

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125377Orig1s000

CHEMISTRY REVIEW(S)

Laughner, Erik

Subject: FW: FINAL TB-EER Request; STN 125377 (BMS); YERVOY original BLA submission
Attachments: TB-EER 125377.doc

From: Ramanadham, Mahesh
Sent: Tuesday, March 08, 2011 1:18 PM
To: Laughner, Erik; CDER-TB-EER
Subject: RE: FINAL TB-EER Request; STN 125377 (BMS); YERVOY original BLA submission

Dear Erik

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 125377/0. Please see the attached form for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.



TB-EER 125377.doc
(36 KB)

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Division of Manufacturing and Product Quality,
Manufacturing Assessment and Pre-Approval Compliance Branch
(301)796-3272

From: Laughner, Erik
Sent: Monday, February 28, 2011 9:49 AM
To: CDER-TB-EER
Subject: FINAL TB-EER Request; STN 125377 (BMS); YERVOY original BLA submission
Importance: High

Hello,

DBOP is nearing completion of the review of new original BLA STN 125377 for YERVOY (ipilimumab). A final compliance check is requested.

The PDFUA DATE IS 03/26/11.

<< File: 125377 TB- EER BMS.pdf >>

Thanks,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit: 1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: March 26, 2011

Applicant Name: Bristol-Myers Squibb Company

U.S. License #: 1713 STN(s): 125377 Product(s): YERVOY (ipilimumab) **Short summary of application:** DBOP is completing the review of new original BLA STN 125377 for YERVOY for treatment of advanced melanoma.

FACILITY INFORMATION

(b) (4)

Summary: Drug substance manufacturing, release and stability testing (b) (4)

(b) (4) Drug Product release and stability testing.

Inspected by CDER-DMPQ from 10/11/10-10/15/10 and classified NAI. This was a preapproval inspection in support of manufacturing operations for Yervoy. This site is acceptable for this supplement.

(b) (4)

Summary: [REDACTED] (b) (4)

Inspected 2/2-2/18/09 by [REDACTED] (b) (4) and classified VAI. This GMP inspection covered the Quality, Facilities/Equipment, and Laboratory control systems. The CTL profile was updated and considered acceptable.

[REDACTED] (b) (4)

FEI: none

Summary: [REDACTED] (b) (4)

An establishment evaluation is not necessary for the responsibilities of this facility as listed in this TB-EER.

[REDACTED] (b) (4)

Short summary of manufacturing activities performed: [REDACTED] (b) (4)

[REDACTED] (b) (4),
Inspected 6/8-6/11/09 by [REDACTED] (b) (4) and classified VAI. This was a GMP inspection of this [REDACTED] (b) (4). The CTL profile was updated and found acceptable

[REDACTED] (b) (4)

Short summary of manufacturing activities performed: [REDACTED] (b) (4)

[REDACTED] (b) (4)
Inspected 1/5-1/6/10 by [REDACTED] (b) (4) and classified NAI. This was a comprehensive GMP inspection that covered the laboratory control systems. The [REDACTED] (b) (4) profile was updated and considered acceptable.

Bristol Meyers Squibb
6000 Thompson Road
East Syracuse NY 13057
FEI: 1317461

Summary: Drug substance release and stability, cell bank storage, manufacturer's working cell bank preparation. Drug Product release and stability testing (in vitro cell based bioassay and

[REDACTED] (b) (4)

Inspected by NYK-DO from 8/16/10-8/20/10 and classified NAI. This was a routine GMP inspection that also covered testing operations for drug substance and drug product. The CTL and [REDACTED] (b) (4) profiles were updated and considered acceptable.

[REDACTED] (b) (4)

(b) (4)

Summary: Drug substance release testing (b) (4)

Inspected by (b) (4) from 7/22/09-7/24/09 and classified NAI. This was a GMP inspection that covered control testing operations. The CTL profile was updated and considered acceptable.

(b) (4)

Summary: Drug Product manufacturing, (b) (4) Drug product release and stability testing (b) (4)

Inspected by (b) (4) from 9/14/10-9/23/10 and classified VAI. This was a routine GMP inspection that gave coverage to (b) (4) operations. While the (b) (4) profile has yet to be updated, (b) (4) of the (b) (4) states that the firm's profiles are currently acceptable.

Review Cover Sheet

BLA STN 125377

Antibody Name: Ipilimumab

**Manufacturer Name: Bristol-Myers Squibb
Company**

Subramanian Muthukkumar, PhD
Carla Lankford, MD, PhD
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

1. **BLA#** STN 125377
2. **REVIEW #:** 1
3. **REVIEW DATE:** 24-Feb-2011
4. **REVIEWERS:** Subramanian Muthukkumar, PhD, Carla Lankford, MD, PhD
Barbara Rellahan, MS, PhD Team Leader

5. **PRIMARY COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

<u>Communication/Document</u>	<u>Date</u>
Filing Review Memo	07/30/2010
Information Request Letter #1	08/30/2010
Information Request Letter #2	09/22/2010
Information Request Letter #3	10/18/2010
Information Request Letter #4	12/14/2010
Information Request Letter #5	02/9/2011

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 125377/0(eCTD)	06/25/2010
STN 125377/0.12	8/30/2010
STN 125377/0.17	9/22/2010
STN 125377/0.25	10/18/2010
STN 125377/0.42	1/13/2011
STN 125377/0.55	2/10/2011
STN 125377/0.57	2/22/2011

BLA E-link: <\\cber-fs3\m\eCTD_Submissions\STN125377\125377.enx>]

7. **NAME & ADDRESS OF APPLICANT:**

Name: Bristol-Myers Squibb Company
Address: 5 Research Parkway
Wallingford, CT 06492
FDA registration number: 1821
Representative: A. Heather Knight-Trent
Telephone: 1-203-677-3858

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

- a) Proprietary Name: Yervoy
- b) Non-Proprietary/USAN: Ipilimumab
- c) Code name: CAS #477202-00-9
- d) Common name: BMS-734016, MDX010, 5022 (([REDACTED] ^{(b)(4)}), MDX-010 Product Code)
- e) Drug Review Status: Original Application
- f) Chemical Type: Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ -chain), disulfide with human κ -chain, dimer.

g) CAS index/registry number: 477202-00-9

9. **PHARMACOL. CATEGORY:** Monoclonal antibody to CTLA4.

10. **DOSAGE FORM:** Sterile parenteral solution.

11. **STRENGTH/POTENCY:**

a) The concentration of Ipilimumab Drug Product is 5 mg/ml.

b) Potency is defined as

(b) (4)

c) Dating period for vial drug product is 36 months when stored at $5 \pm 3^\circ\text{C}$ and protected from light. Expiry, however, should not exceed (b) (4) from production of the drug substance. Vial product should not be frozen.

d) The ipilimumab 50 mg presentation is filled into 10-cc (b) (4) glass vials which contains 10 ml of a 5 mg/ml antibody solution and the 200 mg presentation is packaged in (b) (4) (b) (4) glass vials at a concentration of 5 mg/ml antibody solution.

12. **ROUTE OF ADMINISTRATION:** Intravenous.

13. **ACID (Animal Component Information Database)**

Refer to BLA 125377 review for animal/human derived component information.

Also see section 3.2.S.2.3.1 Control of Source and Starting Materials of Biological Origin.

14. **RELATED/SUPPORTING DOCUMENTS:**

DMF #	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
		(b) (4)	1	adequate	2-15-2011	Pertinent sections of MF reviewed and found acceptable
		(b) (4)	7	I	12-28-2010	The microbiology reviewer requested data from the latest endotoxin clearance method's re-validation (IR letter 1-5-2011). However, the BLA information assures that the level of endotoxin in drug product is adequately controlled. Final

						assessment on the adequacy of the response to the IR letter is deferred to BMT reviewer.
		(b) (4)	3	A	6-28-2007	The BLA contains adequate controls for vial integrity.
			3	A	4-10-2007	The BLA contains adequate controls for vial integrity.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

15. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Environmental Assessment	Approve	03-Feb-2011	Subramanian Muthukkumar
OBP Carton and vial labeling	Approve	23-Feb-11	Kimberly Rains
DMEPA – tradename review	Approve	13-Sept-2010	DMEPA contact-Jibril Abdus-Samad
EIR for (b) (4)	Approve	05-Dec-10	Subramanian Muthukkumar and Kalavathi Suvarna

16. **Inspectional Activities**

A pre-approval inspection (PAI) of the biologics drug substance manufacturing facility was conducted following a request by the Biotech Manufacturing Team, Office of Compliance, CDER, under FACTS assignment #1208554 (Inspection No.BMT-10-12). The inspection covered the manufacturing operations for BLA STN 125377/0 for the Ipilimumab drug substance at (b) (4). The inspection was conducted on October 11-15, 2010 by BMT inspector, Kalavathi Suvarna and product reviewer Subramanian Muthukkumar in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of Ipilimumab. This PAI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

No items that required 483 citations were identified during the PAI.

The following product quality items were identified and communicated verbally to the firm during the closeout meeting:

- Drug substance storage (b)(4) were found to be used beyond the manufacturer specified expiration date. During the inspection additional data from the vendor (b)(4) was provided in support of continuation of shelf life of (b)(4) (e.g., shelf-life was extended to 36 months). Therefore, it was recommended that sufficient data should be in place to ensure quality and safety of the drug substance for the period of its storage in the (b)(4). If there is any extension of its use beyond the expiration date, additional data generated in support of the extension should be formally submitted to the agency for review and concurrence.
- QC testing of samples from shipping validation study did not include particulate measurement. Though visible particulates are measured as an appearance test upon receiving the drug substance at (b)(4), it was recommended that particulate analysis should be included in the future for formal validation of shipping process.

17. Quality Assessment

a) Review of Module 3.2: Body of Data

The review of module 3.2 is attached as a separate document that also includes review of the immunogenicity assay and the assay to detect neutralizing antibodies.

b) Module 1: Environmental Assessment

Statement of Categorical Exclusion for Ipilimumab Solution for Infusion: The subject of the proposed action (BLA for new drug substance - 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, Bristol-Myers Squibb indicated that to the 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.

c) List of Deficiencies: None.

18. Recommendations on Approvability: From a Product Quality standpoint, the BLA is recommended for approval.

IV Administrative

A. Reviewers' Signature

Product Reviewer: Subramanian Muthukummar, Ph.D. (b) (6)



Product Reviewer: Carla Lankford, M.D., Ph.D. (b) (6)

B. Endorsement Block

Product Division Team Leader: Barbara Rellahan, MS, Ph.D. (b) (6)

Product Division Deputy: Patrick Swann, Ph.D. (b) (6)

Handwritten: 4/27/011

Product Division Director: Kathleen A. Clouse, Ph.D. (b) (6)

C. CC Block

OND/OODP/DBOP Project Manager: Erik Laughner
Division of Monoclonal Antibodies File/BLA STN 125377/0

150 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies

The Quality Team Leader’s Executive Summary

From: Barbara Rellahan, MS, PhD
Division of Monoclonal Antibodies (DMA),
CDER, FDA

Through: Patrick Swann, PhD
Deputy Director DMA

Kathleen Clouse, PhD
Director, DMA

BLA Number: 125377/0
Product: Ipilimumab (Yervoy™)
Sponsor:

Date of Review: 21-Feb-2011
Due Date of TL Memo: 02-Mar-2011

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SIGNATURE BLOCK 11

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, has completed review of BLA 125377 for ipilimumab (Yervoy™) manufactured by Bristol Myers Squibb. The data submitted in this application are adequate to support the conclusion that the manufacture of ipilimumab is well controlled, and leads to a product that is pure and potent. From a CMC standpoint it is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

The following information can be included in the approval letter:

Under this license, you are approved to manufacture ipilimumab drug substance at (b) (4). The final formulated product will be manufactured, filled, labeled and packaged at (b) (4). You may label your product with the proprietary name Yervoy and will market 50 mg/10 mL and 200 mg/40 mL single-use vials.

The dating period for ipilimumab drug product shall be 36 months, from the date of manufacture when stored at 2-8°C, but should not exceed (b) (4), from the date of drug substance manufacture. The date of manufacture shall be defined as the date of (b) (4) the formulated drug product. The dating period for your drug substance shall be 36 months when stored at 2-8°C. The expiration date for the packaged product, ipilimumab single-use vials, shall be dependent on the shortest expiration date of any component. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

III. POST MARKETING COMMITMENTS AND REQUIREMENTS
DMA CMC PMCs

1. To develop and validate a semi-quantitative assay to evaluate visible particulates in drug product. The assay will be incorporated into the drug product release and stability testing programs. The final validation report with the specifications and method validation will be submitted as a CBE-30 by May 30, 2011.
2. To replace the IEF assay with the CEX assay for the release of drug product after sufficient data have been acquired to support establishment of CEX acceptance criteria. The final study report will be submitted as a CBE-30 by June 30, 2011.
3. To replace the IEF assay with the CEX assay as a specification for charge in the drug substance and drug product stability programs after three years of market life data are collected for the CEX assay on three batches of drug substance and three batches of either presentation of drug product. The final results and proposed CEX specification will be submitted as a CBE-30 by March 31, 2014.

SUMMARY BLA 125377 Ipilimumab

4. To perform studies to confirm that clearance of (b) (4) is well controlled by the manufacturing process and provide a risk assessment for (b) (4) that may be present in the drug product. The final study report will be submitted as a CBE-0 by July 29, 2011.
5. To develop and validate a process-specific host cell protein (HCP) ELISA. This assay will replace and perform as well or better than the current Cygnus Kit ELISA being used in the drug substance release program. In the event a process-specific assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided. The final study and validation reports will be submitted as a CBE-30 by May 30, 2012.
6. To reassess release and stability specifications for ipilimumab drug substance and drug product through April 30, 2013. The assessment will be submitted in the 2013 Annual Report.
7. To submit the final concurrent column life-time study reports for the Poros HS50, Q-Sepharose and CHT Type II columns. The final report will be submitted in the 2013 Annual Report.
8. To submit the final study reports for studies performed to confirm product stability over the course of the in-process hold times of (b) (4). Final study results will be submitted in the 2012 Annual Report.
9. To submit the final study reports for the drug substance storage container leachate studies to assess the volatile organic compounds (VOC), semi-VOC, non-VOC and trace metals in drug substance and formulation buffer samples held at 2 to 8°C for up to 3 years and under accelerated aging conditions of 40°C to simulate 3 years at 2 to 8°C. Final study reports will be submitted in the 2013 Annual Report.

PMRs

These PMRs have been agreed to by the whole review team. As of the writing of this TL summary the sponsor has not yet provided dates by which each will be completed.

10. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to Ipilimumab, including procedures for accurate detection of antibodies to Ipilimumab in the presence of Ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling.
11. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to Ipilimumab, including procedures for accurate detection of neutralizing antibodies to Ipilimumab in the presence of Ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling. In the event such an assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided.
12. To conduct an assessment of anti-drug antibody (ADA) response to Ipilimumab with a validated assay (required in PMR 1 and 2) capable of sensitively detecting ADA responses in the presence of Ipilimumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least

300 Ipilimumab-treated patients enrolled in the required postmarketing study comparing 3 mg/kg versus 10 mg/kg of Ipilimumab monotherapy. The final report will include information on the level of Ipilimumab in each patient's test sample at each sampling time point.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None identified from a DMA CMC perspective.

V. EXECUTIVE SUMMARY

A. Description of Ipilimumab (Yervoy)

Yervoy is supplied as a sterile liquid for injection and will be available at 5 mg/mL in two different sized container closure systems. One vial presentation will contain 50 mg in a 10 mL glass vial; the second presentation will contain 200 mg in a 40 mL glass vial. The 50 mg vial has a (b) (4) overfill and the 200 mg vial has a (b) (4) overfill. Both overfill volumes were deemed appropriate.

Yervoy is a clear to slightly opalescent, colorless to pale yellow liquid (b) (4)

Yervoy is formulated in 20 mM Tris hydrochloride (b) (4), 100 mM sodium chloride, 1.0% w/v mannitol, 0.1 mM pentetic acid, 0.01% w/v polysorbate 80 at pH 7.0.

The recommended storage temperature for Yervoy is 2-8 °C, protected from light. The product should not be frozen.

(b) (4)

B. Clinical Trial Information

Ipilimumab is proposed for the treatment of advanced melanoma in patients who have received prior therapy. The proposed induction regimen is 3 mg/kg administered intravenously every 3 weeks for a total of four doses as tolerated. (b) (4)

Clinical efficacy and safety data from a pivotal study, MDX010-20 with supporting data from phase 2 trials (CA184022, CA184004 and CA184008) forms the basis of the application.

C. Stability

The BLA submission contained adequate stability data to support establishment of a drug substance and drug product shelf-life. Drug substance and drug product stability protocols

including specifications, conditions and testing intervals were provided and found acceptable.

- The data support a drug substance shelf-life of 36 months at 2-8°C.
- The data support a drug product shelf-life of 36-months when stored at 2-8°C.
- Several lots of drug product were produced from drug substance lots that had been stored for at least (b) (4). Because both the drug substance and drug product are stored at 2-8°C, the end-to-end shelf-life for the drug product should not exceed (b) (4) from the date of drug substance manufacture.
- Photostability studies indicated ipilimumab is light sensitive and should be stored protected from light.
- Freeze/thaw studies indicated that ipilimumab is sensitive to freeze/thaw cycles and should not be frozen.
- Drug product does not contain preservatives. Drug product vials are single-use and should be discarded after use.
- The primary degradation pathways determined for ipilimumab were said to be (b) (4). These alterations did not appear to impact antigen binding.

D. Complexity

BMS did not submit an assessment of the criticality of product attributes. Below is a description of ipilimumab and a summary of the major product attributes identified in the submission.

- Ipilimumab is a human IgG1κ recombinant monoclonal antibody specific for the CTLA4 (CD152) antigen. Results from epitope mapping studies performed by BMS suggest that the epitope for ipilimumab consists of (b) (4). Information on the sequence of these epitopes was provided.
- CTLA4 is a receptor expressed by activated T lymphocytes. It is expressed by T- helper, T-cytotoxic and T-regulatory cells. Engagement of CTLA4 by its ligands, CD80 (B7.1) and CD86 (B7.2), induces a negative regulatory signal which results in the down modulation of T cell activation on T-helper and T-cytotoxic cells. Its role in T-regulatory cell activity is not well understood.
- CTLA4 and CD28, the primary co-stimulatory receptor for T cells, bind to the same ligands. CTLA4 however, has a high affinity for the ligands compared to CD28 and is able to out-compete CD28 for binding to CD80/86. CTLA4's ability to compete with CD28 for binding to CD80/86 also plays a role in CTLA4's ability to down-modulate T-cell immune responses.
- Data provided in the BLA indicates that ipilimumab binds to recombinant human CTLA4 with high affinity ((b) (4)) and binds to cells expressing human CTLA4 with an EC50 value of (b) (4) achieving saturation at (b) (4). Ipilimumab blocks in vitro binding of the CTLA4 ligands, CD80/86, to human CTLA4 at EC50 values of approximately (b) (4), with maximal blockade at concentrations (b) (4) for CD80 and (b) (4) for CD86.
- Ipilimumab binding to activated human T cells induced low to moderate ADCC activity, but no significant complement-dependent cytotoxicity of CTLA4-expressing cells.

(b) (4)

- The molecular weight of ipilimumab is 147,857 Daltons and has an apparent isoelectric point of (b) (4)

(b) (4)

E. Homology to Other Products

The variable and constant regions of ipilimumab have homology to other human IgG molecules, though the sequence of the complementarity determining region is unique to ipilimumab. There are no safety concerns related to its homology to human IgG molecules.

F. Mechanism of Action

Ipilimumab binds CTLA4 and directly interferes with the interaction of CTLA4 with its ligands, B7.1 (CD80) and B7.2 (CD86). Ipilimumab has no demonstrable agonistic activity

and is thought to mediate a clinical effect solely via its ability to block the interaction of CTLA4 with its ligands. CTLA4 is expressed on activated T-cells and its ligands are expressed on antigen presenting cells (APC). Engagement of CTLA4 by CD80/86 induces a negative regulatory signal to the T cell which down-regulates T cell activation. CTLA4 also competes with CD28 (a co-stimulatory receptor on T cells) for binding to CD80/86. Blockage of CTLA4 by ipilimumab therefore may not only interfere with the inhibitory activity of CTLA4, but it may also increase the ability of CD28 to interact with CD80/86. These combined events are hypothesized to lead to enhanced T cell activity both by maintaining T-cell proliferative responses and the differentiation of T-cell effectors.

T cell immunity has been demonstrated to be reduced in cancer patients in part due to the up-regulation of negative regulatory mechanisms such as expression of CTLA4 on T cells. Therefore the proposed mechanism of action of ipilimumab in melanoma patients is that the blockage of CTLA4 by ipilimumab alleviates CTLA4-mediated inhibitory activity and allows T cells with anti-tumor activity to proliferate and mediate anti-tumor activity. Blockage of CTLA4 by ipilimumab also interferes with pathways that help maintain self-tolerance and can result in the activation of autoimmune T cells.

Activated T regulatory cells also express CTLA4 and it has been postulated that CTLA4 plays a role in their ability to down-regulate activated T cells. Studies in mice indicated that the anti-tumor activity observed after blockage of CTLA4 involved two pathways. One was the direct augmentation of T-helper and T-cytotoxic cell activation via disruption of the blockage of CTLA4 that was expressed by the cells. A second pathway involves the inhibition of T regulatory activity. T regulatory cells are reported to have higher CTLA4 expression levels than helper T cells.

Because ipilimumab can mediate ADCC, I thought another potential mechanism of action could be ipilimumab-mediated lysis of T regulatory cells. After a more extensive search of the literature and speaking to Jack Ragheb in DTP/OBP/CDER, who has worked with T regulatory cells, it became apparent that, while the intracellular level of CTLA4 is higher in T regulatory cells compared to T helper cells, their surface expression is comparable. I therefore decided against having BMS investigate this as a possible mechanism of action.

The assay used to monitor ipilimumab potency is designed to monitor the ability of ipilimumab to inhibit CTLA4-mediated down-regulation of T cell activation. (b) (4)

Ipilimumab activity is assessed by its ability to inhibit CTLA4-IG activity in this assay. Potency is defined as the percent activity relative to the reference standard. The potency assay therefore reflects a presumed primary mechanism of action of ipilimumab.

G. Manufacturing Process

(b) (4)

(b) (4)

(b) (4) Measures such as testing of cell banks and raw materials, lot traceability, and acceptance criteria have been implemented to prevent product contamination from potential viral and non-viral adventitious agents.

No information was provided on removal of (b) (4) by the process and it is not currently being tested for as a component of drug substance release or as an in-process test.

(b) (4)

The issue of confirmation of (b) (4) clearance by the manufacturing process is therefore being addressed as a post-marketing commitment.

BMS switched from using a qualitative IEF assay for monitoring product charge to a quantitative CEX method late in development. While there was sufficient data from drug substance (DS) lots to support establishment of a DS release specification, there were insufficient data to support establishment of a release specification for drug product (DP), and stability specifications for DS and DP. BMS therefore agreed to continue using the IEF for DP release, and DS and DP stability monitoring until more data using the CEX method are gathered and a specification can be established. BMS also committed to developing CEX acceptance criteria for these programs when sufficient data have been acquired.

H. Comparability

Several manufacturing processes have been used during the development of ipilimumab.

(b) (4)

I. Immunogenicity

A three tiered approach was taken for analysis of product immunogenicity. Samples were first screened for reactivity to ipilimumab. Positive samples were then confirmed by assessing whether the response could be inhibited by addition of ipilimumab. Any samples that were inhibited would be considered confirmed positives and evaluated for neutralizing activity.

SUMMARY BLA 125377 Ipilimumab

Different screening assays were used for the phase II and pivotal trials. The phase II trials used a serum electro chemiluminescent (ECL) immunoassay with a bridging format that was developed by BMS. The assay used in the pivotal trial was a plasma ECL immunoassay developed by Medarex. Though the sensitivity of the plasma ECL assay (b)(4) used for the pivotal trial is sufficient to detect clinically meaningful immunogenicity responses in the absence of ipilimumab, it is only about half as sensitive as the serum ECL assay used for the phase II trials (b)(4). In addition, the plasma ECL assay has a lower drug tolerance limit (b)(4) compared to the serum ECL assay (b)(4).

Of the patients tested in the pivotal trial, none had a confirmed positive response. However, because immunogenicity samples were collected at baseline and prior to the administration of each dose of ipilimumab, it is likely there was always sufficient ipilimumab present in the samples (predicted levels were said to be between 5.4-69.3 µg/mL) to interfere with detection of ADA responses. Data from these analyses therefore are unlikely to reflect the true rate of immunogenicity.

Data from the phase II trials are attached below. This table was copied directly from the submission. The serum ECL assay was used for assessment of ADA in these samples. In addition, a lower clinical dose was included in the studies. Data from these studies indicate an ADA rate of 2.9% at a 3 mg/kg dose and a rate of 6.9% at the 0.3 mg/kg dose. Because of the concerns with product interference and the fact that samples collected from patients given a 0.3 mg/kg dose would be expected to have lower concentration of ipilimumab on board, data from the 0.3 mg/kg may be closer to the actual rate of immunogenicity.

Table 16. Immunogenicity Summary by Ipilimumab Dose¹

Treatment	Positive at any Timepoint	Positive Post-Baseline	90% CI
	No. positive/ No. evaluated (%)	No. positive/ No. evaluated (%)	
0.3 mg/kg	6/71 (8.5%)	4/58 (6.9%)	(2.4%, 15.1%)
3.0 mg/kg	8/109 (7.3%)	3/102 (2.9%)	(0.8%, 7.4%)
10 mg/kg	12/380 (3.2%)	4/353 (1.1%)	(0.4%, 2.6%)
Total	26/560 (4.6%)	11/513 (2.1%)	(1.2%, 3.5%)

¹Includes anti-ipilimumab, anti-Ig, or both types of antibodies confirmed by an immunodepletion assay

²Denominator includes patients with both a baseline and a post-baseline measurement

The sponsor could argue that giving higher doses induces something akin to high dose tolerance and so the rate at 0.3 mg/kg is an overestimate of the rate of ADA at the 3 mg/kg dose. However, given the issues with assay sensitivity and product interference, I think it is more likely that the detection of ADA is being masked at the higher doses. Data provided on the product levels at the time of ADA testing in the phase II trials indicate that the majority of the 0.3 mg/kg group had trough ipilimumab concentrations of < 5µg/mL which would not interfere appreciatively with the ADA assay, while the higher dose cohort had concentrations > 10 µg/mL that would interfere with the assay. Therefore, I recommend that the rate seen in the 0.3 mg/kg group (6.9%) be included in the label in the immunogenicity section. I recommend that consideration be given to establishing PMRs that would 1.) require development of a immunogenicity assay with the capability to detect

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ADA responses in the presence of product levels that are present in patient samples or provide evidence of due diligence to develop such an assay and, 2.) require BMS to conduct assessment of ADA responses to ipilimumab with a sufficient number of patients using this assay. BMS agreed to these PMRs.

The review of module 3.2 is included in the DMA CMC BLA review document and includes review of the human anti-drug antibody immunogenicity assays.

VI. SIGNATURE BLOCK

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