BLA 125514/S-59 through S-64, S-69, S-76 through S-83

ACCELERATED APPROVAL

Merck Sharp & Dohme Corp.
Attention: Anisha Wharton, M.B.A.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG4D-34
North Wales, PA 19454

Dear Ms. Wharton:

Please refer to your supplemental biologics license applications (sBLAs), submitted and received on April 18, 2019 (S-59), April 23, 2019 (S-60 through S-64), September 23, 2019 (S-69), April 14, 2020 (S-76 through S-80), April 15, 2020 (S-81 and S-82), and April 20, 2020 (S-83), and your amendments, submitted under section 351(a) of the Public Health Service Act for KEYTRUDA (pembrolizumab) injection, for intravenous use.

We acknowledge receipt of your April 13, 2020, amendment to S-59 through S-64 and S-69 which constituted a complete response to our February 18, 2020, action letter.

These Prior Approval supplemental biologics license applications provide for an alternate dose/schedule of 400mg every 6 weeks for adult patients with:

- Melanoma – S-59
- Classical Hodgkin lymphoma – S-60
- Primary mediastinal B-cell lymphoma – S-61
- Hepatocellular carcinoma – S-62
- Merkel cell carcinoma – S-63
- Gastric cancer – S-64
- Non-small cell lung cancer – S-69
- Renal cell carcinoma – S-76
- Endometrial carcinoma – S-77
- Cervical carcinoma – S-78
- Urothelial carcinoma – S-79
- Head and neck squamous cell carcinoma – S-80
- Small cell lung cancer – S-81
- Esophageal cancer – S-82
- Microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors – S-83

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 FDA.gov,[1] 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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. We remind you of your postmarketing requirement specified in your submission dated April 27, 2020. These requirements, along with required completion dates, are listed below.

S-59, S-62, S-63, S-64, S-69, and S-76 through S-83

3850-1 Submit the final analysis of overall response rate, duration of response, and safety from Cohort B of the KEYNOTE-555 trial titled, "*A Phase 1 Randomized Clinical Study of Pembrolizumab (MK-3475) to Evaluate the Relative Bioavailability of Subcutaneous Injection Versus Intravenous Infusion in Participants With Advanced Melanoma*" to verify and describe the anticipated effects of the alternative dosing regimen for pembrolizumab 400 mg every six weeks, that may inform product labeling across indications. All responding patients should be followed for at least 12 months from the onset of response. Provide pharmacokinetic data at first cycle and at steady state from Cohort B and the datasets in the final report.

Final Protocol Submission:	Completed
Trial Completion (Cohort B):	08/2021
Final Report Submission (Cohort B):	02/2022

S-60 and S-61

3853-1 Submit the final analysis of overall response rate, duration of response, and safety from a trial evaluating pembrolizumab 400 mg every six weeks in participants with classical Hodgkin lymphoma and primary mediastinal B-cell lymphoma to verify and describe the anticipated effects of the alternative dosing regimen of pembrolizumab 400 mg administered every six weeks, that may inform product labeling across indications. All responding patients should be followed for at least 12 months from the onset of response. Provide pharmacokinetic data at first cycle and at steady state and the datasets in the final report.

Final Protocol Submission:	01/2021
Trial Completion:	03/2025
Final Report Submission:	09/2025

Submit clinical protocols to your IND 118604 for this product. In addition, under 21 CFR 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 (which includes new salts and new fixed combinations), 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.

Regarding S-59 through S-64, S-81 and S-82:
Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

Regarding S-69, S-76 through S-80:
We are waiving the pediatric studies requirement for these supplements because the necessary studies are impossible or highly impracticable as non-small cell lung cancer, renal cell carcinoma, endometrial carcinoma, cervical carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma do not occur in children.

Regarding S-83:
We are waiving the pediatric studies requirement for this supplement because the necessary studies are impossible or highly impracticable due to the extremely low number of pediatric patients with unresectable or metastatic MSI-H or mismatch repair deficient solid tumors.

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 Package Insert (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.[3]

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).

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, please call Sharon Sickafuse, Senior Regulatory Health Project Manager, at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D.
Acting Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN J LEMERY
04/28/2020 12:08:23 PM