

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125377Orig1s000

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: March 3, 2011
To: Administrative File, STN 125377/0
From: Patricia F. Hughes, Ph.D., Team leader, CDER/OC/DMPQ/BMT
Subject: Team Leader Review Memo for Original BLA
US License: 1713
Applicant: Bristol-Myers Squibb Company
Mfg Facility: For drug substance: [redacted] (b) (4)

For drug product: [redacted] (b) (4)

Product: Yervoy (Ipilimumab, BMS-734016, MDX010)
Dosage: Injection for intravenous administration (50 mg/10 mL and 200 mg/40 mL in 10 cc and 50 cc glass vials)
Indication: Treatment of advanced melanoma in patients who have received prior therapy
PDUFA Date: March 26, 2011

Recommendation for Approvability:

Microbiology Product Quality:

The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

Post-marketing commitment 1: The bioburden test is performed [redacted] (b) (4). A [redacted] (b) (4) sample volume should be tested to improve the sensitivity of the test method. Re-assess the bioburden action limits for the [redacted] (b) (4) based on the manufacturing scale data from [redacted] (b) (4) sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013.

Post marketing commitment 2: Develop and implement a container closure integrity test to replace the sterility test in the drug product post-approval stability protocol by December [redacted] (b) (4) 2011. This change will be submitted as a CBE-0.

CGMP Status of Facilities:

[redacted] (b) (4) was inspected October 11-15, 2010 by Dr. Kalavati Suvarna and Dr. Muthukkumar Subramanian during the

review of this BLA and was found to be acceptable from a CGMP perspective. The drug product manufacturing site, (b) (4) was inspected by (b) (4) on September 14-23, 2010 and has an acceptable CGMP compliance status. All other manufacturing and testing facilities listed in the BLA are acceptable from a CGMP perspective. However, a final TB-EER should be requested by the OND RPM 15- 30 days before BLA approval.

SUMMARY:

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1 κ) that binds specifically to the cytotoxic T-lymphocyte antigen 4 (CTLA-4; CD152) and is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system.

Ipilimumab drug substance is manufactured by (b) (4). Drug substance is packaged in (b) (4). A 36-month shelf life is proposed for the drug substance stored at 2°-8°C.

The drug product, Ipilimumab injection, is manufactured at (b) (4). Ipilimumab injection will be marketed as 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL) single-use presentations. Both presentations are manufactured using the same 5 mg/mL bulk solution. The 50-mg presentation is packaged in a 10-cc, (b) (4) glass tubing vial and sealed with a 20-mm gray (b) (4) stopper and an aluminum, flip-off seal. The 200-mg presentation is packaged in a 50-cc (b) (4) glass molded vial and sealed with a 20-mm gray (b) (4) stopper and an aluminum, flip-off seal. Based on long-term stability data, a (b) (4) shelf life is proposed for the drug product when stored refrigerated (2°-8°C) and protected from light.

During the review of this BLA, the (b) (4), was inspected October 11-15, 2010 by Dr. Kalavati Suvarna and Dr. Muthukkumar Subramanian. The inspection was classified as NAI and the facility is classified as acceptable from a CGMP perspective.

The drug product is manufactured at (b) (4). This site was inspected by (b) (4) on September 14-23, 2010 and has an acceptable CGMP compliance status.

ASSESSMENT:

Drug substance:

The manufacturing process as conducted at (b) (4) is adequately described and microbial controls are in place. However, the volume of sample used for bioburden testing of (b) (4)

(b) (4). To improve sensitivity of the method, at least (b) (4) of the sample should be tested. Also, the bioburden and endotoxin action limits should be based on actual manufacturing process capability and re-adjusted. The applicant has stated that the action limits will be adjusted after data from (b) (4) become available. The revised bioburden action limits (b) (4) based on increased sample volume will be requested as a post-marketing commitment.

Post-marketing commitment 1: The bioburden test is performed (b) (4). A (b) (4) sample volume should be tested to improve the sensitivity of the test method. Re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4), sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013.

Media and buffer hold conditions were adequately validated. Additional information was requested to address in process (b) (4) hold studies. Bioburden and/or endotoxin are monitored routinely at each step (b) (4). However, microbial control at the end of established hold has not been validated. In an amendment eCTD sequence 0057 dated 2/22/2011 and as requested, the applicant revised the hold times based on actual manufacturing data. The revised hold limits are based on the (b) (4) hold times observed during actual manufacturing. The revised hold times are satisfactory.

All process validation lots met the acceptance criteria for bioburden and endotoxin. Data supporting qualification of the bioburden and endotoxin test for (b) (4) was requested and submitted in an amendment (eCTD 0012 dated 8/30/2010). The data submitted was satisfactory and demonstrated that the bioburden and endotoxin tests were suitable for their intended use.

The data supporting microbial control (b) (4) over the lifetime was not provided in the original BLA submission and was requested from the applicant. Currently data is being generated (b) (4) and bioburden and endotoxin are routinely monitored at these steps during manufacture. The routine monitoring and trending of generated data during manufacturing is acceptable

The qualification of storage and expiration limits for chromatography resins packed in commercial-scale columns and stored unpacked in containers used during commercial-scale manufacturing is ongoing. Bioburden and endotoxin data obtained from stored resins demonstrate that these results are within acceptable limits as specified in the protocol.

The shipping of ipilimumab bulk drug substance from (b) (4) to the drug product manufacturing site was qualified and shown to maintain temperature and not impact microbial product quality.

The shipping studies are satisfactory.

Drug substance process validation lots met the bioburden and endotoxin specifications. The specifications are for bioburden (b) (4) and for bacterial endotoxin (LAL), (b) (4).

The release specifications for the bulk drug substance are satisfactory.

Container closure system for the bulk drug substance consists of (b) (4). These containers were shown to maintain integrity for (b) (4). Bioburden and endotoxin testing was performed on 3 lots of drug substance during the shipping qualification studies and the 3 lots met the bioburden and endotoxin acceptance criteria.

The container closure system for the bulk drug substance is adequate.

BMS has committed to complete the on-going stability studies and to perform stability routinely on (b) (4) commercial batch per year. Bioburden (acceptance criterion (b) (4)) and endotoxin (b) (4) are part of post-approval stability testing. These tests will be performed at the initial and 36 month time-point.

The stability plan is acceptable from a microbiology product quality perspective.

Drug Product:

The manufacturing process for the drug product at (b) (4) is adequately described and appropriate microbial controls are in place. Bioburden data at the beginning and end of (b) (4) demonstrates control of microbial growth (b) (4) and is acceptable. Time limits are in place for critical hold steps and supported by process validation data from three lots.

(b) (4)

(b) (4)

Validation data and information in DMF # (b) (4) was reviewed in support of the (b) (4) for the manufacture of the ipilimumab drug product. The DMF contain adequate supportive sterility assurance information and data.

The manufacturing process is monitored for bioburden and the drug product is tested at release for sterility and endotoxin. The drug product release specifications for endotoxin are (b) (4) for finished vials and bulk are “sterile, meet USP and EP requirements”. The release criteria are acceptable.

Additional information and data for validation of the microbial ingress test for container closure integrity was provided during the course of the BLA review (amendment 0060 dated 3/1/11) including information relating to (b) (4) used on the vials and the (b) (4) used in the performance of the test. The sensitivity of the test was determined to be (b) (4) and is adequate.

BMS provided complete shipping data from validation studies in response to an information request during the BLA review and the data is supportive of worst shipping conditions and is adequate.

The available data for the 50 mg/10 mL drug product show that it is stable at the recommended storage condition of 2°-8°C through at least 30 months and the 200 mg/40 mL product show that it is stable at least 24 months. The product shows similar stability characteristics when stored either in an upright or horizontal position. Currently the drug product samples on stability will be tested for sterility. However, a recommended was made to the sponsor to replace the stability sterility test with a container closure integrity test. BMS agreed to develop and implement a container closure test to replace the sterility test in the stability program as a post marketing commitment by December 2011.

Post marketing commitment 2: Develop and implement a container closure integrity test to replace the sterility test in the drug product post-approval stability protocol by December 31, 2011. This change will be submitted as a CBE-0.

Conclusions

I. The BLA, as amended, is recommended for approval from a microbiology product quality perspective. The sponsor has committed to fulfill two (2) post marketing commitments:

- A. The bioburden test is performed using a (b) (4) [redacted]. A (b) (4) volume should be tested to improve the sensitivity of the test method. Re-assess the bioburden action limits for the (b) (4) [redacted] based on the manufacturing scale data from (b) (4) [redacted] sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013.
- B. Develop and implement a container closure integrity test to replace the sterility test in the drug product post-approval stability protocol by December 31, 2011. This change will be submitted as a CBE-0.

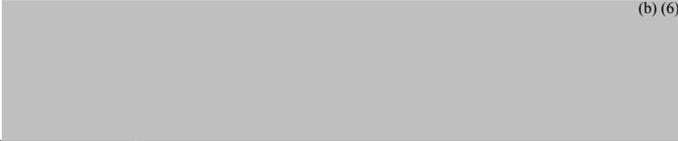
II. Information and data in this submission not related to product quality microbiology should be assessed by OBP/DMA reviewers.

III. All manufacturing and testing facilities listed in the BLA are acceptable from a CGMP perspective. A TB-EER should be submitted to the CDER TB-EER mail box to obtain an updated status of all facilities listed in the BLA 15-30 days prior to the official action date by OND.

CC: DMPQ/BMT/Building 51, Hong
DMPQ/BMT/Building 51, Hughes
HFD-107, Laughner, Erik
DMPQ/BMT/Building 51, eCTD Files (STN 125377)

Archived File: S:\archive\BLA\125377\STN125377.TL.rev.mem.BLA.03-03-11.doc

SIGNATURES/DISTRIBUTION LIST



BMT Team Leader: Patricia Hughes, Ph.D.

8/3/11

Date



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

Date: March 1, 2011
To: Administrative File, STN 125377/0
From: Donald C. Obenhuber, Ph.D., Reviewer, CDER/OC/DMPQ/MAPCB/BMT
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT
Subject: BLA submitted in support of the use of ipilimumab, a fully human cytotoxic T-lymphocyte antigen-4 (CTLA 4) blocking monoclonal antibody, for the treatment of advanced melanoma in patients who have received prior therapy.
Applicant: Bristol-Myers Squibb
US License: 1713
Facility: [REDACTED] (b)(4)
Product: Yervoy (Ipilimumab)
Dosage: 50-mg or 200-mg single-use vials each containing 10 mL or 40 mL of a 5 mg/mL sterile isotonic solution.
Indication: Treatment of advanced melanoma in patients who have received prior therapy.
PDUFA date: March 26, 2011

Recommendation: The drug product section of this application is recommended for approval from sterility assurance and product quality microbiology perspective. One post marketing commitments has been accepted.

1. BMS commits to develop and implement a container closure integrity test to replace the sterility test in the drug product post-approval stability protocol by December 31, 2011. This change will be submitted as a CBE-0.

Review Summary

Bristol-Myers Squibb submitted in CTD format a BLA 125377/0 to support the approval of Ipilimumab in 50-mg or 200-mg single-use vials each containing 10 mL or 40 mL of a 5 mg/mL sterile isotonic solution. A Type V Drug Master File (DMF) (b)(4) is referenced describing (b)(4) drug

product manufacturing facility, equipment, and (b) (4) operations (b) (4) of drug products into vials.

Assessment

Description and Composition of the Drug Product (ipilimumab, Injection 50 mg/10 mL)

Ipilimumab Injection (50 mg/10 mL and 200 mg/40 mL) is a sterile, non pyrogenic, clear to slightly opalescent, colorless to pale yellow, single-use, preservative-free, isotonic aqueous solution for intravenous (IV) administration. The 50 mg/10 mL drug product is packaged in 10-cc (b) (4) tubing glass vials and the 200 mg/40 mL drug product is packaged in 50-cc (b) (4) molded glass vials each stoppered with (b) (4) 20-mm gray (b) (4) serum stoppers, and sealed with 20-mm aluminum flip-off seals. The composition of Ipilimumab Injection, 50 mg/10 mL and 200 mg/40 mL, and the function of each component are listed in Tables below.

Table 3.2.P.1.T01: Composition of Drug Product

Component ^a	Quality Standard	Function	Quantity per 50 mg Vial (mg) ^b
Ipilimumab	BMS Specification	(b) (4)	(b) (4)
Tris Hydrochloride ^c	Vendor Specification		
Sodium Chloride	USP/Ph.Eur.		
Mannitol	USP/Ph.Eur.		
Pentetic Acid ^d	Vendor Specification		
Polysorbate 80	NF/Ph.Eur.		
(b) (4)	NF		
(b) (4)	NF/USP/Ph.Eur./JP		
Water for Injection	USP/Ph.Eur.		
(b) (4)	NF/Ph.Eur.		

^d Diethylenetriaminepentaacetic acid (DTPA).

A surveillance inspection of this site by (b) (4) was conducted September 14-23, 2010 and classified VAI. The (b) (4) profiles were covered and are acceptable.

Batch Formula

(b) (4)



Description of Manufacturing Process and Process Controls

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Environmental Assessment:

BLA 125377 for ipilimumab will not significantly affect the quality of the human environment and meets the requirements for a categorical exclusion from submitting an environmental assessment, 21 CFR 25.31(c). In addition, to Bristol-Myers Squibb Company's knowledge, no extraordinary circumstances exist [21 CFR 25.15 (d)]. This drug is a protein which is expected to rapidly degrade to amino acids and mineralize to carbon dioxide. It is not derived from any wild-sourced plant and/or animal material.

cGMP Status:

(b) (4) was inspected by (b) (4) on September 14-23, 2010 and the inspection was classified VAI. The (b) (4) profiles were covered and are acceptable. This drug product manufacturing site is considered to be acceptable from a cGMP perspective.

Conclusion

- I. The drug product part of this application is recommended for approval from sterility assurance and product quality microbiology perspective. One post marketing commitments has been accepted.
 1. BMS commits to develop and implement a container closure integrity test to replace the sterility test in the drug product post-approval stability protocol by December 31, 2011. This change will be submitted as a CBE-0.
- 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 additional inspectional follow-up items were identified.

CC: DMPQ/BMT/Building 51, Obenhuber
DMPQ/BMT/Building 51, Hughes
HFD-107, Laughner, Erik
DMPQ/BMT/Building 51, eCTD Files (STN:125377)

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SIGNATURES/DISTRIBUTION LIST

 (b) (6)

Primary BMT Reviewer: Donald C. Obenhuber, Ph.D.

3/2/11
Date

 (b) (6)

Concurring BMT Team Leader: Patricia Hughes, Ph.D.

5/2/11
Date

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

BLA: 125377/0

APPLICANT: Bristol-Myers Squibb

DRUG PRODUCT: Ipilimumab, 50-mg or 200-mg single-use vials each containing 10 mL or 40 mL of a 5 mg/mL sterile isotonic solution.

Microbiology Deficiency:



(b) (4)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: February 23, 2011
To: Administrative File, STN 125377/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT
Subject: Original BLA
US License: 1713
Applicant: Bristol-Myers Squibb Company
Mfg Facility: For drug substance: (b) (4)

Product: Yervoy (Ipilimumab, BMS-734016, MDX010)
Dosage: Injection for intravenous administration (50 mg/10 mL and 200 mg/40 mL in 10 cc and (b) (4) glass vials)
Indication: Treatment of advanced melanoma in patients who have received prior therapy.
PDUFA Date: March 26, 2011

Recommendation for Approvability: The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment:

Post-marketing commitment 1: The bioburden test is performed using a (b) (4) A (b) (4) sample volume should be tested to improve the sensitivity of the test method. Re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4) sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013.

SUMMARY:

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1κ) that binds specifically to the cytotoxic T-lymphocyte antigen 4 (CTLA-4; CD152) and induces immune-mediated destruction of tumors by potentiation of a T-cell response to tumor specific antigens and enhancement of tumor-directed humoral immunity. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. The proposed indication is the treatment of patients with pretreated advanced melanoma. Ipilimumab drug substance is manufactured by (b) (4). Drug substance is packaged in (b) (4).

(b) (4). Based on long-term stability studies, a 36-month shelf life is proposed for the drug substance stored at 2°-8°C and protected from light.

Ipilimumab injection is manufactured at (b) (4).
Ipilimumab injection will be marketed as 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL) single-use presentations. (b) (4)
(b) (4). The 50-mg presentation is packaged in a 10-cc, (b) (4) vial and sealed with a 20-mm gray (b) (4) stopper and an aluminum, flip-off seal. The 200-mg presentation is packaged in a 50-cc (b) (4) vial and sealed with a 20-mm gray (b) (4) stopper and an aluminum, flip-off seal. Based on long-term stability data, a 30-month shelf life is proposed for the drug product when stored refrigerated (2°-8°C) and protected from light.

The BLA was submitted in eCTD format. This review covers the evaluation of the drug substance aspects of the application from a microbial control and microbiology product quality perspective. The original submission and amendments to the original submission (eCTD sequence numbers: 0012 dated 8/30/2010; 0017 dated 9/22/2010; 0025 dated 10/18/2010; 0041 dated 1/12/2011; and 0057 dated 2/22/2011) are reviewed here.

ASSESSMENT:

This is a new BLA requesting approval of ipilimumab, a fully human immunoglobulin (IgG1κ) for the treatment of patients with pretreated advanced melanoma. Ipilimumab is produced in a Chinese hamster ovary (CHO) cell line (b) (4).
Ipilimumab injection is available as 50 mg/10 mL or 200 mg/40 mL (5 mg/mL drug substance) single-use preparation in glass vials (10 cc or 50 cc). The manufacturing process consists of (b) (4).

The application contains information to support commercial production of ipilimumab drug substance at (b) (4) as well as drug product manufacture at (b) (4).

This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Dr. Donald Obenhuber.

3.2.S. DRUG SUBSTANCE

3.2.S.1. GENERAL INFORMATION

Ipilimumab (BMS-734016, MDX-010) is a fully human immunoglobulin (IgG1κ) that directly interferes with the interaction of CTLA-4 expressed on T-cells and CD80/CD86 on APCs, maintaining T-cell proliferative responses (IL-2 secretion) and differentiation of T-cell effectors.

This section should be reviewed by OBP/DMA reviewer.

CONCLUSION:

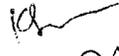
- I. Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective with the following post-marketing commitments:

Post-marketing commitment 1: The bioburden test is performed using a (b) (4) sample volume should be tested to improve the sensitivity of the test method. Re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4), sample volume and submit the summary report in a CBE-0 supplement by March 31, 2013.

- II. CMC product specific information and data should be reviewed by the OBP/DMA reviewer.
- III. The (b) (4) was inspected by a team of investigators [Kalavati Suvarna, Ph.D., (DMPQ/BMT) and Muthukkumar Subramanian, Ph.D

(OPS/OBP/DMA)] from October 11-15, 2010. The inspection was classified as NAI.

SIGNATURES/DISTRIBUTION LIST

Primary BMT Reviewer: Kalavati Suvarna, Ph.D. 

Date: 2/23/2011

Concurring BMT Team Leader: Patricia Hughes, Ph.D. 

Date: 3/1/11

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