolumab is a human IgG4 monoclonal antibody

(b) (4)

(b) (4)

Nivolumab binds to human PD-1 and blocks interaction of PD-1 to its ligands, PD-L1 and PD-L2. As nivolumab is an IgG4, it is expected to not mediate significant antibody dependent cell-mediated cytotoxicity or complement dependent cytotoxicity, and this was demonstrated in vitro. The drug substance is formulated (b) (4) in (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) mannitol, (b) (4) pentetic acid, and (b) (4) polysorbate 80, at pH 6.0. It is a clear to opalescent, colorless to pale yellow liquid. (b) (4)

d. Mechanism of action

PD-1 is a type 1 membrane protein (b) (4) and is a member of the CD28/CTLA-4 family of T-cell regulators. PD-1 has two ligands, PD-L1 and PD-L2. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. The binding of PD-1 to its ligands results in the down regulation of immune activation. Thus, nivolumab, by inhibition of PD-1 binding to its ligands, results in the potential promotion and restoration of immune response and antigen specific T-cell responses.

e. Potency Assay

Potency is assessed using two different assays: a cell based bioassay and a competitive ELISA assay.

(b) (4)

(b) (4)

## f. Reference material(s)

Multiple reference standards were used throughout development; the current reference standard was qualified prior to execution of process performance qualification (PPQ) activities. Currently, this standard is both the primary and working reference standard. The reference standard is from a drug substance lot manufactured with (b) (4) while the commercial process uses (b) (4). Available data support that (b) (4) is representative (b) (4). Of note, the current referenced standard is from a DS lot used to manufacture drug product used in the pivotal clinical study.

The sponsor intends to implement a two-tier reference standard system post-approval in which the current reference standard will be the primary reference standard and a new working reference standard will be qualified. The sponsor indicates that sufficient quantities of the primary reference standard were prepared to last the lifetime of the commercial product.

(b) (4)

The reference standard was qualified using release methods, as well as additional characterization testing. The protocols used to establish the primary reference standard were provided. The criteria used to evaluate the stability of the reference standard were also provided.

## g. Critical starting materials or intermediates

A list of compendial and non-compendial raw materials was provided. Specifications for the non-compendial raw materials were provided. There was also a risk assessment of raw materials and consumables used in the manufacturing process.

(b) (4)

(b) (4)



The recombinant cell line used for production of nivolumab was derived from a (b) (4) obtained from Lonza Biologics

(b) (4)



(b) (4) A two-tiered production cell bank system (i.e., Master and Working) is used.

h. Manufacturing process summary

(b) (4)



The DS manufacturing process was validated. In addition to full scale validation of the (b) (4) manufacturing process, the following studies were performed to support process qualification

- Lifetime studies (b) (4)
- Impurity Clearance and Mapping Study (b) (4)
- Validation of the (b) (4) Manufacturing Process
- Shipping Qualification Studies
- Validation of Viral Clearance and Inactivation
- Bioburden and Endotoxin Control Studies (Reviewed by BMAB)
- Reprocessing Validation
- Validation of intermediate hold times at small scale
- Process characterization studies

i. Container closure

Nivolumab drug substance is filled into single-use, (b) (4) containers (b) (4)

j. Dating period and storage conditions

- The BLA contained (b) (4) data for three DS lots manufactured with (b) (4) and (b) (4) data for three DS lots manufactured with (b) (4). There were sufficient data provided to support that the (b) (4) lots are representative (b) (4).
- The data provided in the BLA were sufficient to establish a (b) (4) shelf life of DS when stored (b) (4)
- The DS stability commitment protocol, which includes placing three lots on stability from the initial commercial campaign and one lot per year thereafter, was provided and found to be acceptable.

**B. Drug Product [Established Name] Quality Summary**

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product specific CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Type	Risk	Introduction	Control Strategy	Other
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- a. **Potency and Strength:** Nivolumab is supplied at 10 mg/mL in single dose vials in both 100 mg/10 mL and 40 mg/4 mL presentations. The compositions of the two presentations are the same and differ only in fill volume.
- b. **Summary of Product Design:** Nivolumab is manufactured and released as single dose vials for administration by intravenous infusion. Nivolumab may be administered undiluted or diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to create nivolumab concentrations as low as 1 mg/mL.
- c. **List of Excipients:** mannitol (b) (4), hydrochloric acid (as needed for pH), sodium chloride (b) (4), sodium citrate (b) (4), sodium hydroxide (as needed for pH), pentetic acid (b) (4), polysorbate 80 (b) (4), and water for injection
- d. **Reference material(s):** same as DS

C. **Manufacturing Process:**

(b) (4)

(b) (4)

The DP manufacturing process was validated. Validation included full scale validation with three lots manufactured for each presentation. This included two maximum size batches and one minimum size batch for each presentation.

Validation also included:

- Validation of Components
  - Validation of (b) (4) (reviewed by BMAB)
  - Shipping Study Qualification
  - Validation of Media Fill (reviewed by BMAB)
  - Validation of Environmental Monitoring (reviewed by BMAB)
- f. Container Closure: Both the 100 mg/10 mL and 40 mg/4 mL presentations use the same container closure system. It consists of (b) (4) Type I (b) (4) glass vials, stoppered (b) (4) and sealed (b) (4). The 100 mg and 40 mg presentations differ only in the (b) (4) seal cover. The cover for the 100 mg/10 mL vial is (b) (4) and cover for the 40 mg/4 mL vial is dark blue.
- g. Dating Period & Storage Conditions:
- For the 100 mg/mL presentation, the BLA contained 36 month of data for one DP lot manufactured at small scale at the previous DP site using (b) (4) DS, 24 months of data for one DP lot manufactured at the intended scale and site using (b) (4) DS, 18 months of data for three DP lots manufactured at the commercial site and scale using the (b) (4) DS, and 18 months of data for three DP lots manufactured at the commercial site and scale using the (b) (4) DS.
  - For the 40 mg/mL presentation, the BLA contained 9 months of data for three DP lots manufactured with (b) (4) DS; stability trends were consistent with the 100 mg/mL presentation.
  - Additionally, accelerated stability (25°C/60%RH) was evaluated for each batch on stability. Stressed conditions (40°C/75%RH), photostability

(including both ambient temperature/light and ultraviolet), and freeze/thaw cycles were also evaluated.

- The data provided in the BLA were sufficient to establish a 24 month shelf life for DP, for both the 100 mg/mL and 40 mg/ml presentations, when stored at 2-8<sup>o</sup>C.
- The drug product stability commitment includes completing all on-going stability studies and placing the first three commercial lots and at least one lot per year thereafter on real time stability. The stability commitment protocol was reviewed and found to acceptable.

**C. Novel Approaches/Precedents:** None

**D. Any Special Product Quality Labeling Recommendations**

Nivolumab is sensitive to photodegradation and should be protected from light.

**E. Establishment Information**

<b>OVERALL RECOMMENDATION: TBER-EER status results not in DARRTS</b>				
<b>DRUG SUBSTANCE</b>				
<b>FUNCTION</b>	<b>SITE INFORMAT-ION</b>	<b>FEI NUMBER</b>	<b>INSPECTIONAL OBSERVATIONS</b>	<b>FINAL RECOM-MENDATION</b>
Working Cell Bank (WCB) Manufacture, Drug Substance Release Testing (Cell-Based Potency Assay), Drug Substance Storage, Drug Substance Stability Testing (Cell-Based Potency Assay), Master Cell Bank Storage, Working Cell Bank Storage	Bristol-Myers Squibb Company  6000 Thompson Road East Syracuse, New York 13057, USA	<b>1317461</b>		TBER-EER status results not in DARRTS
Drug Substance Manufacturing, Drug Substance Release Testing, Drug Substance Storage,	Lonza Biologics, Incorporated  101 International Drive Portsmouth, New	<b>3001451441</b>	<i>1. The Bioburden assay has been validated to use diluent which is formulated at Lonza but does not undergo routine testing to ensure that it has no antimicrobial effects.</i>	TBER-EER status results not in DARRTS

<p>Drug Substance Stability Testing, Working Cell Bank Storage</p>	<p>Hampshire 03801, USA</p>		<p>2. <i>The timeframes associated with your stability program are inadequate. Specifically:</i></p> <ul style="list-style-type: none"><li>a. <i>Tolerances associated with pull dates are unnecessarily broad and allow for pulling of samples prior to timepoint (i.e., <math>\pm 1</math> month for any timepoint <math>\geq 12</math> months, and <math>\pm 2</math> weeks for any timepoint <math>&lt; 12</math> months).</i></li><li>b. <i>Test windows for some cGMP stability programs are only considered targets and have no established maxima.</i></li></ul> <p>3. <i>Discrepancies were identified between the BLA submission 125554 and operations at the Lonza Portsmouth facility. Specifically:</i></p> <ul style="list-style-type: none"><li>a. <i>(b) (4) volumes associated with the final drug substance (b) (4) in executed batch records are inconsistent with section 3.2.S.2.5.5.4.</i></li><li>b. <i>The tests listed for the purposes of establishing identity are not the same in USPO-10759 and 3.2.S.4.1.</i></li></ul> <p>4. <i>The (b) (4) program is inadequate:</i></p> <p>(b) (4)</p>	
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(b) (4)				
(b) (4)				
Pre-harvest Samples - Mycoplasma Testing, WCB Testing (Mycoplasma, In Vivo Viral Assay)				TBER-EER status results not in DARRTS
Pre-harvest Samples - In Vitro Viral Testing, MVM WCB Testing (In Vivo Viral Assay, In Vitro Viral Assay, Cell Identification and Characterization)				TBER-EER status results not in DARRTS
WCB Testing (Sterility)				TBER-EER status results not in DARRTS
Pre-harvest Samples - In Vitro Viral Testing, Mycoplasma Testing				TBER-EER status results not in DARRTS
Pre-harvest Samples - MVM				TBER-EER status results not in DARRTS
<b>DRUG PRODUCT</b>				
FUNCTION	SITE	DUNS/FEI	INSPECTIONAL	FINAL RECOM-

	<b>INFORMATION</b>	<b>NUMBER</b>	<b>OBSERVATIONS</b>	<b>RECOMMENDATION</b>
Manufacture, release and stability testing, release, secondary packaging, and labeling	Bristol-Myers Squibb Holdings Pharma, Ltd. Liability Company  Road 686, Km 2.3 Bo. Tierras Nuevas Manatí, Puerto Rico 00674 USA	<b>2650089</b>	<b>Inspection waived</b>	TBER-EER status results not in DARRTS
Long term stability study storage and testing (protein concentration, ELISA binding, ELISA potency, pH, SE-HPLC, SDS-PAGE, IEF, appearance, and particulate matter	Lonza Biologics, Inc.  101 International Drive Portsmouth, New Hampshire 03801 USA)	<b>3001451441</b>		TBER-EER status results not in DARRTS
Release and stability testing (bioassay)	Bristol-Myers Squibb Company  6000 Thompson Road East Syracuse, New York 13057 USA	<b>1317461</b>		TBER-EER status results not in DARRTS

**F. Lifecycle Knowledge Management**

**a. Drug Substance**

- i. Protocols approved: Annual GMP stability protocol. The sponsor's plans for validation of reprocessing steps and for validation [REDACTED] (b) (4) [REDACTED] at commercial scale were also reviewed and found to be acceptable.
- ii. Outstanding review issues/residual risk: see PMCs.
- iii. Future inspection points to consider: follow up on 483 citations

**b. Drug Product**

- i. Protocols approved: Annual GMP stability protocol

- ii. Outstanding review issues/residual risk: follow up on PMCs
- iii. Future inspection points to consider: None at this time

*Quality Assessment Summary Tables*

**Table 1: Noteworthy Elements of the Application**

#	Checklist	Yes	No	N/A
<b>Product Type</b>				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material	X		
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other _____		X	
<b>Regulatory Considerations</b>				

15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (# _____)			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other _____			X	
<b>Quality Considerations</b>					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements		X		
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods				Defer to BMAB
30.	Process Analytical Technology in Commercial Production			X	

31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____			X	



**QUALITY REVIEW**



**Signatures**

**Laurie Graham, MS**

**CDER/OPS/OBP/DMA/Team Leader**

**Laurie J.  
Graham -S**

Digitally signed by Laurie J. Graham -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300080688  
, cn=Laurie J. Graham -S  
Date: 2014.12.12 15:19:49 -05'00'

**Sarah Kennett, PhD**

**CDER/OPS/OBP/DMA/Review Chief**

**Sarah B.  
Kennett -S**

Digitally signed by Sarah B. Kennett -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2000597165,  
, cn=Sarah B. Kennett -S  
Date: 2014.12.12 15:32:59 -05'00'

**Kathleen Clouse, PhD**

**CDER/OPS/OBP/DMA/Division Director**

**Kathleen A.  
Clouse Strebel -S**

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=1300054511,  
, cn=Kathleen A. Clouse Strebel -S  
Date: 2014.12.12 16:07:24 -05'00'

APPEARS THIS WAY ON ORIGINAL

# **BLA STN 125554**

**Nivolumab**

**Bristol-Myers Squibb**

**Joel Welch, Ph.D.**

**Laurie Graham, M.S.**

**Division of Monoclonal Antibodies**

**OBP CMC Review Data Sheet**

1. **BLA#: 125554**

2. **REVIEW DATE: December 05, 2014**

3. **PRIMARY REVIEW TEAM:**

**Medical Officer:** Meredith Chuk (Marc Theoret TL)  
Maitreyee Hazarika  
**Pharm/Tox:** Shawna Weis (Whitney Helms TL)  
**Product Quality Team:** Joel Welch (Laurie Graham TL)  
**BMAB or Facilities:** Bo Chi (Patricia Hughes TL)  
Steve Fong  
**Clinical Pharmacology:** XianHua Cao (Stacy Shord TL)  
**Statistics:** Sirisha Mushti (Kun He TL)  
**OBP Labeling:** Jibril Adbus-Samad  
**RPM:** Meredith Libeg

4. **MAJOR GRMP DEADLINES**

**Filing Meeting:** September 12, 2014  
**Mid-Cycle Meeting:** November 3, 2014  
**Wrap-Up Meeting:** December 19, 2014  
**Primary Review Due:** December 5, 2014  
**Secondary Review Due:** December 12, 2014  
**PDUFA Action Date:** December 19, 2014

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

Communication/Document	Date
CMC Only Pre-BLA Meeting	April 18, 2014
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6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)

125554/0	July 30, 2014	Yes
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125554/0.22	November 19, 2014	Yes
125554/0.25	December 1, 2014	Yes
125554/0.28	December 3, 2014	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: Opdivo
- b. Trade Name: Opdivo
- c. Non-Proprietary/USAN: Nivolumab
- d. CAS name: 946414-94-4
- e. Common name: BMS-936558
- f. INN Name: Nivolumab
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMAN (IGG4) ANTI Q15116 (PD1\_HUMAN) [BMS936558].
- i. Other Names: None

8. **PHARMACOLOGICAL CATEGORY:**

Human IgG4 monoclonal antibody against (programmed cell death 1) PD-1 receptor.

9. **DOSAGE FORM:**

OPDIVO for injection

10. **STRENGTH/POTENCY:**

- (i) 100 mg/10 mL and 40 mg/4 mL
- (ii) Type of potency assay (s):  
Potency is assessed by two assays: An ELISA based competition assay and a cell-based bioassay.

**Cell-Based Bioassay**

The bioassay assesses the ability of nivolumab to block the PD-1/PD-L1 mediated inhibition of T cells and elicit IL-2 production. (b) (4)

(b) (4)

**Potency ELISA**

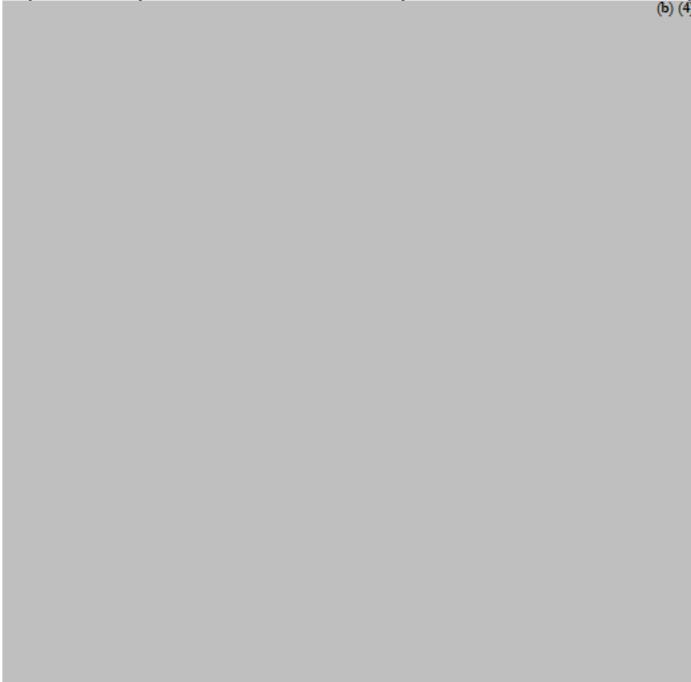
This assay quantitates the potency by perturbing the binding equilibrium of PD-1 and PD-L1. (b) (4)



**11. ROUTE OF ADMINISTRATION:**

Intravenous Infusion

**12. REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
			Yes	Adequate Leachables /Extractables information provided. Reviewed by BMAB. No review required.
			Yes	Adequate Leachables /Extractables information provided. Reviewed by BMAB. No review required.
			Yes	Adequate Leachables /Extractables information provided. No review required.
			Yes	Deferred to BMAB
			Yes	Adequate Leachables /Extractables information provided. No review required.

**13. INSPECTIONAL ACTIVITIES**

The inspection of the drug product manufacturing site in Manati Puerto Rico was waived (waiver approved on October 10). An inspection occurred at the drug substance manufacturing facility at Lonza Portsmouth from September 29-October 3. The EIR included a recommendation to classify the site as VAI.

*1. The Bioburden assay has been validated to use diluent which is formulated at Lonza but does not undergo routine testing to ensure that it has no antimicrobial effects.*

2. *The timeframes associated with your stability program are inadequate. Specifically:*
  - a. *Tolerances associated with pull dates are unnecessarily broad and allow for pulling of samples prior to timepoint (i.e., ±1 month for any timepoint ≥ 12 months, and ±2 weeks for any timepoint < 12 months).*
  - b. *Test windows for some cGMP stability programs are only considered targets and have no established maxima.*
  
3. *Discrepancies were identified between the BLA submission 125554 and operations at the Lonza Portsmouth facility. Specifically:*
  - a. *(b) (4) volumes associated with the final drug substance (b) (4) in executed batch records are inconsistent with section 3.2.S.2.5.5.4.*
  - b. *The tests listed for the purposes of establishing identity are not the same in USPO-10759 and 3.2.S.4.1.*



(b) (4)

**14. CONSULTS REQUESTED BY OBP**

None

**15. QUALITY BY DESIGN ELEMENTS**

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

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

The sponsor includes a risk assessment for each potential product related attribute. An assessment of whether each attribute is critical or not is also included. The assessment includes a summary of the knowledge used to justify the assessment.

**16. PRECEDENTS**

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

**17. ADMINISTRATIVE**



A. Signature Block

Name and Title	Signature and Date
Sarah Kennett, Ph.D. Review Chief, Division of Monoclonal Antibodies	Sarah B. Kennett -S <small>Digitally signed by Sarah B. Kennett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000597165, cn=Sarah B. Kennett -S Date: 2014.12.05 18:46:43 -05'00'</small>
Laurie Graham, M.S. Team Leader, Division of Monoclonal Antibodies	Laurie J. Graham -S <small>Digitally signed by Laurie J. Graham -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300080688, cn=Laurie J. Graham -S Date: 2014.12.05 18:27:38 -05'00'</small>
Joel Welch, Ph.D. Primary Reviewer (s) Division of Monoclonal Antibodies	Joel T. Welch -A <small>Digitally signed by Joel T. Welch -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch -A, 0.9.2342.19200300.100.1.1=2000443745 Date: 2014.12.05 18:18:48 -05'00'</small>

B. CC Block

Recipient	Date
Meredith Libeg	Provided Electronically

236 Pages Withheld in Full as B4 (CCI/TS) Immediately  
Following this Page

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

**Date:** 10/06/2014

**From:** Steven E. Fong, Ph.D. OC/OMPQ/DGMPA/BMAB  
Joel Welch, Ph.D., OPS/OBP/DMA

**To:** BLA File, STN 125554/0

**Through:** Peter Qiu, Ph.D., Branch Chief, OC/OMPQ/DGMPA/BMAB

**Subject:** Inspection waiver memo for manufacture of Nivolumab drug product at the Bristol-Myers Squibb facility in Manati, Puerto Rico.

**Applicant:** Bristol-Myers Squibb, Inc. (BMS)

**Facility:** Bristol-Myers Squibb Holdings Pharma, Ltd. (BMS-Manati)  
Liability Company  
Road 686, Km 2.3  
Bo. Tierras Neuvas  
Manati, Puerto Rico 00674  
FEI #2650089

**Product:** Nivolumab (BMS-936558/MDX-1106)

**Dosage:** 100 mg/10 mL and 40 mg/4 mL nivolumab drug substance per vial administered intravenously.

**Indication:** Therapy for malignant melanoma.

**Waiver Recommendation**

Based on the compliance history of the firm, the current GMP status, and the fact that Bristol-Myers Squibb Holdings Pharma, Ltd. (BMS-Manati) has been approved to manufacture multiple CDER products using the same manufacturing process, we recommend that pre-approval inspection of BMS-Manati be waived for STN 125554/0.

**Summary**

STN 125554/0 for Nivolumab was submitted by BMS for the treatment of unresectable melanoma in patients previously treated with ipilimumab. The BLA contains information and data to support manufacture of sterile Nivolumab finished drug product at BMS-Manati (FEI #2650089).

Facility Information

Manufacture of Nivolumab drug product will take place in the Parenteral Vial Area at BMS-Manati. The manufacturing process consists of

(b) (4)

(b) (4)

### Evaluation of criteria that may warrant inspection

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

BMS-Manati is currently approved under license 1713 for manufacture of three sterile biologics: Orencia (abatacept, BLA 125118), Yervoy (ipilimumab, BLA 125377), and Nulojix (belatacept, BLA 125288). These products are manufactured in the same Parenteral Vial Area proposed for Nivolumab manufacture.

2. *FDA has not inspected the establishment in the last 2 years.*

The facility was last inspected by SJN-DO from May 5-16, 2014 and classified NAI. This was a routine cGMP surveillance inspection covering biotech drug product manufacturing operations, and included inspection of the Parenteral Vial Area proposed for Nivolumab manufacture. The (b) (4) profile was updated and is acceptable.

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

The previous inspection on May 5 – 16, 2014 covered Profile Class (b) (4) and was classified NAI.

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

The Parenteral Vial Area at BMS-Manati proposed for Nivolumab manufacture is currently approved for manufacture of Orencia, Yervoy, and Nujolix (b) (4).

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

The proposed manufacturing scheme for Nivolumab is similar to the approved process for Yervoy liquid injectable. It is also similar to the approved processes for Orencia and Nujolix (b) (4)

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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.**  
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/s/  
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STEVEN FONG  
10/06/2014

PATRICIA F HUGHES TROOST  
10/10/2014

JOEL T WELCH  
10/10/2014

KATHLEEN A CLOUSE STREBEL  
10/10/2014

ZHIHAO PETER QIU  
10/10/2014

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

**BLA/NDA Number:** 125554      **Applicant:** Bristol-Myers Squibb      **Stamp Date:** July 30, 2014

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

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

<b>CTD Module 1 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Cover Letter	Y N	
Form 356h completed	Y N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Labeling:	Y N	A separate diluent not proposed.
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing	Y N	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Quality overall summary [2.3]	Y N	No comparability protocols are proposed.
<input type="checkbox"/> Drug Substance	Y N	
<input type="checkbox"/> Drug Product	Y N	
<input type="checkbox"/> Facilities and Equipment	Y N	
<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]		
<input type="checkbox"/> general info	Y N	
<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 N	
<input type="checkbox"/> description of manufacturing process and process control	Y N	
<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		
<input type="checkbox"/> control of critical steps and intermediates	Y N	
<input type="checkbox"/> justification of specifications		

**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"> <li><input type="checkbox"/> stability</li> <li><input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> characterization of drug substance <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> control of drug substance <span style="float: right;">Y N</span> <ul style="list-style-type: none"> <li><input type="checkbox"/> specifications</li> <li><input type="checkbox"/> justification of specs.</li> <li><input type="checkbox"/> analytical procedures</li> <li><input type="checkbox"/> analytical method validation</li> <li><input type="checkbox"/> batch analyses</li> </ul> </li> <li><input type="checkbox"/> reference standards <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> container closure system <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> stability <ul style="list-style-type: none"> <li><input type="checkbox"/> summary <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> post-approval protocol and commitment <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> pre-approval <span style="float: right;">Y N</span> <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul> </li> </ul>		
<p>Drug Product [3.2.P] [Dosage Form]</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> pharmaceutical development <span style="float: right;">Y N</span> <ul style="list-style-type: none"> <li><input type="checkbox"/> preservative effectiveness</li> <li><input type="checkbox"/> container-closure integrity</li> </ul> </li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> batch formula <span style="float: right;">Y N</span></li> <li><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) <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> controls of critical steps and intermediates <span style="float: right;">Y N</span></li> <li><input type="checkbox"/> process validation including aseptic processing &amp; sterility assurance: <span style="float: right;">Y N</span> <ul style="list-style-type: none"> <li><input type="checkbox"/> Filter validation</li> <li><input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation</li> <li><input type="checkbox"/> Validation of aseptic</li> </ul> </li> </ul>		Sterility is deferred to BMAB

**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"> <li>processing (media simulations)               <ul style="list-style-type: none"> <li>○ Environmental Monitoring Program</li> <li>○ Lyophilizer validation</li> <li>○ Other needed validation data (hold times)</li> </ul> </li> <li><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)</li> <li><input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)</li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system [3.2.P.7]               <ul style="list-style-type: none"> <li>○ specifications (vial, elastomer, drawings)</li> <li>○ availability of DMF &amp; LOAs</li> <li>○ administration device(s)</li> </ul> </li> <li><input type="checkbox"/> stability               <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval                   <ul style="list-style-type: none"> <li>○ protocol</li> <li>○ results</li> <li>○ method validation</li> </ul> </li> </ul> </li> </ul>	<p align="center">Y    N</p>	
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition of diluent</li> <li><input type="checkbox"/> pharmaceutical development               <ul style="list-style-type: none"> <li>○ preservative effectiveness</li> <li>○ container-closure integrity</li> </ul> </li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><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)</li> <li><input type="checkbox"/> controls of critical steps and intermediates</li> <li><input type="checkbox"/> process validation including aseptic</li> </ul>	<p align="center">Y    N</p>	<p>A separate diluent is not proposed.</p>

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

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
processing & sterility assurance:	Y <i>N</i>	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation	Y <i>N</i>	
○ Validation of aseptic processing (media simulations)	Y <i>N</i>	
○ Environmental Monitoring Program		
○ Lyophilizer sterilization validation	Y <i>N</i>	
○ Other needed validation data (hold times)	Y <i>N</i>	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y <i>N</i>	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y <i>N</i>	
<input type="checkbox"/> reference standards	Y <i>N</i>	
<input type="checkbox"/> container closure system	Y <i>N</i>	
○ specifications (vial, elastomer, drawings)		
○ availability of DMF & LOAs		
<input type="checkbox"/> stability	Y <i>N</i>	
<input type="checkbox"/> summary		
<input type="checkbox"/> post-approval protocol and commitment		
<input type="checkbox"/> pre-approval		
○ protocol		
○ results		
Other components to be marketed (full description and supporting data, as listed above):		No other components are included.
<input type="checkbox"/> other devices	Y <i>N</i>	
<input type="checkbox"/> other marketed chemicals (e.g. part of kit)	Y <i>N</i>	
Appendices for Biotech Products [3.2.A]		
<input type="checkbox"/> facilities and equipment		
○ manufacturing flow; adjacent areas	Y <i>N</i>	
○ other products in facility		



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

<b>Examples of Filing Issues</b>	<b>Yes?</b>	<b>If not, justification, action &amp; status</b>
methods used and time intervals for product assessment.		
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    N Y    N Y    N	Deferred to BMAB
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	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y    N	
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	

**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**            Yes    No

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.  
**NONE**

*{See appended electronic signature page}*

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Joel Welch, Ph.D. Date  
 CMC/Product Quality Reviewer  
 OPS/OBP/DMA

*{See appended electronic signature page}*

---

Laurie Graham, M.S. Date  
 CMC/Product Quality Team Leader  
 OPS/OBP/DMA

*{See appended electronic signature page}*

---

Kathleen A. Clouse, Ph.D. Date  
 Division Director  
 OPS/OBP/DMA

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOEL T WELCH  
09/19/2014

LAURIE J GRAHAM  
09/22/2014

KATHLEEN A CLOUSE STREBEL  
09/22/2014