CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125514	NDA Supplement # BLA Supplement # 24	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Keytruda Established/Proper Name: Pembrolizumab Dosage Form: 50 mg lyophilized powder; 100 mg/4mL solution		Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Sharon Sickafuse		Division: DOP2

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☒ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 9-22-2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) \ssessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☒ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 9-22-2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included 8-8-2017
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide 8-8-2017 ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 8-7-2017 DMEPA: ☒ None DMPP/PLT (DRISK): 9-5-2017 OPDP: 9-1-2017 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5-19-2017 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Keytruda received Orphan Drug Designation for treatment of gastric cancer, including gastroesophageal junction carcinoma, on 6-16-2015.	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Revised Med Guide email 9-14-2017 Revised PI email 9-13-2017 PMC request email 9-13-2017 Revised PMR request email 9-12-2017 Stat IR email 9-6-2017 Revised Med Guide email 9-5-2017 Revised PI email 8-29-2017 Clinical IR email 8-29-2017 Clinical IR email 8-28-2017 Clinical IR email 8-14-2017 PMR request email 8-8-2017 Clinical IR email 8-1-2017 Clinical IR email 7-25-2017 Filing Review Deficiencies Identified LTR 5-19-2017 ACK LTR 4-6-2017
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Midcycle MS 7-17-2017
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 1-31-2017
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None signed concurrence on 9-22-2017 review
Cross-Discipline Team Leader Review *(indicate date for each review)*	9-22-2017
PMR/PMC Development Templates *(indicate total number)*	9-27-2017
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review signed concurrence on 9-19-2017 review
• Clinical review(s) *(indicate date for each review)*	9-19-2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Pages 23 &24 of 9-19-2017 review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review signed concurrence on 8-28-2017 review
Statistical Review(s) *(indicate date for each review)*	8-28-2017

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review signed concurrence on 8-25-2017 review
Clinical Pharmacology review(s) *(indicate date for each review)*	8-25-2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	signed concurrence on 9-22-2017 review
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	9-22-2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9-22-2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable ☐ Withhold recommendation ☒ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-24

REVISED MEDICATION GUIDE

Merck Sharp & Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG2C050
North Wales, PA 19454

Dear Dr. Miller:

Please refer to your supplemental Biologics License Applications (sBLAs) dated March 22, 2017, received March 22, 2017, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

Attached is FDA's proposed revised Medication Guide.

If you have any questions, please call me at (301) 796-0137 or Sharon Sickafuse at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Kristin Jarrell, Pharm.D.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment:
Revised Medication Guide

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KRISTIN D JARRELL
09/14/2017

From:	Jarrell, Kristin
To:	Miller, Mike (GRA)
Cc:	Griffin, Norma; Sickafuse, Sharon
Subject:	BLA 125514 - S-24: FDA proposed new PMC
Date:	Wednesday, September 13, 2017 11:46:00 AM
Attachments:	image001.png
Importance:	High

Hello Mike,
I will be covering for Sharon this week while she is out-of-office.

With regard to your Keytruda (pembrolizumab) BLA 125514 Supplement 24, we have the following new PMC:

> Proposed PMC: Submit the final report, including datasets, from patients with PD-L1 positive microsatellite stable or microsatellite instability (MSI)-unknown recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma enrolled in Cohort 1 of Study KEYNOTE-059. In order to further characterize the duration of response in patients who achieve a complete or partial response to pembrolizumab, responding patients will be followed for at least 12 months from the onset of response and duration of response will be assessed by independent central review.

Please submit Merck's proposed milestones, and **provide your response by Thursday, September 14, 2017 at 1:00 pm EST**. This deadline applies to *both* the aforementioned new PMC as well as the revised PMR sent to you via email from Sharon on September 12, 2017 at 11:39am EST.

Please direct any inquiries to me, and CC Sharon during that time frame.

Kind regards,
Kristin Jarrell, Pharm.D
Regulatory Project Manager
CDER || OHOP || DOP2
U.S. Food and Drug Administration
10903 New Hampshire Ave, Silver Spring, MD 20993 | USA
☎ +1 301 796 0137 | ✉: Kristin.jarrell@fda.hhs.gov

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/s/

KRISTIN D JARRELL
09/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-24

REVISED LABELING

Merck Sharp & Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG2C050
North Wales, PA 19454

Dear Dr. Miller:

Please refer to your supplemental Biologics License Applications (sBLAs) dated March 22, 2017, received March 22, 2017, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

Attached is FDA's proposed revised labeling.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment:
Revised labeling

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/s/

KRISTIN D JARRELL
09/13/2017

From: Sickafuse, Sharon
Sent: Tuesday, September 12, 2017 11:39 AM
To: 'Miller, Mike (GRA)'
Subject: Keytruda S-24 PMR

Hi Mike,

We've revised the PMR language to:

Conduct and submit the results of one or more randomized trials to verify and describe the clinical benefit of pembrolizumab over standard therapy based on a clinically meaningful improvement in overall survival in patients with PD-L1 positive, microsatellite stable/mismatch repair (MMR) proficient metastatic gastric or gastro-esophageal junction adenocarcinoma.

Please send me Merck's proposed milestones. Thanks

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/s/

SHARON K SICKAFUSE
09/12/2017

From: Sickafuse, Sharon
Sent: Wednesday, September 06, 2017 10:44 AM
To: 'Miller, Mike (GRA)'
Subject: Keytruda S-24 stat IR

Hi Mike,

We have the following IR:

> Please clarify why the four patients below were not counted as censored as they received new anticancer therapy prior to PD.

Part of USUSBJD	No-PD assessment prior new anti-cancer therapy	PD date	DOR date	Censoring Status
000700018	2016-03-17	2016-04-28	2016-04-28	Event
001800010	2016-09-14	2016-10-25	2016-10-25	Event
007100011	2016-06-24	2016-08-09	2016-08-09	Event
011800007	2016-04-12	2016-05-17	2016-05-17	Event

Please email me your response by COB Friday, September 8 with a follow-up amendment to the sBLA.

Thanks

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/s/

SHARON K SICKAFUSE
09/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-24

REVISED LABELING

Merck Sharp & Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG2C050
North Wales, PA 19454

Dear Dr. Miller:

Please refer to your supplemental Biologics License Applications (sBLAs) dated March 22, 2017, received March 22, 2017, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

Attached are FDA's proposed revisions to the Medication Guide submitted on August 8, 2017.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment:
Revised labeling

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/s/

SHARON K SICKAFUSE
09/05/2017

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, August 29, 2017 6:58 AM
To: 'Miller, Mike (GRA)'
Cc: Sickafuse, Sharon
Subject: FDA Request for data reviewed by DMC for Keynote 61 trial (supporting sBLA 125514/S-024 Keytruda (pembrolizumab, MK-3475)

Importance: High

Dear Mr. Miller,

I am sending this information request on behalf of your Regulatory Contact, Sharon Sickafuse, who is currently on leave.

Please find below our additional new information request from the clinical team:

"Patients with SUBJID 590034 and 590184 are responders who have been identified in the submission as having protocol deviations related to the efficacy assessment, consent form, and/or the safety assessment. For each of these patients, provide details characterizing the protocol deviations beyond what is provided in the sBLA submission. Additionally, describe the reasons why the protocol deviations do not compromise the results of KEYNOTE-059 (Cohort 1)."

Please have this submitted to the sBLA by 9 AM, EST, August 30, 2017. In the past, for information sent to the FDA that only a few company employees had access to, the company has send the information on CD (which is then loaded into the EDR) instead of through the gateway. Please let me know if you'll be able to do this.

Please acknowledge receipt of this email.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
08/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-24

REVISED LABELING

Merck Sharp & Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG2C050
North Wales, PA 19454

Dear Dr. Miller:

Please refer to your supplemental Biologics License Applications (sBLAs) dated March 22, 2017, received March 22, 2017, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

Attached is FDA's proposed revised labeling. Comments regarding the Medication Guide submitted on August 8, 2017, will be forthcoming in a separate letter.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Attachment:
Revised labeling

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/s/

ANUJA PATEL
08/29/2017

Patel, Anuja

From: Patel, Anuja
Sent: Monday, August 28, 2017 4:16 PM
To: 'michael_miller1@merck.com'
Cc: Sickafuse, Sharon
Subject: FDA Request for data reviewed by DMC for Keynote 61 trial (supporting sBLA 125514/S-024 Keytruda (pembrolizumab, MK-3475)

Importance: High

Dear Mr. Miller,

I am sending this information request on behalf of your Regulatory Contact, Sharon Sickafuse, who is currently on leave.

Please find below our information request from the clinical team:

"Please submit a copy of the Keynote 61 data package (including but not necessarily limited to data on serious adverse events by PD-L1 status and overall survival data by PD-L1 status and by ECOG performance status) reviewed by the eDMC in preparation for their March 11, 2016 and March 18, 2016 meetings (data cutoff January 15, 2016). Please also submit a copy of the updated data package for the Keynote 61 trial reviewed by the eDMC (based on subjects enrolled as of March 11, 2016) for the April 29, 2016 eDMC meeting. Also provide a copy of any presentations of Keynote 61 data by (b) (4) *that were provided for those meetings.*

Finally, please provide copies of all data packages for Keynote 61 reviewed by the eDMC in preparation for subsequent meetings."

If possible, we would like to have this submitted as a formal amendment to the sBLA by 2 PM, EST, August 30, 2017.

Please acknowledge receipt of this email.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
08/28/2017

From: Sickafuse, Sharon
Sent: Monday, August 14, 2017 1:15 PM
To: 'Miller, Mike (GRA)'
Subject: Keytruda S-24 clinical IR

Hi Mike,

My clinical reviewer has the following IR:

Please provide an analysis of efficacy as shown in Sections 2.1.5.2, 2.1.5.3, 2.1.5.4, 2.1.8, and 3.3 of the Summary of Clinical Efficacy and submitted to BLA 125514 (S-24) on June 21, 2017, that reflects updated data on duration of response based on a data cut-off date of April 21, 2017 for responders identified based on the data cut-off date of January 16, 2017 (i.e., 30 responders as reported in the sBLA submission).

She would like to have this information by noon Wednesday August 16th. You can email to email to me with a follow-up sBLA amendment.

Thank you

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/s/

SHARON K SICKAFUSE
08/14/2017

From: Sickafuse, Sharon
Sent: Tuesday, August 08, 2017 10:55 AM
To: 'Miller, Mike (GRA)'
Subject: Keytruda S-24 request for PMR

Hi Mike,

We have the following request for a PMR:

Conduct and submit the results of a randomized trial (or trials) to verify and describe the clinical benefit of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy, that is demonstrated by a clinically meaningful improvement in overall survival.

Please submit proposed milestones.

Thanks

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/s/

SHARON K SICKAFUSE
08/08/2017

From: Sickafuse, Sharon
Sent: Tuesday, August 01, 2017 9:30 AM
To: 'Miller, Mike (GRA)'
Subject: Keytruda S-24 clinical IR

Hi Mike,

My team has the following IR:

Please refer to FDA's request for additional information submitted via email on July 25, 2017, and to your response submitted via email on July 28, 2017. Based upon your response to item #3 regarding the procedures for evaluating PDL1 status and which also included the submission of a subject level dataset, provide the following additional information:

- Specify the criteria used to designate a tissue specimen 'spectype' = 'NEWLY OBTAINED' versus 'ARCHIVAL.' In your response, also state what the variable 'age of tumor' represents (e.g., the *age of tumor specimen at time of PDL1 assessment).*

They would like a response by noon Thursday, August 3rd. Thank you

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/s/

SHARON K SICKAFUSE
08/01/2017

From: Sickafuse, Sharon
Sent: Tuesday, July 25, 2017 1:41 PM
To: 'Miller, Mike (GRA)'
Subject: Keytruda S-24 clinical IR

Hi Mike,

My team has the following IR:

1. Please refer to IND 123482 and to the amendment submitted on October 26, 2017, for KEYNOTE-061, "A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine." In the submission, you state that rationale for halting enrollment of patients with PD-L1 negative tumors is "based on recommendations from an external Data Monitoring Committee (eDMC)."

   Provide the minutes for the eDMC discussion leading to that recommendation, including any communication from Merck to the eDMC and from the eDMC to Merck regarding this decision.

2. Clarify whether microsatellite instability (MSI) testing was performed on all patients enrolled in KEYNOTE-061. If possible, indicate what proportion of patients who are enrolled in each study arm are MSI-High.

3. Describe the protocol-specified process for evaluating tumor specimens for PD-L1 status, including requirements for processing times that may impact antigen stability. If available, provide the following subject-level information in your response:

   a. For newly obtained tissue, age of tissue at testing,(include age of block as well as cut slide)
   b. Age of archived tissue
   c. For subjects whose specimens were collected as slides, age of cut slide (in days) at the time of testing

Please submit your response by 3pm Friday, July 28th. You can email me followed by an amendment to the supplement.

Thanks

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/s/

SHARON K SICKAFUSE
07/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: **July 17, 2017**

From: **Sharon Sickafuse, RPM**

BLA: **125514/S-24**

Product: **Keytruda (pembrolizumab)**

Applicant: **Merck Sharp & Dohme Corp.**

Subject: **Midcycle Review Meeting**

Major Findings/Issues:

Benefit

- Study design supports accelerated approval
  - Endpoint: objective response rate (ORR) by RECIST; independent radiology review
- Magnitude of ORR
  - Modest but durable

Safety

No new or unexpected adverse events.

Clinical Pharmacology

- Systemic exposures are consistent with the approved indications for pembrolizumab.
- The immunogenicity rate for patients with melanoma, NSCLC, HNSCC is low (2.1%).
  - The effect of anti-drug antibody formation on pembrolizumab safety and pharmacokinetic profile is minimal and is not clinically meaningful
- Neutralizing assay under review by OBP.
- The proposed dosing regimen of 200 mg Q3W pembrolizumab in patients with gastric cancer appears acceptable .

PMRs/PMCs:

A confirmatory PMR will be requested. Data from study KEYNOTE-061, "A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine," will be used to fulfill the PMR. This study is fully enrolled as of July 2016. The analysis of survival will occur in approximately December 2017.

Upcoming Meetings:

Labeling: August 21, 2017

[Labeling due to Merck: August 29, 2017

Wrap-Up meeting: September 6, 2017

Review Due Dates:

Primary Reviews	August 29, 2017
Division Director Review	September 22, 2017

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/s/

SHARON K SICKAFUSE
07/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-24

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Merck Sharp & Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG2C050
North Wales, PA 19454

Dear Dr. Miller:

Please refer to your supplemental Biologics License Application (sBLA) dated March 22, 2017, received March 22, 2017, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) for injection 50 mg and for Keytruda (pembrolizumab) injection 100 mg/4 mL.

We also refer to your amendments dated April 7, 2017 (2).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR: 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 22, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 29, 2017.

During our filing review of your application, we identified the following potential review issue:

> Please provide the location or submit the immunogenicity study reports for studies KN012 and 059 by June 5, 2017.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 601.45, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the

material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (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).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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 the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

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

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/s/

PATRICIA KEEGAN
05/19/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125514/S-24

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Merck Sharp & Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000
UG2C050
North Wales, PA 19454

Dear Dr. Miller:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER: 125514

SUPPLEMENT NUMBER: 24

PRODUCT NAME: Keytruda (pembrolizumab)

DATE OF SUBMISSION: March 22, 2017

DATE OF RECEIPT: March 22, 2017

This supplemental application proposes to add a new indication for the treatment of patients with recurrent locally advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma [redacted (b) (4)].

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 21, 2017, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

SHARON K SICKAFUSE
04/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123482

MEETING MINUTES

Merck Sharp and Dohme Corp.
Attention: Michael Miller, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
UG-2C27, P.O. Box 1000
North Wales, PA 19454

Dear Dr. Miller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Pembrolizumab."

We also refer to the meeting between representatives of your firm and the FDA on January 31, 2017. The purpose of the meeting was to discuss a proposed sBLA submitted under the provisions of accelerated approval to support a new indication for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinom (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: pre-sBLA

Meeting Date: January 31, 2017

Application Number: IND 123482
Product Name: Pembrolizumab
Indication: Teatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (b) (4)

Sponsor/Applicant Name: Merck Sharp and Dohme Corp. (Merck)

FDA ATTENDEES
Center for Drug Evaluation and Research
Office of Hematology and Oncology
Division of Oncology Products 2
Brendan Baggot, Regulatory Health Project Manager
Martha Donoghue, M.D., Associate Director (Acting)
Patricia Keegan, M.D., Director
Steven Lemery, M.D., M.H.S., Clinical Team Leader
Leigh Marcus, M.D., Clinical Reviewer
Sharon Sickafuse, M.S., Senior Regulatory Health Project Manager

Office of Biostatistics
Division V
Lisa Rodriguez, Ph.D, Statistics Team Leader
Weishi (Vivian) Yuan, Ph.D., Statistics Reviewer

Office of Clinical Pharmacology
Division V
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader

Center for Device Evaluation and Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology
Prakash Jha, Ph.D.

Janaki Veeraraghavan, Ph.D.

SPONSOR ATTENDEES
Merck Sharp & Dohme Corp.
Michael Miller, Ph.D., Director, Regulatory Affairs
Julie Lepin, BSc, Vice President, Regulatory Affairs
Nahid Latif, BSc, Executive Director, Regulatory Affairs
Roger Dansey, M.D., Senior V.P., Clinical research
Minori Koshiji, M.D., Ph.D., Executive Director, Clinical Research
Rita Dalal, MBBS, M.P.H., Clinical Director, Clinical Research
Jonathan Cheng, M.D., Executive Director, Clinical Research
Linda Sun, Ph.D., Director, Biostatistics
Christine Gause, Ph.D., Executive Director, Biostatistics
Tomoko Freshwater, M.D., Associate Principal Scientist, Quantitative Sciences, PPDM,
Sid Mathur, MBS, Associate Director, Regulatory Affairs
Kenneth Emancipator, M.D., Executive Director, Clinical Research

(b) (4)
(b) (4)

BACKGROUND

On November 10, 2016, Merck submitted a meeting request (SDN 351) to discuss a proposed sBLA for the treatment of patients with (b) (4) . Primary efficacy and safety data are from KEYNOTE-059, "A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin Plus 5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma," and from Cohort D of KN-012, "A Phase 1b Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors." The meeting package was submitted on December 20, 2016, as SDN 369.

Regulatory

Pembrolizumab is approved in the U.S. for:

- the treatment of patients with previously-treated metastatic NSCLC whose tumors express PD-L1 with a tumor proportion score (TPS) $\geq$ 1%;
- the treatment of patients with previously untreated metastatic NSCLC whose tumors express high levels of PD-L1 (TPS $\geq$ 50%);
- the treatment of patients with unresectable or metastatic melanoma; and,
- the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

Clinical Development

Merck's clinical development of pembrolizumab for gastric cancer includes six studies, including four that are randomized, controlled studies. FDA held a Type B meeting with Merck

pertaining to the designs of Studies KN-061 and KN-062 (see below) on March 5, 2015. On June 25, 2015, FDA granted Dako North America, Inc., an Investigational Device Exemption (IDE) for the Dako PD-L1 IHC 22C3 pharmDx Kit to assess PD-L1 expression in gastric cancer tissues in support of Merck clinical studies KN-059, KN-061, and KN-062 (G140139/S002). FDA granted Orphan Drug designation for pembrolizumab for gastric cancer on June 16, 2015.

- KN-012 is a multicenter, non-randomized, multi-cohort study of pembrolizumab in subjects with advanced solid tumors. Thirty nine patients with PD-L1-postive gastric cancer were enrolled in a gastric cancer cohort (cohort D). Although there was no limit on prior therapy, 69% of patients received two or more prior lines of therapy.

- KN-059 is an ongoing (enrollment completed), multicenter, non-randomized, non-comparative study of pembrolizumab as a single agent or pembrolizumab in combination with cisplatin plus 5-fluorouracil (5FU) in patients with gastric or gastroesophageal junction adenocarcinoma. Cohort 1 enrolled 259 patients, irrespective of PD-L1 status, who received at least two prior therapies for advanced disease (3L+) to receive pembrolizumab as a single agent. Cohort 3 enrolled PD-L1 positive patients (n=39) in the first-line metastatic setting.

- KN-061 is a randomized, multi-center, open-label study of pembrolizumab versus paclitaxel in subjects with advanced gastric or gastro-esophageal adenocarcinoma who progressed after first-line therapy with platinum and a fluoropyrimidine. This study planned to randomize approximately 590 patients (and is fully enrolled).

- KN-062 is an ongoing (submitted on June 29, 2015), randomized, active controlled, partially blinded study of pembrolizumab as a single agent and in combination with cisplatin plus 5FU versus cisplatin plus 5FU as a first-line treatment for patients with PD-L1-positive, HER2-*neu*-negative subjects with advanced gastric or gastro-esophageal adenocarcinoma. This study will randomize approximately 750 patients.

- KN-063 is a randomized, open-label clinical trial of pembrolizumab versus paclitaxel in Asian subjects with advanced gastric or gastro-esophageal adenocarcinoma who progressed after first-line therapy with platinum and a fluoropyrimidine. Like KN-061, the trial will enroll patients with advanced gastric or gastro-esophageal adenocarcinoma who progressed after first-line therapy with platinum and a fluoropyrimidine; however, the study will select patients based on PD-L1 status. This study will randomize approximately 360 patients.

- KN-585 is a (planned) randomized, double-blind study of pembrolizumab plus chemotherapy versus placebo plus chemotherapy (cisplatin plus capecitabine or 5FU) as neoadjuvant/adjuvant treatment for gastric or esophageal adenocarcinoma. The study will enroll approximately 800 patients.

Summary Results

Merck is planning to submit data from monotherapy cohorts of two single-arm studies in support of a planned sBLA (KN-012 and KN-059). To address the patient population with unmet medical need, Merck is specifically proposing to submit data from Cohort 1 of KN-059. Patients

in KN-059 received pembrolizumab 200 mg every three weeks. Patients in KN-012 received pembrolizumab 10 mg/kg every two weeks.

KN-059 was originally submitted to IND 123482 on November 21, 2014. The original plan for cohort 1 was to enroll 115 to 180 subjects, depending on the results of a futility analysis for PD-L1-negative subjects at the time of an interim analysis [after ORR data from approximately 25 PD-L1-negative patients (~40 all-comers) were available]. Futility in the PD-L1 negative population was to be considered if the upper bound of the 95% CI was less than 20% (consisting of 1 or fewer responses out of 25 patients). Enrollment was intended to stop after enrollment of at least 90 PD-L1-positive patients. PD-L1 positivity was defined as immunohistochemistry staining ≥ 1% based on the combined positive score (CPS). The CPS method captured the sum of all PD-L1 membrane-stained cells at any intensity (tumor cells, macrophages, lymphocytes) in the tumor microenvironment over the total tumor cells present, expressed as a percentage. With 90 PD-L1 positive subjects, if there are no less than 16 responders observed, the lower bound of the 95% confidence interval for ORR will be above 10% (with an estimated historical response rate of 5 to 10%).

The statistical analysis plan for KN-059 was amended on April 15, 2015, lowering the sample sizes of Cohorts 2 and 3 without changing the sample size for Cohort 1. The protocol was again amended on November 6, 2015. This amendment stated that by July 23, 2015, 42 all-comer subjects were enrolled. The futility criterion was not met, so enrollment of PD-L1-negative subjects into Cohort 1 was permitted to continue (enrollment of PD-L1-negative subjects was suspended pending the interim DMC efficacy analysis). The revised protocol stated that enrollment after the interim analysis would not stop until at least 80 all-comer subjects meeting the revised eligibility criteria were enrolled. As implementation of the amendment would take time, it was estimated that approximately 135 all-comer subjects would be enrolled after the interim analysis, including about 55 all-comer subjects enrolled under the original protocol and 80 under the amendment (with an estimated sample size of 210 in cohort 1).

Cohort 1 included patients who progressed on two or more lines of prior systemic therapy. KN-059 ultimately enrolled 259 patients of whom 51.7% received pembrolizumab in the third-line setting and 48.3% received pembrolizumab in the fourth (or greater)-line settings. Most patients were male (76%) and 43% were older than 65 years with a median age of 62 years. Most patients were White 77%; 16% were Asian; and 2% were Black. Nearly half (48%) of the patients were enrolled in the U.S.

PD-L1 status was assessed for 99% of patients; more than half (57%) were PD-1-positive. Other disease characteristics included HER-2-negative 74%; M1 metastatic staging 86%; brain metastasis 1.5%, and histologic tubular adenocarcinoma 94%. All subjects received prior 5FU and platinum agents; 84% received a taxane, 48% capecitabine, 45% irinotecan, 41% anti-VEGF/VEGFR monoclonal antibody, 27% anthracycline, and 24% anti-HER2/*neu* monoclonal antibody. One quarter of the patients had undergone partial or total gastrectomy.

The following table includes results summarized by Merck from the meeting package (from both KN-059 and KN-012). Response rates are those that were confirmed by independent central review.

	CR % 95% CI	PR % 95% CI	ORR % 95% CI	Duration of Response (months)
KN-59 (all comers) (n=259)	1.9 (0.6, 4.4)	9.3 (6.0, 13.5)	11.2 (7.6, 15.7)	8.1 (1.4+, 15.1+)
by line of therapy				
--3rd line (n=134)	3.7 (1.2, 1.85)	11.2 (6.4, 17.8)	14.9 (9.4, 22.1)	6.7 (1.4+, 15.1+)
--4th+ line (n=125)	0.0 (0.0, 2.9)	7.2 (3.3, 13.2)	7.2 (3.3, 13.2)	Not reached (1.4+, 12.2+)
by PD-L1 status				
--PD-L1 positive (n = 148)	2 (0.4, 5.8)	13.5 (8.5, 20.1)	15.5 (10.1, 22.4)	Not reached (1.4+, 15.1+)
--PD-L1 negative (n = 109)	1.8 (0.2, 6.5)	3.7 (1.0, 9.1)	5.5 (2.0, 11.6)	4.3 (2.4, 6.9)
KN-12 (cohort D) N=39	2.6 (0.1, 13.5)	17.9 (7.5, 33.5)	20.5 (9.3, 36.5)	9.5 (5.6, 22.1+)

Merck stated that among the 75 patients with PD-L1-positive disease *in the third-line setting*, the response rate was 21.3% (12.7, 32.3) with a median duration of response of 6.7 months (1.4+, 15.1+). Merck also provided summary data from cohorts 2 and 3 of KN-059. In the first-line setting (monotherapy), ORR was 25.8% (11.9, 44.6) among 31 patients with a median duration of response not reached (2.1, 11.6+).

In KN-012, the response rate was 20.5% (n=8) out of 39 patients. Based on data submitted to an efficacy supplement under review (BLA 125514/S-14), tissue was available from 96 of 297 (30%) subjects for MSI-H testing. Four patients with gastric cancer were identified as MSI-H, of which responses were observed in two.

FDA emailed preliminary comments to Merck on January 28, 2017.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical and Statistical

1. *KEYNOTE-059 Cohort 1 (KN059; N = 259) is a single arm study of pembrolizumab monotherapy in subjects with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (hereafter, "gastric cancer") whose disease has progressed on or after two or more lines of previous systemic therapy including fluoropyrimidine and platinum agents (third-line plus [3L+] patients). This includes third line subjects (N=134) as well as 4L+ subjects (N=125).*

Does the Agency agree that (b) (4)

FDA Response:
No. Given the low response rate and limited durations of response in patients with PD - L1-negative gastric cancer, FDA questions whether there is substantial evidence of a treatment effect likely to predict clinical benefit for all patients with gastric cancer, including those with PD-L1 negative tumors. Furthermore, given the overall modest response rate in patient with PD-L1-positive gastric cancer and lack of data in the submission regarding dMMR/MSI-H status (which according to The Cancer Genome Atlas may occur in an estimated 22% of patients with gastric cancer and which may be a better predictor for response to a checkpoint inhibitor than PD-L1 tumor expression), FDA is likely to seek input from an advisory committee regarding an application for pembrolizumab for the treatment of refractory gastric cancer. FDA recommends that Merck, to the extent possible, further characterize the tumor biology of the patients studied in KN-059 (e.g., dMMR/MSI-H, EBV, and TP53 mutation status).

Furthermore, FDA notes that the study design did not include a prespecified analysis plan and hypothesis to be tested. In the sBLA, please provide sensitivity analyses based on subgoups defined by PD-L1 status for the first 180 subjects (estimated sample size from the original protocol) and for the first 210 subjects (amended sample size based on the revised protocol submitted November 6, 2015) enrolled into the protocol.

The sBLA should contain a minimum of 6 months of follow-up from the onset of response for all patients with an independently confirmed objective response in KN-059 in order to characterize the durability of response. Data on response duration will be necessary to conclude that the observed response rate is reasonably likely to predict clinical benefit.

Discussion:
Merck summarized the available data for the overall population, by PD-L1 status, by dMMR/MSI-H status for the 66% of the population for which this is known, and by various cutpoints for date of enrollment (i.e., based on dates of protocol revisions that modified the protocol eligibility criteria). FDA acknowledged the summary results and stated that FDA's concerns regarding the role of MSI status and PD-L1 status as independent predictive factors for response to treatment should be addressed in the proposed sBLA. FDA again expressed concerns regarding the ability of the observed response rate, including the lower bound of the 95% confidence interval, (b) (4) .

Based on Merck's description of the maturity of the data, FDA stated that it is acceptable for Merck to submit the sBLA with the January 16, 2017, data cut-off date where 3 of the 30 responders have less than 6 months for follow-up for response. FDA requested that Merck submit a proposal for submission, during the review of the sBLA, of updated duration of response data. Merck agreed to do so.

2. *Data from KN059 Cohort 1 (N=259) are proposed as the basis of this sBLA, along with data from a small cohort (N=39) of gastric cancer subjects in study KN012 provided as supportive evidence. Differences in study design for KN012 and KN059 include population (any line of therapy vs. 3L+); PD-L1 status (PD-L1 positive vs. all-comers); and dose (200 mg Q3W vs. 10 mg/kg Q2W). Due to these differences, the Sponsor does not plan to integrate efficacy data from KN012 and KN059. The Sponsor anticipates that the clinical summary of efficacy (2.7.3) will contain all discussion and data necessary to support the review within the expected document size limitations.*

   Does the Agency concur that a dossier consisting of the KEYNOTE-059 CSR, KEYNOTE-012 CSR, and Modules 2.5, 2.7.1, 2.7.2, 2.7.3, 2.7.4, and ISS (but no ISE) would be acceptable to support review of the sBLA?

   FDA Response:
   FDA does not object to Merck's plan for summarizing efficacy data. Although an ISE is required, Merck may submit the narrative portion of the ISE in Module 2 while referencing the narrative portion of Module 2 in Module 5, with additional figures, tables, and appendices, if appropriate, to be submitted in Module 5.

   Discussion:
   Merck did not have any questions or comments.

3. *The CSRs of two studies will be included in this sBLA. KN059 is the pivotal study with N = 259 subjects enrolled in cohort 1 for which the sBLA submission will be based. The KN012 gastric cancer cohort (cohort D) is a supportive study with N = 39.*

   Does the Agency agree that the proposed submission dataset package will support the sBLA submission?

   FDA Response:
   Include the following

   a. SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

      Discussion:
      Merck will submit the requested information.

   b. SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.

      Discussion:
      Merck will submit the requested information.

   c. A mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not

limited to, the variables for reasons of censoring, dates of IRC determined event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should also be included.

Discussion:
FDA stated that Merck's proposed approach as outlined in slides #23 and #24 is acceptable. Merck agreed to provide the algorithms for all derived variables and links to the original variables in the sBLA. In addition, Merck agreed to provide a meta datasheet to link SAS programs to analysis results and to submit a PDF version of define files as well as an XML version.

Safety

4. *The Sponsor proposes the following integrated summary of safety (ISS) approach. For all summaries, safety data for KN059 Cohort 1 (3L+ subjects treated with monotherapy pembrolizumab) will be presented side by side in the same table with the following:*

   - *Reference safety data pooled from KN001 (lung and melanoma), KN002 (melanoma), KN006 (melanoma), and KN010 (lung) studies.*
   - *Pooled safety data for pembrolizumab from KN059, the Reference Safety Dataset consisting of KN001, KN002, KN006, KN010 as well as safety data from KN012 Cohort D and all other Keytruda trials that have been submitted to the Agency up to 4 weeks prior to the database lock (DBL) date for KN059 (referred to as Cumulative Running Safety Dataset).*

   Does the Agency agree with this approach for presenting safety data for pembrolizumab to support the sBLA?

   FDA Response:
   Yes.

   Discussion:
   Merck did not have any questions or comments.

5. *The Sponsor is targeting the sBLA submission for February, 2017 without a subsequent safety update report (SUR) given that the safety profile for Keytruda is well understood.*

   Does the Agency agree with this SUR approach?

   FDA Response:
   FDA does not agree with the proposed timing of the sBLA submission as discussed in FDA's response to Question #1 because there is insufficient information regarding durability of responses. Please provide an alternative date for submission of the sBLA which will ensure inclusion of a minimum of 6 months of follow-up from the onset of response for all patients with an independently confirmed objective response.
   FDA agrees that submission of a 120 day safety update report is not required for this sBLA.

Discussion:
Merck did not have any questions or comments.

Clinical Pharmacology

6. *The Sponsor proposes* [redacted] (b) (4)

Does the Agency agree with this proposal?

FDA Response:
No, FDA recommends that Merck conduct dose/exposure-response modeling for KN-059 (200 mg Q3W) versus KN-012 (10 mg/kg Q2W) in gastric cancer to support justification for the proposed dose.

During the January 13, 2017, clinical pharmacology guidance meeting, FDA stated that questions remain as to 1) the nature of the dose-response or exposure-response relationships as a function of PD-L1 status; and 2) the pembrolizumab dose that maximizes efficacy in various monotherapy indications (especially for MSI-H cancer). Merck should carefully consider whether a dose-response or exposure-response assessment may be needed for the new monotherapy setting in which pembrolizumab could conceivably show different effects by PD-L1 status or for which the regimens proposed may not be optimized.

Discussion:
Merck stated that they have performed the requested modeling (see slides #18-21) and will submit the data in the sBLA. In addition, Merck will include in the sBLA all analyses necessary to bridge safety and efficacy in support of the proposed fixed pembrolizumab dosage regimen of 200 mg every 3 weeks.

OSI

7. *The Sponsor plans to provide site level datasets in the sBLA to aid the Office of Scientific Investigation (OSI) in identifying clinical trial sites for inspections for the trial. Financial disclosure information will not be included in the summary level dataset since this information is sensitive and has extremely limited distribution within Merck. Note that this information is provided by a separate group within Merck and will be available within module 1.3.4 of the sBLA.*

Does the Agency agree that providing site level datasets with no financial disclosure information will satisfy OSI requirements?

FDA Response:
FDA does not object to Merck's proposal.

Discussion:
Merck did not have any questions or comments.

8. *Does the Agency agree that providing summary level clinical site datasets and financial disclosure information for KN059 only, and not for KN012, meets the requirements for review of this sBLA?*

FDA Response:
Yes. This is acceptable for the purposes of determining whether bioresearch monitoring inspections should be conducted.

Discussion:
Merck did not have any questions or comments.

PREA REQUIREMENTS

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to Merck Sharp and Dohme Corp. when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), Merck Sharp and Dohme Corp. must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

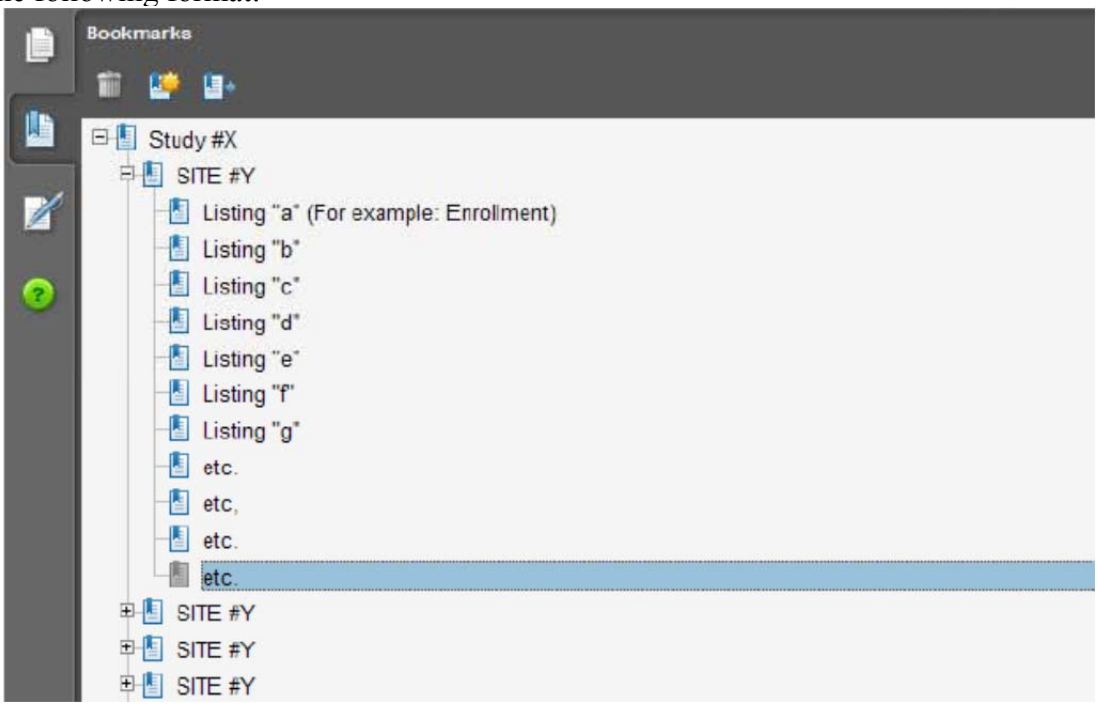
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ACTION ITEMS

Action Item/Description	Owner	Due Date
Proposal regarding submission of updated duration of response data during the review of the sBLA	Merck	ASAP

ATTACHMENTS AND HANDOUTS
Merck's presentation

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

/s/

BRENDAN O BAGGOT
02/09/2017