DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125377/0

**BLA APPROVAL**
March 25, 2011

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, PharmD
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

Please refer to your Biologics License Application (BLA) dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act for YERVOY (ipilimumab).

We acknowledge receipt of all subsequent amendments received through March 24, 2011.

We have approved your BLA for ipilimumab effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ipilimumab, under your existing Department of Health and Human Services U.S. License No. 1713. Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma.

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 it in 50 mg/10 mL and 200 mg/40 mL single-use vials.

Your application for ipilimumab was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

The dating period for ipilimumab 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 drug product 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 from the date of manufacture 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.

You are not currently required to submit samples of future lots of ipilimumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of ipilimumab, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125377/0**."

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on March 11, 2011 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125377/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of embryo-fetal toxicity or anti-drug antibody responses.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. To submit the final report for study DN120020 (Intravenous Study of Pre- and Post-natal Developmental in Cynomolgus Monkeys with a 6-Month Post-natal Evaluation).

   The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 31, 2011

2. 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.

   The timetable you submitted on March 14, 2011, states that you will conduct this assay according to the following schedule:

   Final Report Submission (Assay and Methodology): December 2, 2011

3. 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.

   The timetable you submitted on March 14, 2011, states that you will conduct this assay according to the following schedule:

   Final Report Submission (Assay and Methodology): February 20, 2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to address the following:

- Identify unexpected serious risk of anti-drug antibody responses;
- Assess a signal of serious risk of immune-mediated adverse reactions associated with CD86 gene polymorphisms;
- Assess a known serious risk of fatal and life-threatening immune-mediated adverse reactions

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

4. To conduct an assessment of anti-drug antibody (ADA) response and neutralizing ADA responses to ipilimumab with a validated assay (required in PMR 2 and 3) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling. The ADA response will be evaluated in at least 300 ipilimumab-treated patients enrolled in the required postmarketing trial (PMR 6) 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.

   The timetable you submitted on March 14, 2011, states that you will conduct this assessment from clinical trial data according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | September 30, 2011 |
| Patient Accrual Completed | December 31, 2014 |
| Trial Completion Date: | August 31, 2017 |
| Final Report Submission: | December 29, 2017 |

5. During the conduct of the required postmarketing trial comparing 3mg/kg vs. 10mg/kg ipilimumab monotherapy (PMR 6), you will obtain comprehensive baseline DNA sample acquisition (≥ 95% of ITT) and conduct pharmacogenomic association analyses to assess the potential clinical utility of CD86 gene polymorphisms as genetic determinants of immune mediated adverse events. You will provide a protocol that addresses SNP selection, data analyses approaches, and other methodological issues. You will provide a Final Report including electronic datasets.

   The timetable you submitted on March 14, 2011, states that you will conduct this assessment from clinical trial data according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | November 30, 2011 |
| Final Protocol Submission: | May 30, 2012 |
| Final Report Submission: | December 29, 2016 |

6. Following the assessment of data from Trial CA184024, you will design and conduct a trial to compare the efficacy, with the primary endpoint of overall survival and the safety of ipilimumab at doses of 3mg/kg versus 10mg/kg given as monotherapy every three weeks for four doses in patients with unresectable Stage III or Stage IV melanoma.

   The timetable you submitted on March 14, 2011, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Preliminary CA184024 Data Submission: | June 30, 2011 |
| Draft Protocol Synopsis Submission: | June 30, 2011 |
| Final Protocol Submission: | September 30, 2011 |
| First Patient Accrued to Trial: | March 30, 2012 |
| Last Patient Accrued to Trial: | December 31, 2014 |
| Trial Completion: | August, 31, 2017 |
| Final Report Submission: | December 31, 2017 |

Submit protocols to your IND, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

7. To identify further genetic determinants of immune-mediated adverse events caused by ipilimumab. DNA samples from the required postmarketing study comparing 3 mg/kg vs. 10 mg/kg ipilimumab monotherapy will be used to conduct genome-wide association analyses. The design of these analyses will be reviewed by FDA and a final report with electronic datasets will be provided.

   The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

   | | |
   |---|---|
   | Draft Protocol Submission: | December 29, 2016 |
   | Final Protocol Submission: | July 31, 2017 |
   | Final Report Submission: | December 31, 2018 |

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

8. 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 supplement by May 30, 2011.

   The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission as a CBE-30 supplement: May 30, 2011

9. To replace the IEF assay with the CEX assay for the release of drug product after sufficient data has been acquired to support establishment of CEX acceptance criteria. The final study report will be submitted as a CBE-30 by June 30, 2011.

   The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission as a CBE-30 supplement: June 30, 2011

10. To discontinue the IEF method 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 supplement by March 31, 2014.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-30 supplement: March 31, 2014

11. 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 report will be submitted as a CBE-0 supplement by July 29, 2011.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission as a CBE-30 supplement: July 29, 2011

12. To develop and validate a process-specific host cell protein (HCP) ELISA. This assay will replace the current Cygnus Kit ELISA being used in the drug substance release program. The final study and validation reports will be submitted as a CBE-30 supplement by November 30, 2011.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report/Validation Report Submission
    as a CBE-30 supplement: November 30, 2011

13. 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.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission (Annual Report): May 2013

14. 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.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission (Annual Report): May 2012

15. To submit the final concurrent column life-time study reports for the Poros 50HS, Q-Sepharose and CHT Type II columns. The final report will be submitted in the 2013 Annual Report.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission (Annual Report): May 2013

16. 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 reports will be submitted in the 2013 Annual Report.

    The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

    Final Report Submission (Annual Report): May 2013

17. To 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.

The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission as a CBE-0 supplement: March 31, 2013

18. To develop and implement a container closure integrity test to replace the sterility test in the stability program. The ability of a container closure system to maintain the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf-life should be demonstrated. Submit the summary report and data in a CBE-0 supplement by December 2011.

The timetable you submitted on March 14, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission as a CBE-0 supplement: December 31, 2011

Submit clinical protocols to your IND 9186 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for YERVOY (ipilimumab) to ensure the benefits of the drug outweigh the risks of severe and fatal immune-mediated adverse reactions such as fatal immune-mediated enterocolitis (including gastrointestinal perforation), fatal immune-mediated hepatitis (including hepatic failure), fatal immune-mediated toxicities of the skin (including toxic epidermal necrolysis), fatal nervous system toxicity, and endocrinopathies, associated with the use of YERVOY (ipilimumab).

We have determined that a communication plan targeted to healthcare providers is necessary to support implementation of the REMS.

Your proposed REMS, submitted on June 25, 2010, as amended, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.
The REMS assessment plan should include but is not limited to the following:

a. An evaluation of healthcare providers' (HCPs) understanding of the serious risks of YERVOY (ipilimumab) and the management of the immune-mediated adverse reactions caused by YERVOY.

b. With regard to assessment of the communication plan:
   i The date of product launch and the launch of the communication plan.
   ii The date(s) of mailing and number of recipients of the Dear Healthcare Provider (DHCP) letter and the communication package.
   iii The number of mailings returned.
   iv The sources of the recipient lists.
   v The number of new prescribers prescribing YERVOY (ipilimumab) /new facilities purchasing YERVOY (ipilimumab) during the reporting period. Of the new prescribers/purchasers, the number supplied with the communication materials within the required timeframe; the number not supplied with communication materials within the required timeframe; the reasons for the failure to deliver communication materials within the required timeframe.

c. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

d. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.

e. An analysis of post-marketing cases of immune-mediated adverse events reported for YERVOY that result in the patient's death, including an analysis of the length and reasons for any reported delay in recognition and treatment of the events.

f. Information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Submit the methodology and survey instrument(s) for review at least 90 days before the next evaluation is conducted. Submit both methods and instruments together.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125377**
**REMS ASSESSMENT**

**NEW SUPPLEMENT FOR BLA 125377**
**PROPOSED REMS MODIFICATION**
**REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR BLA 125377**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

## REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

## LETTERS TO HEALTH CARE PROFESSIONALS

We acknowledge that you will issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter); we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

## POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Erik S. Laughner, M.S., RAC (US), Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Richard Pazdur/
Richard Pazdur, M.D.
Director,
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS
REMS Materials