DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-015

ACCELERATED APPROVAL

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Jeffrey Stuart, PhD, RAC
Director, Global Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY34-B188
Rahway, NJ 07065-0900

Dear Mr. Stuart:

Please refer to your supplemental Biologics License Application (sBLA) dated September 15, 2016, received September 15, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda® (pembrolizumab) lyophilized powder for injection and solution, 50 mg and 100 mg/4 mL (25 mg/mL).

This Prior Approval supplemental biologics application provides for a new indication for the treatment of adult and pediatric patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy.

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.

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 prescribing information 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 include 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on February 16, 2017, 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 "*Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (May 2015, Revision 3).* 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 "**Final Printed Carton and Container Labels for approved BLA 125514/S-015**." Approval of this submission by FDA is not required before the labeling is used.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/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. We remind you of your postmarketing requirement specified in your submission dated February 16, 2017. This requirement, along with required completion dates, is listed below.

These postmarketing studies/clinical trials are subject to the reporting requirements of 21 CFR 601.70:

PMR 3188-1 Complete the trial and submit the final report and data to verify and describe the clinical benefit of pembrolizumab, including efficacy and safety, from Trial KN204, a Phase 3 randomized, open-label, active-controlled trial comparing pembrolizumab to brentuximab vedotin for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma. Enroll approximately 300 patients. The primary endpoint should include progression-free survival.

Interim PFS Analysis:	03/2019
Final PFS Analysis:	09/2019
Trial Completion:	11/2020
Final Report Submission:	04/2021

Submit clinical protocols to your IND 118604 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) 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.

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.

Since Keytruda was approved on September 4, 2014, we have become aware of higher than expected occurrences of fatal and serious immune-mediated adverse events in patients who receive allogeneic hematopoietic stem cell transplantation (SCT) after Keytruda. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 assess the signal of a serious risk of immune-mediated adverse events after allogeneic SCT in patients who have received prior Keytruda.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

PMR 3188-2 Characterize complications after allogeneic hematopoietic stem cell transplantation (HSCT) following pembrolizumab in at least 90 patients with

hematologic malignancies, of which at least 30% had received pembrolizumab alone or in combination as the regimen immediately prior to the allogeneic HSCT conditioning regimen. Evaluate toxicities at least through transplant Day 180. Include details of prior pembrolizumab treatment and the transplant regimen. Characterize toxicities including hyperacute graft-versus-host disease (GVHD), severe (grade 3-4) acute GVHD, febrile syndromes treated with steroids, immune mediated adverse events, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal obstruction syndrome, critical illness, and transplant-related mortality. Toxicities may be characterized prospectively, or through a combination of prospective and retrospective data analysis.

The timetable you submitted on February 16, 2017, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	08/2017
Final Analysis Plan Submission:	02/2018
Interim Analysis Report Submission:	12/2020
Study Completion:	06/2024
Final Report Submission:	12/2024

We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of serious toxicity with long-term use of Keytruda in patients with classical Hodgkin lymphoma and to identify an unexpected serious risk of negative developmental effects, including immune-mediated endocrine toxicities with Keytruda in pediatric patients who are pre-pubertal or have not yet completed puberty.

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

PMR 3188-3 Characterize the safety of long-term use in patients with classical Hodgkin lymphoma treated with pembrolizumab 200 mg every 3 weeks. Submit a final report and datasets with safety and efficacy outcomes of trial KN087 with at least 3 years of follow-up data.

The timetable you submitted on February 16, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	04/2021
Final Report Submission:	08/2021

PMR 3188-4 Characterize the long-term safety of pembrolizumab 2 mg/kg every 3 weeks, in pre-pubertal pediatric patients and those who have not completed pubertal development. Submit a report and datasets that include long-term follow-up of patients enrolled on KN051, a Phase I/II Study of Pembrolizumab (MK-3475) in children with advanced melanoma or a PD-L1 positive advanced, relapsed or refractory solid tumor or lymphoma. Enroll at least 20 patients, including at least

5 patients who are pre-pubertal and 10 who have not yet completed pubertal development. For any pre-pubertal patients and those who have not completed pubertal development, perform the following actions: include in the safety evaluation, immune-mediated, endocrine, and reproductive toxicities for subjects with at least 5 years of follow-up or until pubertal development is complete, whichever is longer.

The timetable you submitted on February 16, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2017
Trial Completion:	12/2026
Final Report Submission:	04/2027

ADDITIONAL INFORMATION

All patients must be evaluated for growth and development milestones annually while on treatment. Growth and development milestones must include: weight, height, height standard deviation scores (SDS), height velocity, height velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Luteinizing and follicle stimulating hormones (LH, FSH) and testosterone levels in males and LH, FSH and estradiol levels in females must be measured in patients who have not developed secondary sexual characteristics by age 13 for females and 14 for males. Descriptive statistics including mean and standard deviation values, of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

Submit the protocol(s) to your IND118604, with a cross-reference letter to this BLA. Submit all final report(s) 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.

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 prescribing information (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 Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

ALBERT B DEISSEROTH
03/14/2017