

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125514Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 26, 2014

To: Patricia Keegan, MD  
Director  
**Division of Oncology Products 2 (DOP2)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Jessica N. Cleck-Derenick  
Team Leader  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): KEYTRUDA (pembrolizumab)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 125514

Applicant: Merck Sharp & Dohme Corporation

## 1 INTRODUCTION

On February 27, 2014, Merck Sharp & Dohme Corporation submitted for the Agency's review the final portion of a rolling submission for Original Biologics License Application (BLA) 125514 for KEYTRUDA (pembrolizumab) for injection. KEYTRUDA (pembrolizumab) is indicated for the treatment of unresectable or metastatic melanoma who have progressed following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

On March 10, 2014 DMPP and OPDP received requests from the Division of Oncology Products 2 (DOP2) to review the Applicant's proposed Patient Package Insert (PPI) for KEYTRUDA (pembrolizumab) for injection submitted on February 27, 2014. On August 7, 2014 the Applicant submitted a Medication Guide (MG) in response to the Agency's Late-Cycle Meeting (LCM) Background Package dated July 30, 2014, which included a request for submission of a MG which will become a part of the approved product labeling. This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Oncology Products 2 (DOP2) to review the patient labeling (MG).

## 2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) for injection MG received on August 7, 2014, further revised by the Review Division and received by DMPP and OPDP on August 20 and August 22, 2014.
- Draft KEYTRUDA (pembrolizumab) for injection Prescribing Information (PI) received on February 27, 2014 revised by the Review Division throughout the review cycle, and received by DMPP on August 20 and August 22, 2014.
- Draft KEYTRUDA (pembrolizumab) for injection Prescribing Information (PI) received on February 27, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 13, 2014.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

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/s/  
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SHARON R MILLS  
08/26/2014

JESSICA N CLECK-DERENICK  
08/26/2014

BARBARA A FULLER  
08/26/2014

LASHAWN M GRIFFITHS  
08/26/2014



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research**

Division of Monoclonal Antibodies  
Office of Biotechnology Products

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## **FINAL LABEL AND LABELING REVIEW**

**Date:** August 25, 2014

**Reviewer:** Jibril Abdus-Samad, PharmD  
Division of Monoclonal Antibodies (DMA)

**Through:** Deborah Schmiel, PhD, Product Quality Reviewer  
Division of Monoclonal Antibodies

Sarah Kennett, PhD, Review Chief  
Division of Monoclonal Antibodies

**Application:** BLA 125514

**Product:** Keytruda (Pembrolizumab)

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

**Submission Dates:** December 20, 2013; February 27, 2014;  
May 23, 2014; July 15, 2014; August 8, 2014;  
August 12, 2014; and August 14, 2014

### **Executive Summary**

The container label and carton labeling for Keytruda (Pembrolizumab) were reviewed and found not to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, [8/1/14 to 11/30/14 revision] USP 37/NF32. Labeling deficiencies were identified, mitigated, and resolved. The container label and carton labeling submitted on August 14, 2014 are acceptable.

## Background and Summary Description

BLA 125514, Keytruda (pembrolizumab) has a proposed indication for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab. Keytruda is supplied as a single-dose vial containing 50 mg lyophilized powder for injection. The recommended dose is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

### Materials Reviewed:

- Container Label submitted February 27, 2014; May 23, 2014; July 15, 2014; August 8, 2014; and August 14, 2014
- Carton Labeling submitted May 23, 2014; July 15, 2014; August 8, 2014; and August 14, 2014
- Prescribing Information submitted May 23, 2014

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Start of Sponsor Material

(b) (4)

End of Sponsor Material

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### Subpart G-Labeling Standards Subpart A-General Labeling Provisions

## I. Container

### A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *Conforms.*

(2) The name, address, and license number of manufacturer; **Does not conform. Manufacturer is listed as (b) (4) rather than "Manufactured by." As defined in 21 CFR 600.3(t), manufacturer is the "Applicant." See Information Request (IR).**

(3) The lot number or other lot identification; *Conforms.*

(4) The expiration date; *Conforms.*

(5) The recommended individual dose, for multiple dose containers. *Not applicable. This is a single-dose vial.*

(6) The statement: "Rx only" for prescription biologicals. *Conforms.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable. This product does <sup>(b) (4)</sup> have a Medication Guide.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. **Does not conform. See IR.**

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *Conforms.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *Conforms.*

D. 21 CFR 201.6 Drugs; misleading statements; *Conforms.*

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] *Conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *Conforms*.

G. 21 CFR 201.17 Drugs; location of expiration date; *Conforms*.

H. 21 CFR 201.25 Bar code; *Conforms*.

I. 21 CFR 201.50 Statement of identity; *Conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *Conforms*.

K. 21 CFR 201.55 Statement of dosage; *Conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *Conforms*.

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Start of Sponsor Material

- Carton Labeling for drug substance manufactured in (b) (4)

(b) (4)



- Carton Labeling for drug substance manufactured in the US

(b) (4)

End of Sponsor Material

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## **II. Carton**

### A. 21 CFR 610.61 Package Label

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *Conforms.*
- b) The name, addresses, and license number of manufacturer; **Does not conform. Manufacturer is listed as (b) (4) rather than "Manufactured by." As defined in 21 CFR 600.3(t), manufacturer is the "Applicant. See IR.**
- c) The lot number or other lot identification; *Conforms.*
- d) The expiration date; *Conforms.*

- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative". *Conforms.*
- f) The number of containers, if more than one; *Not applicable.*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *Conforms.*
- h) The recommended storage temperature; *Conforms.*
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *Not applicable.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *Not applicable.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *Conforms.*
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *Not applicable. No sensitizing substances.*
- m) The type and calculated amount of antibiotics added during manufacture; *Not applicable.*
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *Conforms. However, the inactive ingredients should be listed in alphabetical order as per USP 37/NF32 (8/1/14-11/30/14) General Chapters:<1091> Labeling of Inactive Ingredients.*
- o) The adjuvant, if present; *Not applicable.*

p) The source of the product when a factor in safe administration; *Not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *Not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; **Does not conform. Add "No U.S. Standard of Potency"**.

s) The statement "Rx only" for prescription biologicals; *Conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)*]

*Exempt.* Pembrolizumab is a "specified" biological product.

- a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.
- b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.
- c) Legible type. All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *Not applicable*.

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for \_\_\_\_\_". "Distributed by \_\_\_\_\_", "Manufactured by \_\_\_\_\_ for \_\_\_\_\_", "Manufactured for \_\_\_\_\_ by \_\_\_\_\_", "Distributor: \_\_\_\_\_", or "Marketed by \_\_\_\_\_". The qualifying phrases may be abbreviated. *Not applicable*.

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; *Conforms*.

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] *Conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *Conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *Conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] *Conforms*.

J. 21 CFR 201.15 Drugs; prominence of required label statements; *Conforms*.

K. 21 CFR 201.17 Drugs; location of expiration date; *Conforms*.

L. 21 CFR 201.25 Bar code label requirements; *Conforms*.

M. 21 CFR 201.50 Statement of identity; *Conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *Conforms*.

O. 21 CFR 201.55 Statement of dosage; *Conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *Conforms*.

### III. Information Requests (IR)

IR sent on July 7, 2014

This information request references the updated container label and carton labeling submitted on May 23, 2014 for BLA 125514. We identified a few deficiencies that require your response. *The Applicant agreed with recommendations except where noted.*

#### A. General Comments

1. Revise the manufacturer information from [REDACTED] <sup>(b) (4)</sup> to "Manufactured by: Merck" to comply with the definition of manufacturer [21 CFR 600.3(t), 21 CFR 610.60 and 21 CFR 610.61.]. Thus, the manufacturer information should read as follows:

Manufactured by: Merck Sharp & Dohme Corp.,  
a subsidiary of Merck & Co. Inc.  
Whitehouse Station, NJ 08889, USA  
US License No. 0002

\*at

Schering-Plough (Brinny) Co.,  
County Cork, Ireland

*\*this site can be left off the container label if there is limited space.*

*Sponsor Response:*

*Merck accepts this proposal, with minor editorial differences. The vial label and carton labeling have been revised to reflect the proposed revisions.*

Manufactured by: Merck Sharp & Dohme Corp.,  
a subsidiary of

**MERCK & CO., INC.**

Whitehouse Station, NJ 08889, USA

US License No. 0002

At:

Schering-Plough (Brinny) Co.,  
County Cork, Ireland

Note: As suggested, the Schering-Plough Brinny site is not shown on the vial label, due to limited space.

2. Comment if there is any text on the ferrule and cap overseal. A revised USP standard went into effect on December 1, 2013. We refer you to the following address:  
[http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/genChapter1Labeling.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf)

*Sponsor Response:*

*The ferrule and cap overseal used in packaging Keytruda (pembrolizumab) do not contain any text. See photo images below.*



**B. Carton Labeling**

1. Add the statement "No U.S. standard of potency" to the carton labeling to comply with regulation 21CFR 610.61(r).
2. Revise the dosage form (b) (4) to 'For Injection' per United States Pharmacopeia (USP) 37/NF32 (5/1/14-7/31/14) General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature. This product is a lyophilized powder that requires reconstitution, thus 'For Injection' is the correct dosage form designation.
3. Revise the listing of the inactive ingredients to appear in alphabetical order to comply with USP 37/NF32 (5/1/14-7/31/14) General Chapters: <1091> Labeling of Inactive Ingredients.

*Sponsor Response:*

*Merck accepts this proposal. However, the inactive ingredients included on the carton labeling for pH adjustment are listed independently, as these ingredients are only added if required. The carton labeling has been revised to reflect the proposed revisions.*

4. Revise the storage statement [REDACTED] (b) (4) to read as follows:  
"Store vial refrigerated at 2°C - 8°C (36°F - 46°F)."

Note the deletion of [REDACTED] (b) (4)

### C. Container Label

1. When the label is affixed to the container, is there sufficient area on the container that remains uncovered for its full length or circumference to permit inspection of the contents per 21 CFR 610.60(e)?

*Sponsor Response:*

*The vial label used in packaging Keytruda (pembrolizumab) allows enables visual inspection based on the area which remains uncovered. See photo image below.*



2. See Comments B2, B3, and B4.

### IR sent August 5, 2014

This information request references the updated container label and carton labeling submitted on July 15, 2014 for BLA 125514. We identified a few deficiencies that require your response. Please respond by COB August 11, 2014. *The Applicant agreed with recommendations except where noted.*



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JIBRIL ABDUS-SAMAD  
08/25/2014

RASHMI RAWAT on behalf of DEBORAH H SCHMIEL  
08/25/2014

SARAH B KENNETT  
08/25/2014

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA # 125514  
Product Name: KEYTRUDA®

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PMR/PMC Description: A Pharmacology Study to further Investigate the Mechanism of Action of Pembrolizumab

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PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 10/31/2015  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

To further characterize the effect of pembrolizumab on the immune memory response.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The PMC is to conduct an animal study that will measure the effect of PD-1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. tetanus toxoid or KLH). This study will evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved, and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To conduct an animal study that will measure the effect of PD-1 inhibition on the magnitude of the primary (1<sup>st</sup> vaccination) and recall (2<sup>nd</sup> vaccination) antibody responses to antigen challenge (e.g. tetanus toxoid or KLH). This study will evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved, and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)  
Study to further define mechanism of action
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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SHAWNA L WEIS  
08/19/2014

WHITNEY S HELMS  
08/19/2014

JEFFERY L SUMMERS  
08/19/2014

# Internal Consult

\*\*\*Pre-decisional Agency Information\*\*\*

To: Sharon Sickafuse, Senior Regulatory Project Manager  
Division of Oncology Products 2 (DOP-2)  
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

Date: August 15, 2014

Re: **BLA 125514**  
**KEYTRUDA (pembrolizumab) for injection, for intravenous use**  
**OPDP Comments on proposed labeling (PI and Carton/Container)**

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In response to the Division of Oncology Products 2 (DOP-2) March 10, 2014, consult request, OPDP has reviewed proposed labeling (package insert (PI) and Carton/Container) for KEYTRUDA (pembrolizumab) for injection, for intravenous use. The version of the proposed substantially complete PI used in this review was sent via electronic mail from DOP-2 on August 13, 2014, and is titled, "KeytrudaPI\_JAug13.doc." The version of the proposed substantially complete Carton/Container labeling used in this review was sent via electronic mail from DOP-2 on August 15, 2014.

OPDP's comments on the proposed PI are provided directly in the attached document. Please note that OPDP hid DOP-2's deletions and formatting changes so that OPDP's comments are easier to read.

OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions regarding this consult review, please contact Carole Broadnax at 301-796-0575 or [Carole.Broadnax@fda.hhs.gov](mailto:Carole.Broadnax@fda.hhs.gov).

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/s/  
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CAROLE C BROADNAX  
08/15/2014

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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NDA/BLA # 125514  
Product Name: Keytruda (pembrolizumab)

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PMC #1 Description: To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the pembrolizumab drug substance release program. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.

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PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>08/31/2015</u>
Other:	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current assay and acceptance criterion for the assessment of host cell proteins in drug substance release program are sufficient to ensure adequate quality and safety of pembrolizumab for the initial marketed product. However, the improvement and implementation of a process-specific assay for HCP will provide better control of HCP levels in DS.

2. Describe the particular review issue and the goal of the study.

The current pembrolizumab Drug Substance (DS) release specifications include an ELISA method for evaluating HCP levels in DS. This method detects various (b) (4) (b) (4) (b) (4). The implementation of an improved, process-specific HCP assay will provide more accurate control of the host cell related impurities in DS.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Development and validation of a process specific HCP assay with improved sensitivity and capability to detect a greater range of potential HCP.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

---

NDA/BLA # 125514  
Product Name: Keytruda (pembrolizumab)

---

PMC #2 Description: To re-evaluate pembrolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

---

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>10/31/2015</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #3 Description: To re-evaluate pembrolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

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PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Pembrolizumab drug substance and drug product release and stability specifications approved under BLA are sufficient to ensure adequate quality and safety of pembrolizumab for the initial marketed product. Increased manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Pembrolizumab drug substance and drug product release and stability specifications are based on clinical and manufacturing experience provided in the BLA. However, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of pembrolizumab release data acquired following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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DEBORAH H SCHMIEL  
08/15/2014

RASHMI RAWAT on behalf of MARK PACIGA  
08/15/2014

RASHMI RAWAT  
08/15/2014

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

---

BLA # 125514  
Product Name: Keytruda (pembrolizumab)

---

PMR/PMC Description: Confirmatory trial(s) for pembrolizumab

---

PMR/PMC Schedule Milestones:

Study/Trial Completion: 03/30/2016  
Final Report Submission: 01/31/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Pembrolizumab is being approved under subpart E (accelerated approval); therefore, confirmatory trial(s) are required to verify and describe the clinical benefit of pembrolizumab in the proposed population, i.e., patients with unresectable or metastatic melanoma. These patients have a serious and life-threatening condition with an unmet medical need.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

N/A

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Confirmatory trial(s) required under the accelerated approval regulations (Subpart E).
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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JENNIE T CHANG  
08/13/2014

MEREDITH K CHUK  
08/14/2014

MARC R THEORET  
08/14/2014

JEFFERY L SUMMERS  
08/14/2014

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

---

NDA/BLA # 125514  
Product Name: Keytruda (pembrolizumab)

---

PMC #1 Description: To conduct a study to assess the endotoxin recovery at various time-points from 3 drug product lots spiked with Control Standard Endotoxin (7.5 EU/mL and 10 EU/mL) in vials using the Kinetic Turbidometric Assay.

---

PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2014</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>09/30/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: \_\_\_\_\_

---

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

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- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA AA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The application included endotoxin recovery studies performed using one lot of drug product. Data from two additional lots is needed for consistency of results.

2. Describe the particular review issue and the goal of the study.

The drug product formulation contains excipients which can impact endotoxin recovery from product samples. The goal of the study is to ascertain that the endotoxin is not masked and recovery is not impacted by the drug product formulation. The endotoxin masking effect was studied using only one lot of drug product and control standard endotoxin.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

To conduct a study to assess the endotoxin recovery at various time-points from 3 drug product lots spiked with Control Standard Endotoxin (7.5 EU/mL and 10 EU/mL) in vials using the Kinetic Turbidometric Assay. Data from one lot is available currently.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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SHARON K SICKAFUSE  
08/13/2014

PATRICIA F HUGHES TROOST  
08/13/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

DATE: July 21, 2014

TO: Sharon Sickafuse, Regulatory Health Project Manager  
Jennie Chang, Pharm.D., Medical Reviewer  
Meredith Chuk, M.D., Medical Reviewer  
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125514

APPLICANT: Merck Sharp & Dohme Corp.

DRUG: Keytruda™ (pembrolizumab, MK-3475)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of unresectable or metastatic melanoma patients who have been previously treated with ipilimumab.

CONSULTATION REQUEST DATE: March 21, 2014  
INSPECTION SUMMARY GOAL DATE: August 1, 2014  
DIVISION ACTION GOAL DATE: October 28, 2014  
PDUFA DATE: October 28, 2014

## I. BACKGROUND:

Merck Sharp & Dohme, Corporation (Merck), seeks approval to market MK-3475 (pembrolizumab) for the treatment of unresectable or metastatic melanoma patients who have been previously treated with ipilimumab (IPI). The key study supporting this application is 3475-001 [P001], “Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma.”

P001 is a Phase 1 multi-center, open-label study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumor activity of MK-3475 in patients with locally advanced or metastatic melanoma (IPI-naïve or previously treated with IPI), NSCLC, or carcinoma. Although P001 is labeled a Phase 1 study due to its initial dose escalation component, it evolved into multiple Phase 2-like sub-studies in melanoma and NSCLC through a series of expansion cohorts in these types of cancer.

Briefly, the trial was initially designed as a standard dose escalation trial, and was the first in human study of MK-3475. This part of the study is now called Part A of P001. During this part of the study, several patients with melanoma were enrolled and had an objective response to treatment, so the study was expanded to evaluate efficacy in melanoma in Part B (now Part B1). Through a series of amendments, P001 evolved into 4 Phase 2-like melanoma sub-studies, known as Parts B1, B2, B3, and D. **Part B2 is the sub-study in IPI-refractory melanoma that forms the primary basis for approval in the proposed indication in this application, and the focus of the clinical inspections.**

Part B2 was initiated under amendment 05 of P001 and amended once during the enrollment period primarily to increase the sample size of this part of the study, and to change the allocation schedule to achieve a final 1:1 randomization between arms. Subsequent amendments to P001 have not substantively altered the design or conduct of Part B2, except that under amendment 08, the primary method of assessment of the overall response rate (ORR) primary efficacy endpoint was changed from immune-related response criteria (irRC) to RECIST 1.1 by independent central review. The enrollment period was from 28-Aug-2012 until 05-Apr-2013 (the date of the first dose for the first and last patient enrolled, respectively).

As of the data cut-off (18-Oct-2013), the B2 cohort had randomized 173 subjects. The trial [B2] was conducted at 15 centers. Twelve (12) of these trial centers were in the United States; 1 was in Australia, 1 was in France, and 1 was in Canada. This study was conducted under IND 110080.

Three clinical sites were chosen for inspection: Site 12 (Dr. Wen-Jen Hwu, Houston, Texas), Site 20 (Dr. Anthony Joshua, Toronto, Ontario, Canada), and Site 19 (Dr. Naiyer Rizvi, New York, New York), based on enrollment of large numbers of study subjects. Also, Site 12 reported a lack of treatment effect, and Site 19 reported a high number of AEs, a low number of protocol violations and a high level of treatment effect. The study sponsor, Merck Sharp & Dohme Corp., was also inspected because this application is for a new molecular entity.

## II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Wen-Jen Hwu</b> 1515 Holcombe Boulevard Unit Number 430, Room Number Fc11.3010 Houston, TX 77030	Protocol: 3475-001 (Part B2)  Site Number: 12  Number of Subjects: 13	April 28, 2014 – May 2, 2014	Pending  Interim classification: NAI
<b>CI#2: Anthony Joshua</b> 610 University Avenue, 5th Floor, Medical Oncology Toronto, ON M5G 2M9 CAN Canada	Protocol: 3475-001 (Part B2)  Site Number: 20  Number of Subjects: 14	June 2-6, 2014	Pending  Interim classification: NAI
<b>CI#3: Naiyer Rizvi</b> 300 E. 66th Street New York, NY 10065	Protocol: 3475-001 (Part B2)  Site Number: 19  Number of Subjects: 23	April 29, 2014 – May 6, 2014	Pending  Interim classification: VAI
<b>Sponsor: Merck Sharp &amp; Dohme Corp.</b> One Merck Drive Whitehouse Station, NJ 08889-0100	Protocol: 3475-001 (Part B2)  Site Numbers: 12, 20, 19, 15 and 23	April 30, 2014 – May 19, 2014	Pending  Interim classification: NAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. CI#1: Wen-Jen Hwu, M.D. (Site 12)**

- a. What was inspected:** The site screened 14 subjects, 13 subjects were enrolled, and none completed the study. At the time of the inspection five subjects were deceased, and three subjects had withdrawn due to progressive disease and/or AEs, and five subjects are currently in the B2 cohort receiving treatment. The study records of all 14 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125514, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoint for the study is overall response rate (ORR) based on RECIST 1.1 by integrated radiology and oncology analysis (IRO) [independent central review of imaging studies + limited objective clinical data by an independent oncologist]. The source records audited at this site supported the independent central review-reported efficacy outcome measure submitted to BLA 125514. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data for Dr. Hwu's site, associated with Study 3475-001 (Part B2) submitted to the Agency in support of BLA 125514, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**2. CI#2: Anthony Joshua, M.D. (Site 20)**

- a. What was inspected:** The site screened 15 subjects, 14 subjects were enrolled. All study records of all subjects were audited. At the time of the inspection seven subjects were deceased, two subjects were in follow-up for survival, and five subjects were in the B2 cohort receiving treatment. The study records of all 14 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125514, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in

accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoint for the study is overall response rate (ORR) based on RECIST 1.1 by integrated radiology and oncology analysis (IRO) [independent central review of imaging studies + limited objective clinical data by an independent oncologist]. The source records audited at this site supported the independent central review-reported efficacy outcome measure submitted to BLA 125514. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data for Dr. Joshua's site, associated with Study 3475-001 (Part B2) submitted to the Agency in support of BLA 125514, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### 3. CI#3: Naiyer Rizvi, M.D. (Site 19)

- a. What was inspected:** For all cohorts under protocol 3475-001, the site screened 144 subjects, 89 subjects were enrolled, and none had completed the study. The study records of all 23 subjects enrolled under Part B2 (malignant melanoma) were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125514, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. Per the protocol, the primary efficacy endpoint for the study is overall response rate (ORR) based on RECIST 1.1 by integrated radiology and oncology analysis (IRO) [independent central review of imaging studies plus limited objective clinical data by an independent oncologist]. The source records audited at this site supported the independent central review-reported efficacy outcome measure submitted to BLA 125514. There was some evidence of underreporting of adverse events. Review of source documentation for

eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. There were some instances of missed study-specified procedures, however, they appeared to be limited and should not importantly impact overall study outcome. During the inspection the PI (Dr. Rizvi) indicated that they had already implemented corrective action plans for this observation. A Form FDA 483 was issued citing two inspectional observations.

(b) (4)

*OSI Reviewer Note: The primary analysis data cut-off for Study 3475-001 (Part B2) for this application is October 18, 2013. Therefore, AEs reported in the application for this site as of the data cut-off appear to be incomplete for seven subjects enrolled at this site. On June 12, 2014, OSI reviewer contacted CDTL Mark Theoret and discussed preliminary observations. Dr. Theoret requested that OSI work directly with the clinical reviewer for safety, Meredith Chuk, and determine if the application does not have these AEs listed in SAS datasets. Dr. Chuk confirmed on June 12, 2014, that none of the AEs above are listed in the AE data listings submitted with the application. Dr. Chuk noted that there are other AEs entered (some for the same patients and some after the listed AEs above) for all patients except 0335. Therefore, OSI recommended that an IR be sent to the sponsor communicating the observation and requesting confirmation and correction to the application as needed for these subjects as well as all subjects and all sites for the same study. On June 18, 2014, an IR was sent to the sponsor requesting clarification and corrections to the application as needed. The Sponsor's response was submitted to the application on June 26, 2014.*

*Briefly, Merck conducted a cumulative review of internal audits, Quality Control Visit's, interim monitoring visits, investigator visit reports, as well as the recent FDA inspection findings at Site 19. Specifically, Merck conducted a review of all sites participating in the study (Part B2) and found that sustained incomplete reporting of AEs was limited to Site 19. Further, the sponsor noted that the deficiency at this site did not change the safety profile of the investigational drug, pembrolizumab.*

*Merck agreed that the FDA field investigator identified 27 potential non serious AEs in 7 patients during an inspection at Site 19. However, as indicated in the Form FDA 483 response of Site 19 (Dr. Rizvi) to the inspection, not all of the 27 AEs noted were unreported adverse experiences, as some were part of medical history, and some were symptoms of previously reported adverse experiences or did not meet the definition of a Common Terminology Criteria for Adverse Events (CTCAE). Of the 27 AEs cited by the investigator, 19 AEs in 6 patients were previously unreported and are summarized in the sponsor's response. Of note, all of these were Non Serious Adverse Events (NSAEs), all but one was grade 1, and none were Events of Clinical Interest (ECIs). For these reasons, the addition of these NSAE's has no clinically meaningful impact on the safety profile of pembrolizumab.*

*Merck concluded that the route cause for the inspectional observations at Site 19 were as follows:*

- 1) Despite the monitor's efforts, the site failed to adhere to their own (Site 19), as well as Merck's, process for AE reporting.*
- 2) Merck's maintenance of and subsequent escalation process for unreported AEs was not followed. Although, the CRA and her supervisor documented the missing AE reporting at the site and initiation of re-training of the site staff (IVR February 2013 and July 2013 and QCV July 2013) the subsequent escalation process was not followed and the source data verification (SDV) was decreased after recognition of an AE reporting issue at the site. Additionally, the CRA failed to identify 3 AEs during SDV.*

*The protocol did not specify a time requirement for data entry from study source documents into CRFs. Therefore, while the site had properly documented AEs in source records, they appeared to be quite slow in updating the electronic CRF. OSI concurs with Merck's conclusion based upon available information, and acknowledges that the sponsor has already implemented corrective actions to mitigate these findings moving forward. In addition, Dr. Chuk informed via email on July 18, 2014 that the review division has also reviewed the sponsor's response and believe it is adequate, concurs that the issue appears to be limited to one site (Site 19) and that the missing AEs in datasets should not have a significant effect on the overall safety assessment of MK-3475.*

(b) (4)



*OSI Reviewer Note: According to the FDA field investigator, the site had already implemented a corrective action plan (CAP) to mitigate these inspectional findings moving forward. The plan was implemented prior to the current inspection.*

*However, the current inspection did not verify CAP implementation.*

- c. Assessment of data integrity:** The review division may wish to determine the impact, if any, of missing AEs on the overall safety assessment of MK-3475. Notwithstanding the inspectional observations noted above, the data for Dr. Rizvi's site, associated with Study 3475-001 (Part B2) submitted to the Agency in support of BLA 125514, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

#### **4. Sponsor: Merck Sharp & Dohme Corp.**

- a. What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on adherence to protocol, and review of the firm's SOPs, monitoring reports and actions related to monitoring deficiencies. Ethics Committee/IRB approvals, completed Form FDA 1572s, and communications with the sites were also generally covered. The FDA field investigator specifically audited subject records from five clinical study sites, and assessed the AEs and primary efficacy endpoints. The five audited sites included the three sites listed in the table above, Sites 12, 20, and 19, and two additional sites, Sites 15 (Dr. Antoni Ribas, Los Angeles, CA) and 23 (Dr. Richard Kefford, Westmead, New South Wales, Australia).
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the study. Monitoring appeared to be adequate; AEs and the primary efficacy endpoint data were verifiable. There were no discrepancies between audited subject CRFs and the data listings submitted to BLA 125514; primary endpoints and SAEs from the CRFs appear to have been correctly reported in the CSR. There was no evidence of under-reporting of AEs/SAEs by the sponsor.

There were some late and/or inaccurate monitoring visit records. These observations were discussed with management at the applicant's site. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data generated at this site, as it pertains to Study 3475-001 (Part B2) were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this sponsor submitted to the Agency in support of BLA 125514 appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Wen-Jen Hwu (Site 12), Dr. Anthony Joshua (Site 20), Dr. Naiyer Rizvi (Site 19) and the sponsor, Merck Sharp & Dohme Corp., the Study 3475-001 (Part B2) data appear reliable based on available information. Based on the review of preliminary inspectional findings for clinical investigator Naiyer Rizvi, AEs reported in the application for this site as of the data cut-off appear to be incomplete for seven subjects enrolled at this site. The primary analysis data cut-off for Study 3475-001 (Part B2) for this application is October 18, 2013. On June 18, 2014, an IR was sent to the sponsor requesting clarification and corrections to the application as needed. The Sponsor's response was submitted to the application on June 26, 2014.

The preliminary classification for clinical investigators Dr. Wen-Jen Hwu, Dr. Anthony Joshua, and for the sponsor, Merck Sharp & Dohme Corp., is No Action Indicated (NAI). The preliminary classification for clinical investigator Dr. Naiyer Rizvi is Voluntary Action Indicated (VAI). The record audit of subject records at these clinical sites included comparison of source documentation to CRFs and data listings submitted to BLA 125514, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, the primary efficacy endpoint, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigators also assessed informed consent documents, test article accountability, and monitoring reports. Per the protocol, the primary efficacy endpoint for the study is overall response rate (ORR) based on RECIST 1.1 by integrated radiology and oncology analysis (IRO) [independent central review of imaging studies + limited objective clinical data by an independent oncologist]. The source records audited at the sites supported the independent central review-reported efficacy outcome measure submitted to BLA 125514.

With the exception of Site 19 (Dr. Rizvi), there was no evidence of underreporting of adverse events to the sponsor. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no major discrepancies.

According to Merck's response to the IR regarding inspectional observations at Site 19, they conducted a cumulative review of internal audits, Quality Control Visit's, interim monitoring visits, investigator visit reports, as well as the recent FDA inspection findings at Site 19. Specifically, Merck conducted a review of all sites participating in the study (Part B2) and found that sustained incomplete reporting of AEs was limited to Site 19. Further, the sponsor noted that the deficiency at this site did not change the safety profile of the investigational drug, pembrolizumab. OSI concurs with Merck's conclusion based upon available information, and acknowledges that the sponsor has already implemented corrective actions to mitigate these findings moving forward.

In addition, Dr. Chuk informed via email on July 18, 2014 that the review division has also reviewed the sponsor's response and believe it is adequate, concurs that the issue appears to be limited to one site (Site 19) and that the missing AEs in datasets should not have a significant effect on the overall safety assessment of MK-3475.

The sponsor inspection focused on adherence to the protocol, and review of the firm's SOPs, monitoring reports and actions related to monitoring deficiencies. Comparison of CRFs and the key data listings submitted to BLA 125514 found no major discrepancies. Ethics Committee/IRB approvals, completed Form FDA 1572s, and communications with the sites were also generally covered.

Based upon available information the overall data for Study 3475-001 (Part B2) in support of this application may be considered reliable based on available information.

**Note:** The observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

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/s/  
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LAUREN C IACONO-CONNORS  
07/21/2014

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07/22/2014

KASSA AYALEW  
07/22/2014

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>BLA</b>	125,514
<b>Brand Name</b>	Keytruda
<b>Generic Name</b>	Pembrolizumab
<b>Sponsor</b>	Merck Sharp & Dohme Corp.
<b>Indication</b>	<p>(b) (4) diagnosis of melanoma with progressive locally advanced or metastatic disease (Cohorts B and D)</p> <p>Treatment of unresectable or metastatic melanoma patients who have been previously treated with ipilimumab</p>
<b>Dosage Form</b>	Intravenous Injection
<b>Drug Class</b>	Oncology
<b>Therapeutic Dosing Regimen</b>	2 mg/kg intravenously (IV) every 3 weeks (Q3W)
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Maximum tolerated dose was not determined as doses above 10mg/kg IV every 2 weeks (the maximum administered dose) were not tested
<b>Submission Number and Date</b>	SDN 005 / March 25, 2014
<b>Review Division</b>	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

This study was comprised of five-parts: Part A (including A1 and A2), Part B (including B1 and B2), Part C, Part D (melanoma) and Part F (including F1 and F2). Sponsor submitted ECG data for Parts A, B1, B2, C and D of PN001. No large change (i.e., > 20 ms) in the QTc interval was detected when MK-3475 was administered up to 10 mg/kg Q3W. The sponsor did not submit positive control (moxifloxacin) arms.

This was phase 1, open-label, dose-escalation study, 479 patients received 1 mg/kg Q2W, 2 mg/kg Q2W, 3 mg/kg Q3W, 10 mg/kg Q2W and 10 mg/kg Q3W. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MK-3475 (FDA Pooled Analysis)**

Treatment	$\Delta$ QTcF (ms)	90% CI (ms)
MK-3475 1 mg/kg Q2W	8.0	(1.3, 14.7)
MK-3475 2 mg/kg Q3W	2.0	(0.4, 3.7)
MK-3475 3 mg/kg Q2W	-6.6	(-12.3, -0.9)
MK-3475 10 mg/kg Q2W	3.9	(1.6, 6.2)
MK-3475 10 mg/kg Q3W	3.2	(1.7, 4.6)

The studied MK-3475 exposures are at the expected therapeutic dose range. It is unclear whether intrinsic factors or extrinsic factors will affect the PK of MK-3475 as exposure data in patients with renal or hepatic impairment are not available as is the case for drug-drug interactions. Some of these potential factors are not anticipated to affect the PK of MK-3475 as this product is a monoclonal antibody.

## **2 PROPOSED LABEL**

*There is no QT-related language in the proposed label. Our proposed language is a recommendation only. We defer final labeling language to the Division.*

### 12.6 Cardiac Electrophysiology

The effect MK-3475 at doses up to 10 mg/kg on the QTc interval was evaluated in an open label, Phase I study in more than 500 patients with progressive locally advanced or metastatic carcinomas, melanoma, or non-small cell lung cancer (NSCLC). No large changes in the mean QT interval (i.e., >20 ms) were detected in the study.

## **3 BACKGROUND**

### **3.1 PRODUCT INFORMATION**

MK-3475 is a selective humanized mAb of the IgG4/kappa isotype designed to block directly the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

### **3.2 MARKET APPROVAL STATUS**

MK-3475 is not approved for marketing in any country.

### **3.3 PRECLINICAL INFORMATION**

MK-3475 is a monoclonal antibody and is not expected to be relevant to hERG channels. Thus, the applicant did conduct a hERG assay.

### **3.4 PREVIOUS CLINICAL EXPERIENCE**

There is no previous clinical experience for MK-3475 was provided. Currently, safety data is mainly from study PN001.

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of MK-3475's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study under IND 110,080. However, QT-IRT reviewed the sponsor's QT waiver request and agreed with that a TQT study report was not needed, but asked the sponsor to provide the study results for their study report P001V01. The sponsor submitted the study report P001V01 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

### 4.2 TQT STUDY

#### 4.2.1 Title

Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma

#### 4.2.2 Protocol Number

P001V01

#### 4.2.3 Study Dates

14-Apr-2011 - 26-Jul-2013

#### 4.2.4 Objectives

Primary:

- 1) To evaluate and characterize the tolerability and safety profile of single agent MK-3475 in adult patients with unresectable advanced carcinoma (including NSCLC or melanoma).
- 2) To evaluate anti-tumor activity of MK-3475 in melanoma and NSCLC per RECIST 1.1.
- 3) To evaluate the extent of tumor response that correlates with the degree of biomarker positivity in the tumors of ipilimumab naïve patients treated with MK-3475 with the intent that the cut point for the PD-L1 assay will be explored and refined with tumor samples from ipilimumab-naïve melanoma.
- 4) To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in unselected melanoma refractory to ipilimumab patients and melanoma patients refractory to ipilimumab with PD-L1 expressing tumors.

Secondary Objectives

- 1) To evaluate the RR of unselected patients with melanoma refractory to ipilimumab and melanoma naïve to ipilimumab, patients with melanoma refractory to ipilimumab and melanoma naïve to ipilimumab whose tumors express PD-L1, and patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1, per immune-related response criteria.

- 2) To characterize the PK profile of single agent MK-3475.
- 3) To evaluate target engagement and modulation in peripheral blood (PD-1 receptor occupancy and modulation of receptor activity).
- 4) To evaluate response duration, progression-free-survival and overall survival of melanoma patients who are treated with MK-3475.

## **4.2.5 Study Description**

### **4.2.5.1 Design**

This was an open-label, Phase I study of intravenous (IV) MK-3475 in patients with progressive locally advanced or metastatic carcinomas, melanoma, or non-small cell lung cancer (NSCLC). Part A of the study involved dose escalation that used a traditional 3+3 design. Cohorts of 3-6 patients were enrolled sequentially at escalating doses of 1, 3 or 10 mg/kg administered every 2 weeks (Q2W). Once the dose escalation was completed, additional patients were enrolled into Parts A1 and A2 to further characterize the pharmacokinetics (PK) and pharmacodynamics of MK-3475. In Parts B and D, patients with metastatic melanoma were enrolled to assess safety and anti-tumor activity of MK-3475. Additionally, Part B explored 3 different dose regimens in patients with metastatic melanoma: 10 mg/kg Q2W, 10 mg/kg every 3 weeks (Q3W), and 2 mg/kg Q3W. In Part C, patients with NSCLC were enrolled at 10 mg/kg Q3W to assess safety and anti-tumor activity in NSCLC. In Part F1 and F2, NSCLC patients without (F1) or with (F2) prior systemic therapy whose tumors express PD-L1 with NSCLC were enrolled at 10 mg/kg Q2W and 10 mg/kg Q3W to characterize safety and anti-cancer activity in NSCLC.

### **4.2.5.2 Controls**

No placebo and positive (moxifloxacin) controls arms.

### **4.2.5.3 Blinding**

This trial was conducted as an open-label study (i.e., patients, investigators, and Sponsor personnel were aware of patient treatment assignments after each patient was enrolled and treatment was assigned).

## **4.2.6 Treatment Regimen**

### **4.2.6.1 Treatment Arms**

Part A included 3 cohorts; A, A1 and A2:

- A: Dose escalation in patients with solid tumors.
- A1: Dose expansion (for PK PD analysis) in patients with solid tumors dose at 10 mg/kg Q2W
- A2: Inpatient dose titration (for PK/PD analysis) in patients with solid tumors randomized to 1 of 3 dose regimens. Titration every 8 days in cycle 1 followed by 2 or 10 mg/kg Q3W thereafter

Part B included 3 cohorts; B1, B2 and B3:

- B1: Advanced melanoma patients IPI naïve and IPI treated, doses to 10 mg/kg 2QW, 10 mg/kg Q3W, or 2 mg/kg Q3W
- B2: Advanced melanoma patients IPI-refractory, doses to 2 mg/kg Q3W or 10 mg/kg Q3W
- B3: (not included in this interim CSR) Advanced melanoma patients IPI-naïve and IPI treated, randomized doses to 10 mg/kg Q3W or 10 mg/kg Q2W

Part C: NSCLC non-randomized cohort dose of 10 mg/kg Q3W

Part D: Advanced melanoma patients, IPI- naïve, randomized doses to 2 mg/kg Q3W or 10 mg/kg Q3W.

Part F included 2 cohorts; F1 and F2 (not included in this interim CSR, but was included in the updated modeling and simulation report):

- F1: PD-L1 positive NSCLC patients with no prior systemic treatment randomized to 2 mg/kg Q3W, 10 mg/kg Q2W or 10 mg/kg Q3W
- F2: PD-L1 positive and PD-L1 negative NSCLC patients with at least 2 prior systemic treatments randomized doses to 10 mg/kg Q2W or 10 mg/kg Q3W

#### 4.2.6.2 Sponsor's Justification for Doses

The functional activity of MK-3475 has been demonstrated by assessing *ex vivo* changes in IL-2 levels (modulation assay) in whole blood samples from 2 cynomolgus monkey studies. Changes in certain cytokines, such as IL-2, have been generally recognized as an informative immune-response marker of potential anti-tumor activity. PK-PD modeling of the *ex vivo* activity data suggests an EC50 of approximately 15 µg/mL (90% CI, 5-36 µg/mL). Available efficacy data using a hamster anti-mouse analogue PD-1 mAb (J43) in mouse syngeneic tumor models suggests robust anti-tumor activity. However, due to poor PK behavior of the hamster anti-mouse mAb, these data are not amenable to PK-PD modeling in order to directly define a target serum concentration in humans. At the expected MK-3475 concentrations present in *ex vivo* samples for the IL-2 modulation assay, PD-1 receptor occupancy is expected to correspond to at least 50%, of the extent of biological response (EC50) observed in the dose-response profile studies. This projection is consistent with clinical data for MDX-1106, where the receptor occupancy was reported to be >70% at serum concentrations of 15 µg/mL [17]. Simulations based on allometrically scaled cynomolgus monkey PK parameters suggests that the target EC50 concentration of 15 µg/mL should be readily attained (as trough levels at steadystate) following IV dosing of 1 mg/kg MK-3475 every 2 weeks.

Based on these considerations, 1 mg/kg administered every 2 weeks (with a 4-week interval between the first and second dose to facilitate adequate sampling for PK analysis) has been selected as the starting dose of MK-3475 for this study. The proposed clinical dosing frequency of once every (b) (4) is based on the half-life observed in monkeys and predicted for humans from PK modeling (see the IB). A 1 mg/kg/2 weeks starting dose represents a 400-fold dose multiple over the NOAEL of 200 mg/kg/week in

cynomolgus monkeys, a pharmacologically-relevant species. A 10 mg/kg/2 weeks dose represents a 40-fold dose multiple over the NOAEL.

In addition, the planned doses in this Phase I study are supported by the safety profile, PK and anti-tumor activity observed in Phase I studies of the same in-class antibody MDX-1106 [16, 17]. In those studies, MDX-1106 was found to be well tolerated at doses of 1, 3, and 10 mg/kg after single and repeat administration, and showed a response rate of approximately 30% in patients with advanced MEL and RCC [16]. MK-3475 has shown similar preclinical characteristics compared to an analogue antibody of MDX-1106 (see Section 3.1.2 and IB), and both MK-3475 and MDX-1106 are humanized IgG4 (S228P) antibodies with no ADCC and CDC activity. The scaled human PK parameters of MK-3475 are similar to the clinical PK parameters reported of MDX-1106 [17]. Thus it has been considered plausible to evaluate MK-3475 at the same 3 dose levels MDX-1106 was tested in the repeat dose Phase I study [16], i.e., at 1, 3 and 10 mg/kg given every 2 weeks.

*Reviewer's Comment: The sponsor's studied doses match their intended therapeutic range and do not cover the supratherapeutic range. As MK-3475 is a monoclonal antibody it is unclear whether renal or hepatic impairment will alter the clearance of the drug.*

#### **4.2.6.3 Instructions with Regard to Meals**

Doses were administered without regards to meals.

*Reviewer's Comment: As this is a product for IV administration, the effect of dosing with or without food is not expected to impact the PK of MK-3475.*

#### **4.2.6.4 ECG and PK Assessments**

Data available for Parts A, B1, B2, C and D of PN001, in these parts of PN001, QTc was monitored through periodic singlet ECGs:

Part A: For most patients, ECGs were collected at screening, within 30 minutes after the end of the first infusion of MK-3475, prior to administration of the second infusion of MK-3475, within 30 minutes after the end of the second administration and every other cycle thereafter, and 30 days after the last dose of MK-3475.

Part B1 and B2: ECGs were collected at screening, within 30 minutes after the end of the first infusion of MK-3475, and 30 days after the last dose of MK-3475.

Part C: ECGs were collected at screening, within 30 minutes after the end of the first infusion of MK-3475, and 30 days after the last dose of MK-3475.

Part D: ECGs were collected at screening, within 30 minutes after the end of the first and second infusions of MK-3475, and 30 days after the last dose of MK-3475 was administered.

Part F: Triplicate ECG measurements were performed at pre-dose assessment as well as the time of maximum MK-3475 serum concentration, which was within 30 minutes after

the end of the first infusion of MK-3475 cycle 1, and or at time of steady-state pharmacokinetic concentration at cycles 6 and or 9.

PK samples were collected on day 1, 2, 3, 8, 15, 22, 29 and post dose for cycle 2 and additional cycles.

*Reviewer's Comment: The timing of PK and ECGs appear reasonable given the long half-life of MK-3475.*

#### **4.2.6.5 Baseline**

The sponsor used pre-dose QTc values on Day 1 as baseline.

#### **4.2.7 ECG Collection**

QTc was monitored through periodic singlet ECGs.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

Part A: Dose escalation in patients with melanoma or carcinoma (n=30).

Part B1 and B2: Advanced melanoma patients (IPI-naïve and IPI-treated) dosed at 2 mg/kg Q3W, 10 mg/kg Q3W or 10 mg/kg Q2W (n=308).

Part C: Single cohort of advanced NSCLC patients dosed at 10 mg/kg Q3W (n=38).

Part D: IPI-naïve advanced melanoma patients dosed at 2 mg/kg Q3W or 10 mg/kg Q3W (n=103).

Part F: Triplicate measures of change from baseline following the initial dose of 10 mg/kg MK-3475 and at the end of infusion at steady state (Q2W and Q3W dosing interval) of approximately 78 patients with data from cycle 1 day 1 and approximately 24 patients with steady state data.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

The primary endpoint was overall response rate (ORR) based on RECIST 1.1 by integrated radiology and oncology analysis (IRO).

*Reviewer's Comments: We will provide our independent analysis result in Section 5.2. Statistical reviewer performs summary statistics and analyses of  $\Delta QTcF$ .*

###### **4.2.8.2.2 Assay Sensitivity**

There is no assay sensitivity established in this study because no positive control arm was included in the study.

###### **4.2.8.2.3 Categorical Analysis**

A summary of the categorical analysis of maximum QTcF change from baseline is provided in Table 2. Categorical analysis of the absolute maximum QTc interval of the

388 patients treated to date who have a baseline ECG and at least one additional ECG after the start of therapy with MK-3475, has identified four subjects with clinically significant prolongation of the QTc interval: two (2) subjects with a single QTc interval > 500 msec (Table 1) and three (3) subjects with maximal QTc interval change from baseline > 60 msec (Table 2). (Note: one of the subjects with QTc interval > 500 msec also had a QTc interval change from baseline of > 60 msec.) Follow-up information on these subjects is clearly limited to exclude a role of MK-3475 in the observed changes in QTc interval. However, all four subjects had underlying cardiac disease or medication use that may have contributed to changes in QTc interval.

**Table 2: Sponsor’s Summary of Maximum QTcF on Post Baseline ECGs**

	Part A				Part B				Part C			
	Baseline ECG		Post Baseline ECG		Baseline ECG		Post Baseline ECG		Baseline ECG		Post Baseline ECG	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	30		30		308		308		38		38	
Patients with at least one measurement	30		27		307		258		37		18	
QTc 450-480 msec <sup>†</sup>	2	(6.7)	6	(22.2)	21	(6.8)	20	(7.8)	0	(0.0)	1	(5.6)
QTc 481-500 msec <sup>†</sup>	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.2)	0	(0.0)	0	(0.0)
QTc ≥ 501 msec <sup>†</sup>	0	(0.0)	0	(0.0)	1	(0.3)	2	(0.8)	0	(0.0)	0	(0.0)
On 2 or more post baseline ECG	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	Part D				Total			
	Baseline ECG		Post Baseline ECG		Baseline ECG		Post Baseline ECG	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	103		103		479		479	
Patients with at least one measurement	102		88		476		391	
QTc 450-480 msec <sup>†</sup>	1	(1.0)	8	(9.1)	24	(5.0)	35	(9.0)
QTc 481-500 msec <sup>†</sup>	1	(1.0)	1	(1.1)	1	(0.2)	4	(1.0)
QTc ≥ 501 msec <sup>†</sup>	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.5)
On 2 or more post baseline ECG	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

<sup>†</sup> Only the highest reported ECG is counted for an individual subject.  
ECG values used are from FRIDERICA correction.  
(Database Cutoff Date: 26JUL2013)

Data Source: [16.4]

**Table 12-80**  
**Categorical Analysis of Maximum QTc Change From Baseline**  
**All Patients**  
**(APaT Population)**

	Part A		Part B		Part C		Part D		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	30		308		38		103		479	
Patients with post baseline ECG	27		258		18		88		391	
Patients with baseline and post baseline ECG <sup>†</sup>	27		257		17		87		388	
QTc change from Baseline ≤ 30 msec	23	(85.2)	245	(95.3)	16	(94.1)	79	(90.8)	363	(93.6)
QTc change from Baseline > 30 and ≤ 60 msec	4	(14.8)	11	(4.3)	1	(5.9)	6	(6.9)	22	(5.7)
QTc change from Baseline > 60 msec	0	(0.0)	1	(0.4)	0	(0.0)	2	(2.3)	3	(0.8)

QTc interval: Friderica derived.  
<sup>†</sup> QTc summaries are based on patients with baseline and at least one post-dose measurement. Only the highest reported post-baseline ECG is counted as post baseline ECG for an individual subject.  
(Database Cutoff Date: 18OCT2013)

Data Source: [16.4]

*Reviewer’s comments: Two subjects reported a single QTc interval > 500 ms and three subjects with maximal QTc interval change from baseline > 60 ms. One of the subjects had QTc > 500 ms and post-baseline increase > 60 ms. Sponsor did not collect follow-up ECGs for those subjects. No sudden cardiac deaths were reported in this study.*

#### 4.2.8.3 Safety Analysis

There were 7 deaths in P001 at the time of the data cut off within the A, B1, B2, C and D cohorts. One death was considered possible related was from Cryptococcal infection (AN 014) in a patient in Part A (10 mg/kg Q2W group).

In melanoma patients, SAEs did not predominantly occur in any one system organ class. With the exception of colitis (n=4, 1.0%), pyrexia (n=4, 1.0%), dyspnea (n=3, 0.7%) and

pneumonitis (n=3, 0.7%), no single AE was reported as serious and drug related for more than 2 patients. Although occurring infrequently renal failure (n=2), nephritis (n=1) and acute renal failure (n=2), as well microscopic colitis (n=1) are noteworthy.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in **Table 2**. C<sub>max</sub> and AUC values in the thorough QT study were studied at the intended clinical dose and not higher.

**Table 3. Geometric mean PK Parameter Values for MK-3475 Following IV Administration of 1, 3, or 10 mg/kg to Patients wit solid Tumors in Cycle 1 of Part A and A1.**

Treatment	N	C <sub>max</sub> (μg/mL)	T <sub>max</sub> <sup>†</sup> (day)	AUC <sub>0-28</sub> (day·μg /mL)	AUC <sub>0-∞</sub> (day·μg /mL)	t <sub>1/2</sub> <sup>‡</sup> (day)	CL (mL/day/kg)	V <sub>z</sub> (mL/kg)
1.0 mg/kg	4	16.4 (22)	0.05 (0.02-0.17)	158 (20) <sup>§</sup>	212 (36) <sup>§,¶</sup>	14.1 (51) <sup>§</sup>	4.72 (36) <sup>§</sup>	96.0 (17) <sup>§</sup>
3.0 mg/kg	3	107 (26)	0.17 (0.17-0.17)	955 (23)	1530 (28) <sup>¶</sup>	21.6 (10)	1.96 (28)	61.2 (28)
10 mg/kg	10 <sup>¶</sup>	256 (37)	0.17 (0.03-0.99)	2150 (31) <sup>  </sup>	3270 (44) <sup>  ,¶</sup>	17.7 (56) <sup>  ,††</sup>	3.06 (44) <sup>  </sup>	78.0 (42) <sup>  </sup>

CV = coefficient of variation; C<sub>max</sub> = maximum observed serum concentration;  
T<sub>max</sub> = time of occurrence of the maximum concentration; AUC<sub>0-28</sub> Area under the concentration-time curve from day 0 up to day 28; AUC<sub>0-∞</sub> = Area under the concentration-time curve from time 0 to infinity; t<sub>1/2</sub> = elimination half-life;  
CL = clearance; V<sub>z</sub> = volume of distribution during the terminal phase ;  
†: T<sub>max</sub>: Median (range);  
‡: PK sampling up to 28 days following first I.V. administration;  
§: N=3 Excluded one patient due to discontinuation (AN0002);  
|| : N=9 Excluded one patient due to discontinuation (AN0018);  
¶: 3 patients in Part A and 7 patients in Part A-1;  
#: %AUC-extrapolated >25% for N=2 in treatment 1.0 mg/kg, N=3 in 3.0 mg/kg and N=6 in 10 mg/kg;  
††: patients (N=2) with a t<sub>1/2</sub> > T<sub>last</sub> are included in mean value;

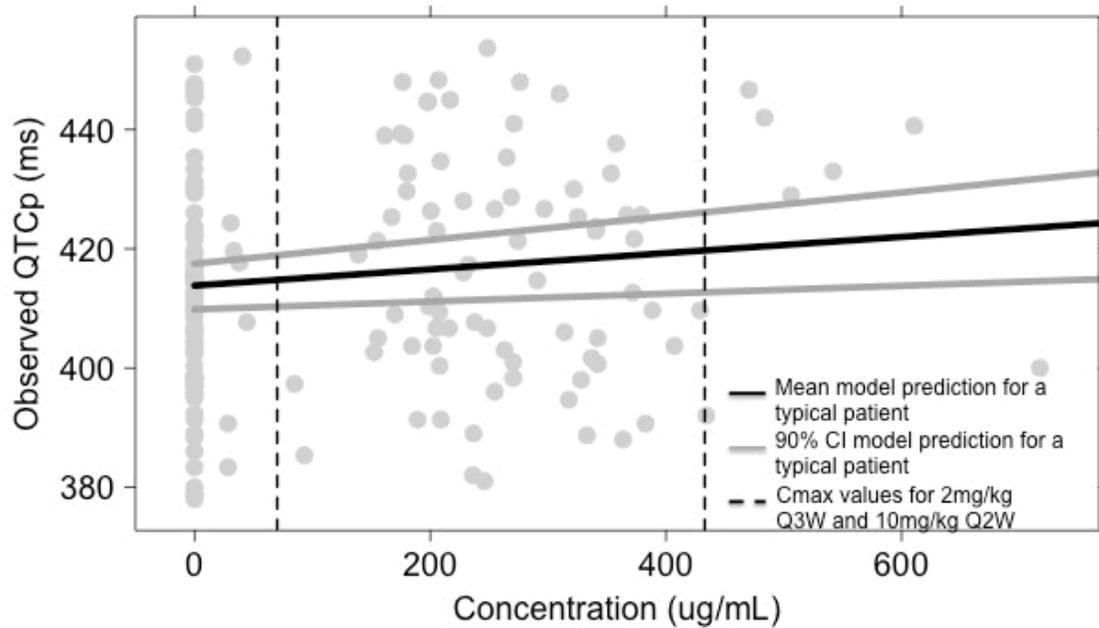
(Source: Sponsor’s Clinical Study Report, Table 11-63)

##### 4.2.8.4.2 Exposure-Response Analysis

An exposure-response analysis was conducted to assess the potential relationship between MK-3475 serum concentrations and QTc was conducted on 73 patients with ECG and matched concentration data from Part F. The sponsor concluded there is no clinically meaningful association between QTc interval and MK-3475 serum concentrations. Based on the triplicate ECG data from Part F, at the proposed dose regimen of 2 mg/kg Q3W, the estimated mean change in QTc interval at peak concentrations is 0.91 ms (upper 90% CI of 1.4 ms). Similarly, at the dose regimen of 10 mg/kg Q2W, achieving approximately 6-fold higher peak exposure, the estimated mean change at peak concentrations is 5.6 ms (upper 90% CI of 8.6 ms). In both cases, estimated changes remain well below 20 ms, the level of concern in the setting of advanced cancer.

**Figure 1. Observed QTc versus MK-3475 serum concentrations together with exposure-response model prediction. Solid markers represent observed QTc data. Black solid line represents estimated relationship between QTc and MK-3475 concentrations for a typical patient with grey solid lines representing the two sided 90% confidence interval of that relationship. Dashed vertical lines represent**

predictive mean steady state peak concentrations at 2 mg/kg Q3W (70.2 µg/mL) and 10 mg/kg Q2W (433 µg/mL).



(Source: Sponsor’s Summary of Clinical Safety, Figure 2.7.4: 4)

*Reviewer’s Analysis: A plot of  $\Delta QTcF$  vs. drug concentrations is presented in Section 5.*

## 5 REVIEWERS’ ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

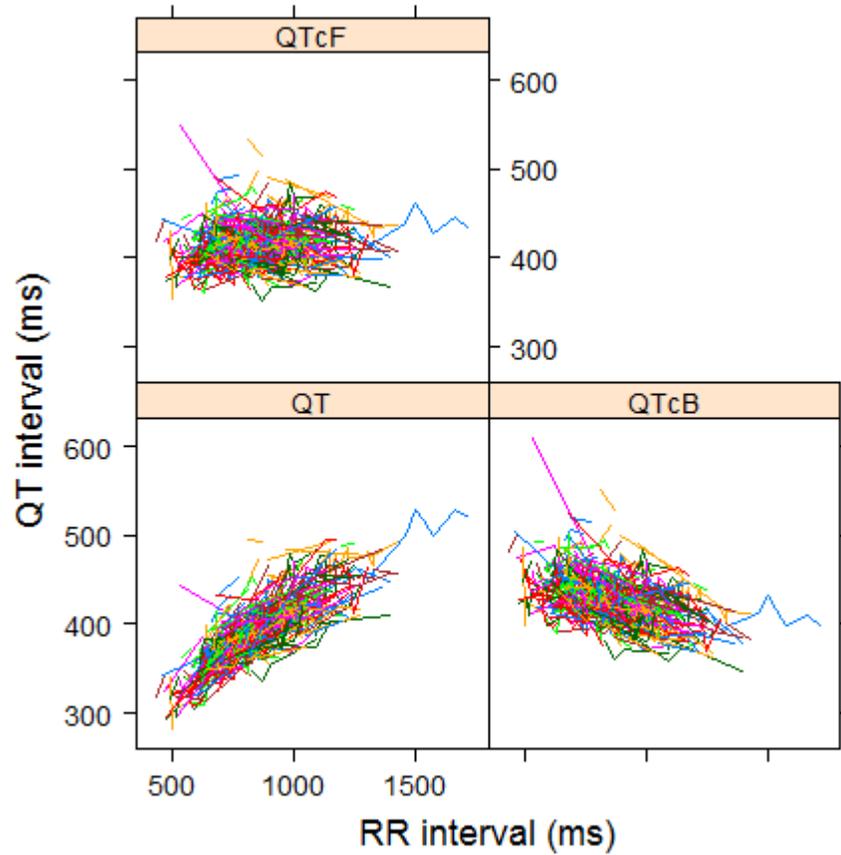
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in **Table 4**, it appears that QTcF is better than QTcB. To be consistent with the sponsor’s analyses, this reviewer used QTcF for the primary statistical analysis.

**Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

<b>Treatment Group</b>	<b>QTcB</b>		<b>QTcF</b>	
	<b>N</b>	<b>MSSS</b>	<b>N</b>	<b>MSSS</b>
MK-3475 1 mg/kg Q2W	4	0.01978	4	0.01509
MK-3475 2 mg/kg Q3W	156	0.11702	156	0.10836
MK-3475 3 mg/kg Q2W	3	0.01614	3	0.01019
MK-3475 10 mg/kg Q3W	218	0.11032	218	0.11455
MK-3475 10 mg/kg Q2W	66	0.11334	66	0.10182
All	447	0.11166	447	0.10892

The relationship between different correction methods and RR is presented in Figure 2.

**Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The primary endpoint is change from the baseline of QTcF. The descriptive statistics are listed in Table 5, Table 6, Table 7, and Table 8. The largest upper bounds of the 2-sided 90% CI for the mean difference of MK-3475 1 mg/kg Q2W is 20.6 ms in visit of cycle 1 (of sample size =4).

**Table 5: Analysis Results of  $\Delta$ QTcF for MK-3475 by Part and by Treatment**

Part	Treatment	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	19	8.0	16.9	(1.3, 14.7)
	MK-3475 3 mg/kg Q2W	33	-6.6	19.3	(-12.3, -0.9)
	MK-3475 10 mg/kg Q2W	50	6.2	14.4	(2.8, 9.6)
Part B	MK-3475 2 mg/kg Q3W	160	2.4	15.5	(0.3, 4.4)
	MK-3475 10 mg/kg Q2W	73	2.3	16.2	(-0.8, 5.5)
	MK-3475 10 mg/kg Q3W	202	2.8	18.8	(0.6, 4.9)
Part C	MK-3475 10 mg/kg Q3W	45	1.7	13.3	(-1.6, 5.0)
Part D	MK-3475 2 mg/kg Q3W	112	1.5	17.7	(-1.3, 4.3)
	MK-3475 10 mg/kg Q3W	117	4.5	14.3	(2.3, 6.7)

**Table 6: Analysis Results of  $\Delta$ QTcF for MK-3475 by Part, by Treatment and by Visit (Pooling cycle 2 and above)**

Part	Treatment	Visit	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	1	4	2.8	15.2	(-15.1, 20.6)
		2	15	9.4	17.5	(1.4, 17.4)
	MK-3475 3 mg/kg Q2W	1	3	8.0	2.6	(3.5, 12.5)
		2	30	-8.0	19.6	(-14.1, -2.0)
	MK-3475 10 mg/kg Q2W	1	10	-0.5	13.9	(-8.5, 7.5)
		2	40	7.8	14.2	(4.0, 11.6)
Part B	MK-3475 2 mg/kg Q3W	2	160	2.4	15.5	(0.3, 4.4)
	MK-3475 10 mg/kg Q2W	2	73	2.3	16.2	(-0.8, 5.5)
	MK-3475 10 mg/kg Q3W	2	202	2.8	18.8	(0.6, 4.9)
Part C	MK-3475 10 mg/kg Q3W	2	45	1.7	13.3	(-1.6, 5.0)
Part D	MK-3475 2 mg/kg Q3W	2	112	1.5	17.7	(-1.3, 4.3)
	MK-3475 10 mg/kg Q3W	2	117	4.5	14.3	(2.3, 6.7)

**Table 7: Analysis Results of  $\Delta$ QTcF for MK-3475 by Treatment and By Visit (Pooled Parts and Cycle 2 and above)**

Treatment	Visit	N	Mean	Std Dev	90% CI for Mean
MK-3475 1 mg/kg Q2W	1	4	2.8	15.2	(-15.1, 20.6)
MK-3475 1 mg/kg Q2W	2	15	9.4	17.5	(1.4, 17.4)
MK-3475 2 mg/kg Q3W	2	272	2.0	16.4	(0.4, 3.7)
MK-3475 3 mg/kg Q2W	1	3	8.0	2.6	(3.5, 12.5)
MK-3475 3 mg/kg Q2W	2	30	-8.0	19.6	(-14.1, -2.0)
MK-3475 10 mg/kg Q2W	1	10	-0.5	13.9	(-8.5, 7.5)
MK-3475 10 mg/kg Q2W	2	113	4.3	15.7	(1.8, 6.7)
MK-3475 10 mg/kg Q3W	2	364	3.2	16.8	(1.7, 4.6)

**Table 8: Analysis Results of  $\Delta$ QTcF for MK-3475 by Treatment (Pooled Parts)**

Treatment	N	Mean	Std Dev	90% CI for Mean
MK-3475 1 mg/kg Q2W	19	8.0	16.9	(1.3, 14.7)
MK-3475 2 mg/kg Q3W	272	2.0	16.4	(0.4, 3.7)
MK-3475 3 mg/kg Q2W	33	-6.6	19.3	(-12.3, -0.9)
MK-3475 10 mg/kg Q2W	123	3.9	15.5	(1.6, 6.2)
MK-3475 10 mg/kg Q3W	364	3.2	16.8	(1.7, 4.6)

### 5.2.1.2 Assay Sensitivity Analysis

No assay sensitivity analysis performed in this study because there was no positive control arm.

### 5.2.1.3 Categorical Analysis

Table 9 and Table 10 list the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $> 500$  ms. Two subjects' QTcF were above 500 ms.

**Table 9: Categorical Analysis for QTcF by Part**

Part	Total N	Value≤450 ms	450 ms<Value≤480 ms	480 ms<Value≤500 ms	Value>500
Part A	32	24 (75%)	8 (25%)	0 (0%)	0 (0%)
Part B	312	273 (87.5%)	32 (10.3%)	5 (1.6%)	2 (0.6%)
Part C	41	40 (97.6%)	1 (2.4%)	0 (0%)	0 (0%)
Part D	103	93 (90.3%)	8 (7.8%)	2 (1.9%)	0 (0%)

**Table 10: Categorical Analysis for QTcF by Treatment**

Treatment	Total N	Value≤450 ms	450 ms<Value≤480 ms	480 ms<Value≤500 ms	Value>500
MK-3475 1 mg/kg Q2W	4	2 (50%)	2 (50%)	0 (0%)	0 (0%)
MK-3475 2 mg/kg Q3W	163	145 (89%)	14 (8.6%)	3 (1.8%)	1 (0.6%)
MK-3475 3 mg/kg Q2W	3	2 (66.7%)	1 (33.3%)	0 (0%)	0 (0%)
MK-3475 10 mg/kg Q2W	69	60 (87%)	7 (10.1%)	2 (2.9%)	0 (0%)
MK-3475 10 mg/kg Q3W	236	212 (89.8%)	21 (8.9%)	2 (0.9%)	1 (0.4%)

Table 11 and Table 12 lists the number of subjects whose changes from baseline QTc ≤30 ms, between 30 and 60 ms and >60 ms. Three subjects' changes from baseline were above 60 ms.

**Table 11: Categorical Analysis of ΔQTcF by Part**

Part	Total N	Value≤30 ms	30 ms<Value≤60 ms	Value>60 ms
Part A	30	24 (80%)	6 (20%)	0 (0%)
Part B	306	288 (94.1%)	17 (5.6%)	1 (0.3%)
Part C	37	36 (97.3%)	1 (2.7%)	0 (0%)
Part D	102	93 (91.3%)	7 (6.9%)	2 (2%)

**Table 12: Categorical Analysis of  $\Delta$ QTcF**

Treatment	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	Value>60 ms
MK-3475 1 mg/kg Q2W	4	3 (75%)	1 (50%)	0 (0%)
MK-3475 2 mg/kg Q3W	161	151 (93.8%)	8 (5%)	2 (1.2%)
MK-3475 3 mg/kg Q2W	3	3 (100%)	0 (0%)	0 (0%)
MK-3475 10 mg/kg Q2W	66	62 (93.90%)	4 (6.1%)	0 (0%)
MK-3475 10 mg/kg Q3W	228	213 (93.4%)	14 (6.1%)	1 (0.4%)

### 5.2.2 HR Analysis

The primary endpoint is change from the baseline of HR. The descriptive statistics are listed in Table 13 and Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences are not higher than 20 bpm. Table 15 and Table 16 present the categorical analysis of HR. Twenty-one subjects who experienced HR interval greater than 100 bpm are in MK-3475 groups.

**Table 13: Analysis Results of  $\Delta$ HR for MK-3475 by Part and by Treatment**

Part	Treatment	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	23	2.3	11.4	(-1.7, 6.4)
	MK-3475 3 mg/kg Q2W	36	2.5	5.1	(1.0, 3.9)
	MK-3475 10 mg/kg Q2W	60	4.2	10.1	(2.0, 6.4)
Part B	MK-3475 2 mg/kg Q3W	269	-1.7	9.6	(-2.6, -0.7)
	MK-3475 10 mg/kg Q2W	129	-0.3	7.5	(-1.4, 0.8)
	MK-3475 10 mg/kg Q3W	338	0.4	8.6	(-0.4, 1.2)
Part C	MK-3475 10 mg/kg Q3W	82	1.8	8.7	(0.2, 3.4)
Part D	MK-3475 2 mg/kg Q3W	157	1.2	7.4	(0.2, 2.1)
	MK-3475 10 mg/kg Q3W	167	-1.7	9.1	(-2.8, -0.5)

**Table 14: Analysis Results of  $\Delta$ HR for MK-3475 by Part, by Treatment and by Visit (Pooling cycle 2 and above)**

Part	Treatment	Visit	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	1	4	0.3	5.3	(-6.0, 6.5)
		2	15	3.5	13.9	(-2.8, 9.9)
	MK-3475 3 mg/kg Q2W	1	3	-2.7	5.0	(-11.2, 5.8)
		2	30	3.2	5.1	(1.7, 4.8)
	MK-3475 10 mg/kg Q2W	1	10	-2.7	6.8	(-6.6, 1.2)
		2	40	7.0	11.0	(4.1, 9.9)
Part B	MK-3475 2 mg/kg Q3W	2	160	-2.4	11.9	(-3.9, -0.8)
		2	73	-1.1	9.0	(-2.8, 0.7)
		2	202	1.1	10.7	(-0.1, 2.3)
Part C	MK-3475 10 mg/kg Q3W	2	45	2.8	10.9	(0.0, 5.5)
Part D	MK-3475 2 mg/kg Q3W	2	112	1.1	8.1	(-0.2, 2.4)
		2	117	-1.6	9.9	(-3.1, -0.1)

**Table 15: Categorical Analysis for HR by Part**

Part	Total N	Value < 100 bpm	Value > 100 bpm
Part A	32	28 (87.5%)	4 (12.5%)
Part B	312	303 (97.1%)	9 (2.9%)
Part C	41	36 (87.8%)	5 (12.2%)
Part D	103	100 (97.1%)	3 (2.9%)

**Table 16: Categorical Analysis for HR By Treatment**

Treatment	Total N	Value < 100 bpm	Value > 100 bpm
MK-3475 1 mg/kg Q2W	4	3 (75%)	1 (25%)
MK-3475 2 mg/kg Q3W	163	160 (98.2%)	3 (1.8%)
MK-3475 3 mg/kg Q2W	3	3 (100%)	0 (0%)
MK-3475 10 mg/kg Q2W	69	65 (94.2%)	4 (5.8%)
MK-3475 10 mg/kg Q3W	236	224 (94.9%)	12 (5.1%)

### 5.2.3 PR Analysis

The primary endpoint is change from the baseline of HR. The descriptive statistics are listed in Table 17 and Table 18. The largest upper bounds of the 2-sided 90% CI for the mean differences of MK-3475 1 mg/kg Q2W and MK-3475 1 mg/kg Q2W are 25.1 ms and 33.7 ms at cycle 1 (of sample size less than 5), respectively. Table 19 and Table 20

present the categorical analysis of HR. Thirty-three subjects who experienced PR interval greater than 200 ms are in MK-3475 groups.

**Table 17: Analysis Results of  $\Delta$ PR for MK-3475 by Part and by Treatment**

Part	Treatment	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	23	11.0	17.6	(4.7, 17.3)
	MK-3475 3 mg/kg Q2W	36	0.9	22.2	(-5.4, 7.1)
	MK-3475 10 mg/kg Q2W	60	1.2	11.5	(-1.2, 3.7)
Part B	MK-3475 2 mg/kg Q3W	269	-0.4	11.1	(-1.6, 0.7)
Part B	MK-3475 10 mg/kg Q2W	129	1.8	11.3	(0.1, 3.4)
	MK-3475 10 mg/kg Q3W	338	1.6	18.5	(-0.0, 3.3)
Part C	MK-3475 10 mg/kg Q3W	82	-3.7	18.2	(-7.0, -0.3)
Part D	MK-3475 2 mg/kg Q3W	157	-0.4	10.4	(-1.8, 1.0)
	MK-3475 10 mg/kg Q3W	167	7.4	38.4	(2.5, 12.3)

**Table 18: Analysis Results of  $\Delta$ PR for MK-3475 by Part, by Treatment and by Cycle (Pooling cycle 2 and above)**

Part	Treatment	Visit	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	1	4	3.0	18.8	(-19.1, 25.1)
		2	15	16.1	18.2	(7.8, 24.4)
	MK-3475 3 mg/kg Q2W	1	3	-20.3	32.0	(-74.3, 33.7)
		2	30	3.1	21.7	(-3.7, 9.8)
	MK-3475 10 mg/kg Q2W	1	10	4.5	14.8	(-4.1, 13.1)
		2	40	0.7	12.0	(-2.5, 3.9)
Part B	MK-3475 2 mg/kg Q3W	2	160	-0.6	13.6	(-2.4, 1.2)
	MK-3475 10 mg/kg Q2W	2	73	3.4	13.1	(0.8, 5.9)
	MK-3475 10 mg/kg Q3W	2	202	2.7	23.7	(-0.1, 5.4)
Part C	MK-3475 10 mg/kg Q3W	2	45	-4.6	15.4	(-8.4, -0.7)
Part D	MK-3475 2 mg/kg Q3W	2	112	-0.5	11.7	(-2.4, 1.3)
	MK-3475 10 mg/kg Q3W	2	117	8.4	40.8	(2.1, 14.6)

**Table 19: Categorical Analysis for PR by Part**

Part	Total N	Value ≤ 200 ms	Value > 200 ms
Part A	32	29 (90.6%)	3 (9.4%)
Part B	312	290 (93%)	22 (7.0%)
Part C	41	39 (95.1%)	2 (4.9%)
Part D	103	97 (94.1%)	6 (5.8%)

**Table 20: Categorical Analysis for PR by Treatment**

Treatment	Total N	Value ≤ 200 ms	Value > 200 ms
MK-3475 1 mg/kg Q2W	4	4 (100%)	0 (0%)
MK-3475 2 mg/kg Q3W	163	152 (93.3%)	11 (6.8%)
MK-3475 3 mg/kg Q2W	3	2 (66.7%)	1 (33.3%)
MK-3475 10 mg/kg Q2W	69	63 (91.3%)	6 (9.1%)
MK-3475 10 mg/kg Q3W	236	221 (93.6%)	15 (6.4%)

#### 5.2.4 QRS Analysis

The primary endpoint is change from the baseline of QRS. The descriptive statistics are listed in Table 21 and Table 22. The largest upper bounds of the 2-sided 90% CI for the mean differences are not higher than 20 ms. Table 23 and Table 24 present the categorical analysis of HR. Forty-two subjects who experienced QRS interval greater than 110 ms are in MK-3475 groups.

**Table 21: Analysis Results of ΔQRS for MK-3475 by Part and by Treatment**

Part	Treatment	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	23	-2.1	4.9	(-3.8, -0.3)
	MK-3475 3 mg/kg Q2W	36	-0.5	7.0	(-2.5, 1.4)
	MK-3475 10 mg/kg Q2W	60	-0.6	5.0	(-1.7, 0.5)
Part B	MK-3475 2 mg/kg Q3W	269	-0.7	6.6	(-1.4, -0.1)
	MK-3475 10 mg/kg Q2W	129	0.2	6.2	(-0.7, 1.1)
	MK-3475 10 mg/kg Q3W	338	0.3	7.6	(-0.4, 0.9)
Part C	MK-3475 10 mg/kg Q3W	82	-0.6	4.5	(-1.5, 0.2)
Part D	MK-3475 2 mg/kg Q3W	157	0.0	4.7	(-0.6, 0.7)
	MK-3475 10 mg/kg Q3W	167	-0.6	6.1	(-1.3, 0.2)

**Table 22: Analysis Results of  $\Delta$ QRS for MK-3475 by Part, by Treatment and by Visit (Pooling cycle 2 and above)**

Part	Treatment	Visit	N	Mean	Std Dev	90% CI for Mean
Part A	MK-3475 1 mg/kg Q2W	1	4	-2.5	5.7	(-9.3, 4.3)
		2	15	-2.5	5.4	(-5.0, -0.1)
	MK-3475 3 mg/kg Q2W	1	3	5.0	1.0	(3.3, 6.7)
		2	30	-1.1	7.5	(-3.4, 1.2)
	MK-3475 10 mg/kg Q2W	1	10	-0.7	5.4	(-3.9, 2.5)
		2	40	-0.8	5.6	(-2.3, 0.7)
Part B	MK-3475 2 mg/kg Q3W	2	160	-1.4	8.0	(-2.4, -0.3)
	MK-3475 10 mg/kg Q2W	2	73	0.2	6.5	(-1.0, 1.5)
	MK-3475 10 mg/kg Q3W	2	202	0.4	9.7	(-0.7, 1.6)
Part C	MK-3475 10 mg/kg Q3W	2	45	-1.1	5.8	(-2.5, 0.4)
Part D	MK-3475 2 mg/kg Q3W	2	112	0.0	5.0	(-0.8, 0.8)
	MK-3475 10 mg/kg Q3W	2	117	-0.5	6.2	(-1.5, 0.4)

**Table 23: Categorical Analysis for QRS by Part**

Part	Total N	Value <110 ms	Value >110 ms
Part A	32	31 (96.9%)	1 (3.1%)
Part B	312	285 (91.4%)	27 (8.7%)
Part C	41	39 (95.1%)	2 (4.9%)
Part D	103	91 (88.4%)	12 (11.7%)

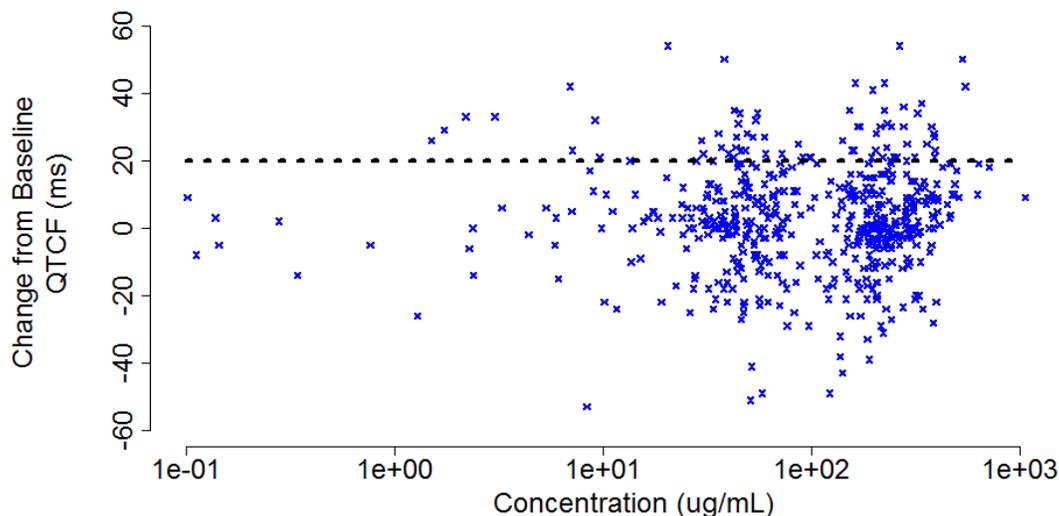
**Table 24: Categorical Analysis for QRS by Treatment**

Treatment	Total N	Value <110 ms	Value >110 ms
MK-3475 1 mg/kg Q2W	4	3 (75%)	1 (25%)
MK-3475 10 mg/kg Q2W	69	62 (89.9%)	7 (10.1%)
MK-3475 10 mg/kg Q3W	236	218 (92.4%)	18 (7.6%)
MK-3475 2 mg/kg Q3W	163	147 (90.2%)	16 (9.8%)
MK-3475 3 mg/kg Q2W	3	3 (100%)	0 (0%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta$  QTcF and MK-3475 concentrations is visualized in Figure 3 with no evident exposure-response relationship.

**Figure 3:  $\Delta$  QTcF vs. MK-3475 concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

One out of 84 patients receiving 10 mg/kg Q3W experienced syncope. One out of 84 patients receiving 10 mg/kg Q3W experienced tachycardia. One out of 4 patients experienced bradycardia in part A1 (dose escalation) of the study at the lowest evaluated dose of 1 mg/kg.

Two subjects reported a single QTc interval > 500 ms and three subjects with maximal QTc interval change from baseline > 60 ms. One of the subjects had QTc > 500 ms and postbaseline increase > 60 ms. Sponsor did not collect follow-up ECGs for those subjects. No cases of Torsade or sudden death were observed.

It is not clear that any of these findings were treatment-related.

### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics—of the ECGs were annotated in the primary lead—, with less than—of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

No clinically relevant effects on PR or QRS were seen.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	2mg/kg intravenously (IV) every 3 weeks (Q3W) 10mg/kg IV every 2 (Q2W) or 3 weeks	
Maximum tolerated dose	Maximum tolerated dose was not determined as doses above 10mg/kg IV every 2 weeks (the maximum administered dose) were not tested	
Principal adverse events	The preliminary AE profile from the ongoing phase 1 study, PN001, shows that the most common AEs, regardless of attribution, were fatigue (28.4%), nausea (23.1%), rash (22.4%), diarrhea (19.4%), cough (18.7%), pruritus (17.9%), arthralgia (14.2%), and headache (14.2%).	
Maximum dose tested	Single Dose	Single dose not tested
	Multiple Dose	10 mg/kg Q2W
Exposures Achieved at Maximum Tested Dose	Single Dose	(1 <sup>st</sup> cycle – 28 days) C <sub>max</sub> : 271 (38) µg/mL AUC <sub>0-∞</sub> : 3680 (44) µg*day/mL AUC <sub>0-28days</sub> : 2282 (31) µg*day/mL
	Multiple Dose	Not available (no AUC after MD) C <sub>trough</sub> Cycle nr. 2: 45.04 (41) µg/mL Cycle nr. 4: 128.39 (35) µg/mL Cycle nr. 6: 179.29 (40) µg/mL Cycle nr. 8: 260.10 (1.4) µg/mL Cycle nr. 10: 200.56 (5) µg/mL Cycle nr. 12: 62.85 (n.a.) µg/mL
Range of linear PK	0.1 mg/kg – 10 mg/kg Q3W	
Accumulation at steady state	Not available (no non-compartmental analysis possible). Calculated from half-life: tau=21days: R <sub>acc</sub> =1.99	
Metabolites	Not applicable for mAb	
Absorption	Absolute/Relative Bioavailability	100% (IV formulation)
	T <sub>max</sub>	0.25 (0.02-1) days
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	86.3 (41) mL/kg
	% bound	NA (mAb)
Elimination	Route	Based on general mAb properties: aspecific catabolism is expected
	Terminal t <sub>1/2</sub>	20.9 (49) days Note: based on sampling up to 28 days after the first dose; t <sub>1/2</sub> therefore poorly characterized

	CL/F or CL	3.17 (39) mL/day/kg
Intrinsic Factors	Age	Not available (none expected for mAb);to be evaluated by popPK analysis of sparse samples
	Sex	Not available (none expected for mAb);to be evaluated by popPK analysis of sparse samples
	Race	Not available (none expected for mAb);to be evaluated by popPK analysis of sparse samples
	Hepatic & Renal Impairment	Not available (none expected for mAb);to be evaluated by popPK analysis of sparse samples
Extrinsic Factors	Drug interactions	Not available (none expected for mAb);to be evaluated by popPK analysis of sparse samples
	Food Effects	Not applicable (IV formulation)
Expected High Clinical Exposure Scenario	No extrinsic factors are anticipated to influence the exposure of a mAb.	

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/s/  
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JUSTIN C EARP  
07/01/2014

JIANG LIU  
07/01/2014

MOH JEE NG  
07/01/2014

QIANYU DANG  
07/01/2014

NORMAN L STOCKBRIDGE  
07/01/2014

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## LABELING MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	May 29, 2014
<b>Requesting Office or Division:</b>	Division of Oncology Products 2 (DOP2)
<b>Application Type and Number:</b>	BLA 125514
<b>Product Name and Strength:</b>	Keytruda (Pembrolizumab) for Injection, 50 mg
<b>Product Type:</b>	Single Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharpe & Dohme Corp.
<b>Submission Date:</b>	May 23, 2014
<b>OSE RCM #:</b>	2014-75-1
<b>DMEPA Primary Reviewer:</b>	Otto L. Townsend, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR MEMORANDUM

This memorandum documents DMEPA's assessment of the proposed Full Prescribing Information submitted by Merck for areas of vulnerability that could lead to medication errors. The May 23, 2014 submission is Merck's response to an April 29, 2014 Filing Communication from DOP2 (see DARRTS BLA 125514 Filing Notification with Deficiencies Identified document dated 4/29/2014). The Filing Communication included our recommended changes to the Dosage and Administration section of the Full Prescribing Information for Keytruda.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck has incorporated our recommended changes into the Full Prescribing Information (See OSE Review # 2014-75; DARRTS Labeling Review dated, 04/08/2014). We noted that our exact phrasing was not incorporated fully, but we don't anticipate that these minor phrasing differences will contribute to medication errors.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude the May 23, 2014 proposed Full Prescribing Information is acceptable from a medication errors perspective.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Keytruda that Merck submitted on February 27, 2014 and May 23, 2014.

<b>Table 2. Relevant Product Information for Keytruda</b>	
<b>Active Ingredient</b>	Pembrolizumab
<b>Indication</b>	Treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.
<b>Route of Administration</b>	Intravenous Infusion
<b>Dosage Form</b>	Lyophilized Powder for Injection
<b>Strength</b>	50 mg
<b>Dose and Frequency</b>	2 mg/kg administered intravenously over 30 minutes every 3 weeks
<b>How Supplied</b>	Single-use vial
<b>Storage</b>	Refrigerate at 2°C to 8°C (36°F to 46°F)

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

To identify reviews previously completed by DMEPA, we searched the L: Drive on May 28, 2014 using the terms, “Keytruda” and “Pembrolizumab”.

### **C.2 Results**

Previously, we reviewed proposed Keytruda container labels, carton labeling and Full Prescribing Information in OSE Review # 2014-75 (see DARRTS Labeling Review dated, 04/08/2014).

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> we reviewed the Full Prescribing Information for Keytruda submitted by Merck on May 23, 2014.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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.**  
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/s/  
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OTTO L TOWNSEND  
05/29/2014

CHI-MING TU  
05/29/2014

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # BLA# 125514/0	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Keytruda Established/Proper Name: pembrolizumab Dosage Form: for intravenous infusion Strengths: 50 mg vial		
Applicant: Merck Sharp and Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: February 27, 2014 Date of Receipt: February 27, 2014 Date clock started after UN:		
PDUFA Goal Date: October 28, 2014		Action Goal Date (if different):
Filing Date: April 28, 2014		Date of Filing Meeting: April 10, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication: Treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>.</i>		
Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 110080

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>  If yes, explain in comment column.	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? <b>If yes</b> , date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Format and Content</b>	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>PREA</b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Product has Orphan Drug designation for the melanoma indication.
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b></p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b></p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>BPCA (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT consult sent on 3-25-2014.
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> CMC: 10-25-2013; Clinical: 10-26-2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** April 10, 2014

**BLA/NDA/Supp #:** 125514/0

**PROPRIETARY NAME:** Keytruda

**ESTABLISHED/PROPER NAME:** pembrolizumab

**DOSAGE FORM/STRENGTH:** 50 mg vial, for intravenous infusion

**APPLICANT:** Merck Sharp and Dohme Corp.

**PROPOSED INDICATION:** Treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab

**BACKGROUND:** Product has Orphan Drug designation and Breakthrough Therapy designation for melanoma.

**Summary of Discussion:** No filing issues were discussed or identified by any of the review divisions during this meeting. There are pending information requests, and additional information requests to be sent; however, they are not potential filing issues.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Mimi Biable covering for Sharon Sickafuse	Y
	CPMS/TL:	Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Marc Theoret		Y
Clinical	Reviewer:	Jennie Chang	Y
	Reviewer:	Meredith Chuk	Y
	TL:	Marc Theoret	Y
Clinical Pharmacology	Reviewer:	Runyan Jin	Y
	TL:	Lillian Zhang covering for Hong Zhao	Y
Biostatistics	Reviewer:	Emmanuel Sampene	Y
	TL:	Vivian Yuan covering for Kun He	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shawna Weis	Y
	TL:	Whitney Helms	Y
Pharmacometrics	Reviewer:	Hongshan Li	Y
	Reviewer:	Jingyu Yu	N
	TL:	Liang Zhao	N
Product Quality (CMC) and Immunogenicity Assay	Reviewer:	Mark Paciga	Y
	Reviewer:	Deborah Schmiel	Y
	TL:	Rashmi Rawat	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Maria Candauchaon (DS)	Y
	Reviewer:	Kalavati Suvarna (DP)	N
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Mark Paciga	Y
	Reviewer:	Deborah Schmiel	Y
	TL:	Rashmi Rawat	Y
Facility Review/Inspection	Reviewer:	Maria Candauchaon (DS)	Y
	Reviewer:	Kalavati Suvarna (DP)	N
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Otto Townsend	Y
	TL:	Chi-Ming (Alice) Tu	N
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:	Cynthia LaCivita	Y
OPDP	Reviewer:	Quynh-Van Tran	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:		
Other reviewers			
Other attendees	Pat Keegan, DOP2 Director Rajeshwari Sridhara, Stat Director Kevin Wright, OSE RPM Peter Waldron, OSE/DPVII MO Katherine Coyle, OSE/DPV Tracy Salaam, OSE/DPVII team leader Sharon Mills, Senior Patient Labeling Reviewer		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>• 505(b)(2) filing issues:           <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>  <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>If no, explain:</b></p>	
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p> <ul style="list-style-type: none"> <li>• The application did not raise significant safety or efficacy issues</li> </ul>
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><b>BIostatistics</b></p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p>

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li>   <li><b>If no</b>, was a complete EA submitted? <input type="checkbox"/> YES  <input type="checkbox"/> NO</li>   <li><b>If EA submitted</b>, consulted to EA officer (OPS)? <input type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <b>Comments:</b>	
<u><b>Facility Inspection</b></u>  <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li>   <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	

**Signatory Authority:** Richard Pazdur

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): June 13, 2014

<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p><a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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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.**  
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/s/  
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SHARON K SICKAFUSE  
04/24/2014

MONICA L HUGHES  
04/24/2014

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** BLA 125514/0

**Application Type:** new BLA

**Name of Drug/Dosage Form:** Keytruda (pembrolizumab) for intravenous infusion

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

**Receipt Date:** February 27, 2014

**Goal Date:** October 28, 2014

### **1. Regulatory History and Applicant's Main Proposals**

This BLA proposes the use of Keytruda for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.

Breakthrough Therapy designation was granted on 1-17-2013.

### **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

### **3. Conclusions/Recommendations**

No SRPI format deficiencies were identified in the review of this PI.

The product title is currently presented as "KEYTRUDA® (pembrolizumab) for intravenous infusion" and should appear as "KEYTRUDA® (pembrolizumab) injection, for intravenous infusion." Merck will be asked to correct the product title in the filing letter to be issued on April 28, 2014.

# Selected Requirements of Prescribing Information

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## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

***Comment:*** No comments.

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

***Comment:*** No comments.

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

***Comment:*** No comments.

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

***Comment:*** No comments.

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

## Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:** *No comments.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:** *No comments.*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:** *No comments.*

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:** *No comments.*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:** *No comments.*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:** *The product title is currently presented as "KEYTRUDA® (pembrolizumab) for*

## Selected Requirements of Prescribing Information

*intravenous infusion" and should appear as "KEYTRUDA® (pembrolizumab) injection, for intravenous infusion."*

### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:** *No comments.*

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:** *N/A*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

**Comment:** *N/A*

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

**Comment:** *N/A*

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

**Comment:** *N/A*

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

**Comment:** *N/A*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

**Comment:** *N/A*

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:** *N/A*

## Selected Requirements of Prescribing Information

### Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:** *In consultation with our Pharm-Tox staff, during our review we may need to establish a new EPC; therefore, this statement will be revised during our review to reflect "KEYTRUDA is a (EPC) indicated for: INSERT INDICATION."*

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

**Comment:** *This product has a single dosage form and strength.*

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

**Comment:** *No comments.*

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

**Comment:** *No comments.*

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

**Comment:** *No comments.*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

**Comment:** *No comments.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
***Comment:** No comments.*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
***Comment:** No comments.*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
***Comment:** N/A*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
***Comment:** No comments.*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
***Comment:** No comments.*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
***Comment:** No comments.*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
***Comment:** No comments.*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:** No comments.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:** No comments.

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:** *N/A*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:** *No comments.*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

**Comment:** *N/A*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:** *N/A*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

**Comment:** *No comments*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:** *No comments.*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:** *N/A*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:** *No comments.*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:** *Currently, the PI and patient labeling are two separate documents. Will combine into one document at the time of final action.*

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

- [text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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SHARON K SICKAFUSE  
04/15/2014

MONICA L HUGHES  
04/17/2014

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	April 7, 2014
<b>Requesting Office or Division:</b>	Division of Oncology Products 2 (DOP2)
<b>Application Type and Number:</b>	BLA 125514
<b>Product Name and Strength:</b>	Keytruda (Pembrolizumab) for Injection, 50 mg
<b>Product Type:</b>	Single Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharpe & Dohme Corp.
<b>Submission Date:</b>	February 27, 2014
<b>OSE RCM #:</b>	2014-75
<b>DMEPA Primary Reviewer:</b>	Otto L. Townsend, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

This review is written in response to a consult from DOP2 requesting DMEPA to assess the proposed Prescribing Information, container labels, and carton labeling for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified that Section 2.3 (Preparation and Administration) of the Full Prescribing Information does not provide

(b) (4)

## 4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed container label and carton labeling are acceptable from a medication errors perspective. We further conclude the Full Prescribing Information can be improved to promote the safe use of the product.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Keytruda that Merck submitted on February 27, 2014.

<b>Table 2. Relevant Product Information for Keytruda</b>	
<b>Active Ingredient</b>	Pembrolizumab
<b>Indication</b>	Treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.
<b>Route of Administration</b>	Intravenous Infusion
<b>Dosage Form</b>	Lyophilized Powder for Injection
<b>Strength</b>	50 mg
<b>Dose and Frequency</b>	2 mg/kg administered intravenously over 30 minutes every 3 weeks
<b>How Supplied</b>	Single-use vial
<b>Storage</b>	Refrigerate at 2°C to 8°C (36°F to 46°F)

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Keytruda labels and labeling submitted by Merck on February 27, 2014.

- Container label
- Carton labeling
- Full Prescribing Information
- Patient information handout

### **G.2 Label and Labeling Images**

Container Label (300%)



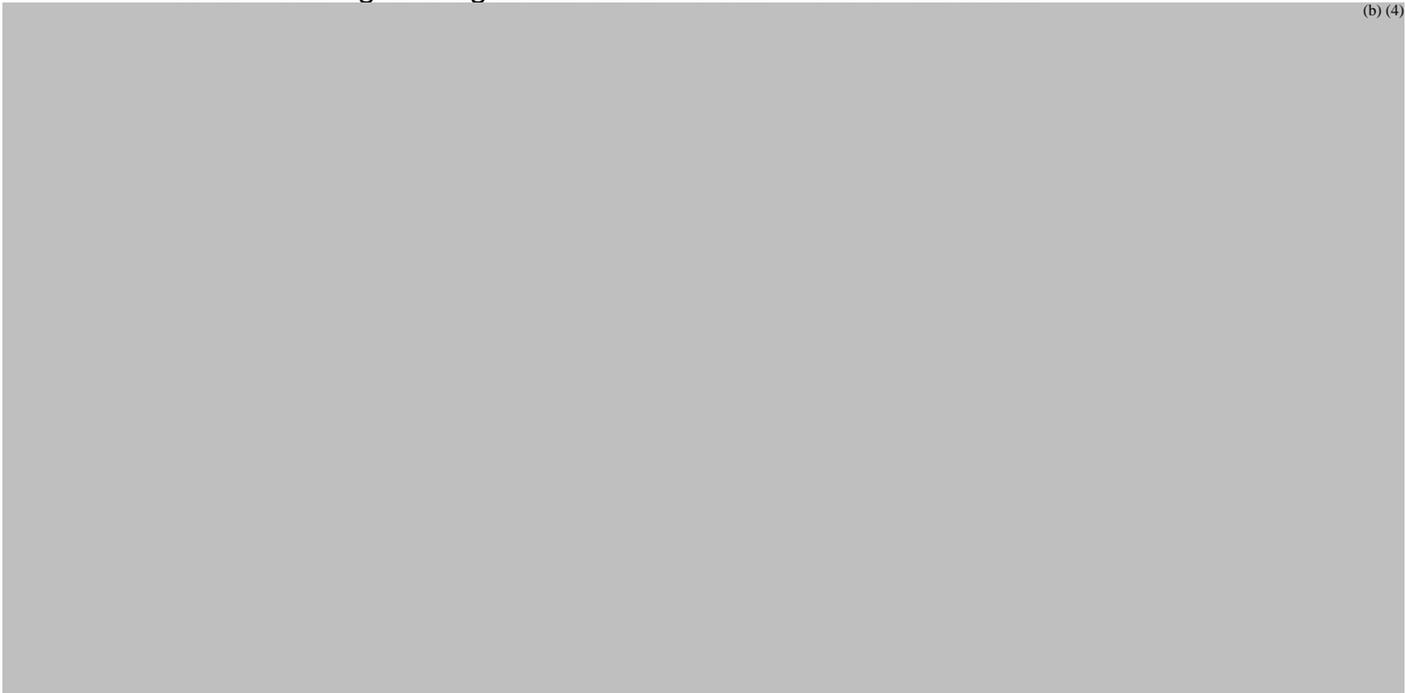
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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling (90%) -

- Carton Labeling for drug substance formulated in the United States

(b) (4)



- Carton Labeling for drug substance formulated in (b) (4)

(b) (4)



(b) (4)

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/s/  
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OTTO L TOWNSEND  
04/07/2014

CHI-MING TU  
04/08/2014