DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

sBLA 125554/007

ACCELERATED APPROVAL
POSTMARKETING REQUIREMENT NOT FULFILLED

Bristol-Myers Squibb Company
Attention: Cynthia Wojtaszek
Regulatory Liaison – U.S. Oncology
Global Regulatory, Safety & Biometrics
P.O. Box 4000
Mailstop D2 204
Princeton, NJ 08543

Dear Ms. Wojtaszek:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 23, 2015, received July 23, 2015, and submitted under section 351of the Public Health Service Act for "Opdivo (nivolumab) Injection."

This Prior Approval supplemental biologics application provides for:

- The expansion of the indication for OPDIVO (nivolumab), in combination with ipilimumab, for the treatment of patients with unresectable or metastatic melanoma to remove the restriction for the treatment of only patients with BRAF wild-type melanoma;
- The expansion of the indication for OPDIVO (nivolumab) as a single agent for the treatment of patients with BRAF V600 mutation positive, unresectable or metastatic melanoma to remove the restriction that such patients should have disease progression following ipilimumab and a BRAF inhibitor; and,
- Inclusion of the results of Study CA209067 in the Clinical Studies section of product labeling.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 CFR 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, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval.

In order to meet the requirements of 21 CFR 601.70, you must conduct and submit the results of a multicenter, randomized trial or trials to verify and describe the clinical benefit, to include the mature or final analysis of overall survival, for:

- nivolumab, as a single agent, for the treatment of patients with BRAF V600 mutation positive, unresectable or metastatic melanoma; and,
- nivolumab, in combination with ipilimumab, for the treatment of patients with unresectable or metastatic melanoma.

We remind you of your existing postmarketing trials required under the regulations at 21 CFR 601 Subpart E for Accelerated Approval identified in your December 22, 2014, and September 30, 2015, approval letters:

2838-1 Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

Final Report Submission: December 2016

2959-1 Conduct and submit the results of a multicenter, randomized trial or trials to verify and describe the clinical benefit of nivolumab in combination with ipilimumab in previously untreated adult patients with unresectable or metastatic, BRAF V600 wild-type melanoma.

Final Report Submission: July 2015

Fulfillment of these requirements may also fulfill the requirement to verify and describe clinical benefit under 21 CFR 601.41 for approval of sBLA 125554/007.

SUBPART E NOT FULFILLED

We approved the original Opdivo (nivolumab) BLA 125554 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. The December 22, 2014, accelerated approval letter contained the postmarketing requirement below:

2838-1 Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

Final Report Submission: December 2016

We have reviewed your final report submission contained in sBLA125554/007 and concluded that the terms of the requirement were not met as this supplement has not verified clinical benefit for the treatment of patients with BRAF mutation positive melanoma. We acknowledge that you have partially fulfilled this PMR, as stated in the November 23, 2015, approval letter under sBLA 125554/001, for a subset of patients with BRAF wild-type, unresectable or metastatic melanoma. You must submit a final report that demonstrates you have met all of the terms of the above-listed requirement by the December 31, 2016, final report due date.

We approved sBLA 125554/002 on September 30, 2015, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. The September 30, 2015, accelerated approval letter contained the postmarketing requirement below:

2959-1 Conduct and submit the results of a multicenter, randomized trial or trials to verify and describe the clinical benefit of nivolumab in combination with ipilimumab in previously untreated adult patients with unresectable or metastatic, BRAF V600 wild-type melanoma.

Final Report Submission: July 2015

We have reviewed your final report submission contained in sBLA125554/007 and conclude that the terms of the requirement were not met. This supplement does not confirm clinical benefit since overall survival data were not provided.

We have determined that the data included in the final report submission does not adequately fulfill the postmarketing requirement. The original milestone due date was not met; therefore, this requirement is considered delayed. This status will be posted on the FDA Postmarketing Requirements and Commitments website: http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

Within 30 days of the date of this letter submit a plan to address this requirement and proposed revised milestones.

We remind you to submit clinical protocols to your IND 104225 for this product for this indication. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report 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.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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(s) 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.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
01/23/2016