

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125514Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 125514/0 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DOP2 PDUFA Goal Date: 10-28-2014 Stamp Date: 2/27/2014

Proprietary Name: Keytruda

Established/Generic Name: pembrolizumab

Dosage Form: 50 mg vial; for intravenous infusion

Applicant/Sponsor: Merck Sharp and Dohme Corp.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

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

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):			
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

**justification):**

## # Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

## \* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

## † Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

## Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

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*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,*

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proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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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  
03/04/2014

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125514	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Keytruda Established/Proper Name: pembrolizumab Dosage Form: 50 mg vial, for intravenous infusion		Applicant: Merck Sharp and Dohme Corp. Agent for Applicant (if applicable):
RPM: Sharon Sickafuse		Division: DOP2
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)            Date of check:</p> <p>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>October 28, 2014</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input checked="" type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

- |  |   |
|--|---|
| <input type="checkbox"/> Fast Track                                  | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates No longer applicable now that BLAs are in DARRTS.
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Approval 9-4-2014
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 2-27-2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 8-7-2014
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	1-27-2014 1-15-2014
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: 4-17-2014 DMEPA: 5-29-2014 & 4-8-2014 DMPP/PLT: 8-26-2014 OPDP: 8-15-2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: OBP review: 8-25-2014
Administrative / Regulatory Documents	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	4-24-2014
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Product has orphan drug designation for melanoma indication.</u></li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	Labeling (Med Guide) email 9-3-2014 Labeling (PI) email 9-3-2014 (2) Labeling (Med Guide) email 8-28-2014 Labeling (PI) email 8-28-2014 Clinical IR email 8-28-2014 (2) Telecon 8-27-2014 Med Guide email 8-27-2014 Clinical IR email 8-27-2014 CMC IR email 8-15-2014 Labeling (PI) IR email 8-13-2014 Labeling (carton) AD email 8-12-2014 Labeling (carton) AD email 8-11-2014 Labeling (carton & container) IR email 8-5-2014 CMC IR/AD email 8-1-2014 CMC IR email 7-31-2014 (3) LCM PKG 7-30-2014 Clinical IR email 7-30-2014 CMC IR email 7-29-2014 Clinical IR email 7-29-2014 Clinical IR email 7-25-2014 CMC IR email 7-24-2014 Clinical IR email 7-23-2014 Clinical IR email 7-18-2014 Clinical IR email 7-17-2014 Qual Mirco IR email 7-17-2014 CMC IR email 7-12-2014 Labeling (carton & container) IR email 7-3-2014 Clinical IR email 7-3-2014 Qual Micro IR email 6-30-2014 Qual Micro IR email 6-20-2014 Clinical IR email 6-18-2014 Clinical IR email 6-9-2014 Qual Micro IR LTR 6-5-2014 Clinical IR LTR 6-5-2014 Clinical IR email 6-3-2014 Clinical IR LTR 6-2-2014 Clin Pharm IR email 5-29-2014 Qual Micro IR LTR 5-28-2014 Clinical IR email 5-23-2014 Clinical IR email 5-21-2014 (2) Clinical IR email 5-14-2014

	<p>CMC IR LTR 5-14-2014  Clinical IR LTR 5-8-2014  Clinical IR email 5-6-2014  Clinical IR email 5-1-2014  Filing &amp; DI LTR 4-29-2014  Qual Micro IR LTR 4-16-2014  Clin Pharm IR email 4-15-2014  Clinical IR email 4-14-2014  Stat IR email 4-10-2014  OSI IR email 3-28-2014  Clinical IR email 3-26-2014  Clinical IR email 3-25-2014  Clin Pharm IR email 3-25-2014  Clinical IR email 3-19-2014  OSE IR email 3-18-2014  Clinical IR email 3-14-2014  ACK LTR 3-5-2014  Nonclinical IR email 2-26-2014  Ack BLA presubmission LTR 11-27-2013</p>
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	<p>Wrap-up meeting 8-26-2014  Mid-cycle meeting 6-13-2014  Team meeting: 5-12-2014  Planning meeting: 3-28-2014</p>
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	Clinical 10-25-2013 CMC 10-24-2013
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Mid-cycle Communication ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A 6-27-2014
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A 8-11-2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	9-4-2014
Division Director Summary Review ( <i>indicate date for each review</i> )	9-3-2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	9-4-2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	4 (1 PMR & 5 PMCs total)
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review Signed concurrence on 8-2-2014 & 4-21-2014 reviews
• Clinical review(s) ( <i>indicate date for each review</i> )	8-2-2014 & 4-21-2014 (filing review)
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 24 & Appendix 9.4 of 8-2-2014 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	7-25-2014
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	7-22-2014
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Signed concurrence on 8-1-2014 & 7-31-2014 reviews
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Signed concurrence on 8-1-2014, 7-31-2014 & 4-17-2014 reviews
Statistical Review(s) ( <i>indicate date for each review</i> )	8-1-2014 (addendum), 7-31-2014, 4-17-2014 (filing review)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Signed concurrence on 8-1-2014 & 4-28-2014 reviews
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	8-1-2014, 7-1-2014 QT-IRT consult review, 4-28-2014 filing review
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	8-22-2014
• Supervisory Review(s) ( <i>indicate date for each review</i> )	8-5-2014. Signed concurrence on 7-30-2014 & 4-10-2014 reviews
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	7-30-2014, 4-10-2014 (filing review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review Signed concurrence on 8-8-2014 team leader review & 8-1-2014 & 4-25-2014 reviews
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )	8-29-2014, 8-8-2014, signed concurrence on 8-1-2014 & 4-25-2014 reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )	8-1-2014 & 4-25-2014 (filing review)
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> )	7-28-2014 (DP review) 7-25-2014 (DS review)
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )	6-9-2014 (PAI waiver) 4-1-2014 (filing)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	8-1-2014 review, page 7
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) ( <i>original and supplemental BLAs</i> )	Date completed: 8-29-2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/  
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SHARON K SICKAFUSE  
09/04/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, September 03, 2014 11:13 AM  
**To:** melissa\_tice@merck.com  
**Subject:** Keytruda PI

**Importance:** High



PI\_FDA changes  
marked 9-3-201...

I will send you the Med Guide a little later. We are still working on the wording of the "What is the most important information...." section. Waiting to hear back from the promotional labeling supervisor.

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/s/  
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SHARON K SICKAFUSE  
09/03/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, September 03, 2014 1:47 PM  
**To:** melissa\_tice@merck.com  
**Subject:** Keytruda PI sentence

Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of KEYTRUDA every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging.

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/s/  
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SHARON K SICKAFUSE  
09/03/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, September 03, 2014 1:10 PM  
**To:** melissa\_tice@merck.com  
**Subject:** Keytruda Med Guide - 1st paragraph

**Importance:** High

KEYTRUDA is a medicine that may treat your melanoma by (b) (4)  
KEYTRUDA can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening.

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/s/  
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SHARON K SICKAFUSE  
09/03/2014

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

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**MEMORANDUM**

**To:** BLA 125514/0

**From:** Sharon Sickafuse, RPM  
Division of Oncology Products 2  
Office of Hematology and Oncology Drug Products

**Date:** August 27, 2014

**Subject:** manufacturing inspection issue

---

Background:

There are 2 manufacturing streams associated with this application; the one associated with MedImmune in Frederock, MD is acceptable. However, the one associated with (b) (4) is problematic as there is a sterility testing site in the manufacturing process stream (b) (4) that has never been inspected by FDA and Office of Compliance cannot recommend approval without an inspection. The earliest an inspection could occur is potentially in October. The purpose of this teleconference was discuss with Merck the option of withdrawing the (b) (4) manufacturing stream from their current application in order to take an earlier action before the October 28, 2014, PDUFA date.

Merck was aware of the inspection issue prior to our teleconference as they had received on August 27, 2014, a notice of inspection for (b) (4) control testing lab.

Discussion:

In order to take an earlier action before the October 28, 2014, PDUFA date, FDA recommended that Merck withdraw the (b) (4) facility as a drug substance (DS) manufacturing site. Before doing so, Merck will need to assess the impact of withdrawing this site on their ability to supply the market for Keytruda. Once the BLA is approved, Merck can submit a manufacturing PAS to add (b) (4) as an additional DS manufacturing site. This supplement is on a 4 month clock and inspection of the testing facility as currently scheduled (mid-October) would occur within the timeframe of the review. In order to withdraw the (b) (4) facility from the BLA, Merck would need to submit a letter and revised 356h form to the BLA.

Merck stated that they will consider FDA's advice. They asked if they could use the testing facility that is part of the MedImmune site manufacturing stream to test the DS produced at (b) (4) as this testing facility has been inspected by FDA. FDA stated that in order for Merck to do this, shipping validation data would need to be submitted for FDA review. Merck expressed understanding and stated that they would meet internally to discuss.

**FDA Attendees****Office of Hematology and Oncology Products**

Paul Kluetz, M.D., Deputy Director

Division of Oncology Products 2

Meredith Chuk, M.D., clinical reviewer

Monica Hughes, Chief, Project Management Staff

Karen Jones, Chief, Project Management Staff

Sharon Sickafuse, M.S., RPM

Mark Theoret, M.D., cross-discipline team leader for this BLA

**Office of Compliance**

Mahesh Ramanadham, Ph.D.

Ranjani Prabhakara, Ph.D.

**Office of Biotechnology Products**

Division of Monoclonal Antibodies

Sarah Kennett, Ph.D., Review Chief

**Merck Attendees**

Nikhil Mehta-Regulatory

Melissa Tice-Regulatory

Parimal Desai: Manufacturing

David Robinson-CMC Regulatory

Gargi Maheshwari-Project management Manufacturing

Ann Niland: External manufacturing biologics Quality assurance

Holger Luebke - Quality

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/s/  
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SHARON K SICKAFUSE  
09/03/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, August 28, 2014 3:20 PM  
**To:** melissa\_tice@merck.com  
**Subject:** Med Guide



Med Guide\_FDA  
changes marked...

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/s/  
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SHARON K SICKAFUSE  
08/28/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, August 28, 2014 1:54 PM  
**To:** melissa\_tice@merck.com  
**Subject:** Keytruda PI

**Importance:** High



PI\_Merck changes  
marked\_8-28-2...

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/s/  
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SHARON K SICKAFUSE  
08/28/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, August 28, 2014 10:26 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR  
**Attachments:** Response to FDA CIR on August 27 .docx

Hi Melissa,

The clinical team has the following IR . We would like a response by this afternoon.

There are discrepancies as to how the staging for metastatic disease was captured by the site investigators. As previously stated, the staging of metastases (TNMMET) does not match the sites metastases (SUPPDM:QVAL where QNAM=MHMETOTH). In your response of June 2, 2014, the sites incorrectly entered the staging of metastatic disease at time of diagnosis rather than enrollment, and you stated that patients had evidence of metastatic disease using TU.xpt; however, in your email response of August 27, 2014, you revert back to MHSCAT in the MH.xpt to categorize M1c disease, which is confusing.

Please correct the discrepancies for the staging for metastatic disease for the 173 patients based on the data provided in the MH.xpt dataset to accurately reflect the staging, i.e., if disease was in the kidney and brain, the patient should be classified as having M1c disease, not M1a, regardless of what the site investigator had entered.

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/s/  
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SHARON K SICKAFUSE  
08/28/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, August 27, 2014 12:32 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

**Importance:** High

Hi Melissa

We have the following information request. We'll need to hear back by COB today.  
Thanks

Regarding M1c disease at baseline, according to the response to IR that you provided to FDA on June 4, 2014 and using TU.xpt, the following patients had M1c disease at baseline:

3475-001_0001000344	M1c
3475-001_0002000391	M1c
3475-001_0010000251	M1c
3475-001_0011000307	M1c
3475-001_0012000305	M1c
3475-001_0015000336	M1c
3475-001_0016000408	M1c
3475-001_0019000348	M1c
3475-001_0019000350	M1c
3475-001_0019000356	M1c
3475-001_0019000367	M1c
3475-001_0019000380	M1c
3475-001_0021000357	M1c
3475-001_0023000345	M1c

Additionally, the following patients had M1b disease:

3475-001_0008000403	M1b
3475-001_0015000271	M1b
3475-001_0020000427	M1b

Please confirm and/or provide clarification of your assessment.

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/s/  
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SHARON K SICKAFUSE  
08/27/2014

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

---

**To:** Melissa Tice

**From:** Sharon Sickafuse, RPM  
Division of Oncology Products 2  
Office of Hematology and Oncology Drug Products

**Date:** August 27, 2014

**Subject:** BLA 125514/0 Med Guide

---

Hi Melissa,

Attached is FDA's proposed Med Guide. Due to all the formatting and wording changes, I'm sending a "clean" version. Please email me your counterproposal with what you agree as "accepted" and what we need to work on as in color. Thanks

4 Pages Of Draft Labeling Have Been Withheld In Full As b4 (CCI/TS) Immediately  
Following This Page

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SHARON K SICKAFUSE  
08/27/2014

**BLA REVIEW WRAP-UP MEETING SUMMARY**  
**August 26, 2014**

**BLA 125514/0**  
**Keytruda (pembrolizumab)**

---

**Proposed Indication:** Treatment of unresectable or metastatic melanoma in patients whose disease has progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor.

**Action Due Date: October 28, 2014**

**Early Action Dates: August 29, 2014, September 2, 2014, or September 4, 2014**

**Outstanding Signed Reviews:**

Patient labeling  
CDRL  
Division Director  
Office Director

**Discuss Remaining Outstanding Pre-Action Items:**

- 1. Labeling:**
  - a. Revised carton & container labeling received August 14<sup>th</sup>. Revised labeling has addressed all FDA comments and is acceptable.
  - b. Revised PI received on August 20<sup>th</sup>. Internal meeting held August 22<sup>nd</sup> and telecon with Merck held on August 25<sup>th</sup>. Labeling is still being negotiated.
  - c. Proposed Med Guide submitted on August 7<sup>th</sup>.
- 2. Compliance Check:** Sent on August 5<sup>th</sup>. Follow-up email on August 22<sup>nd</sup>.
- 3. PMCs and PMRs:** Agreement reached with Merck on language & milestones for 1 clinical PMR, 1 nonclinical PMC & 4 product PMCs.
- 4. Employee list (yes/no) for Action Package:** Emailed August 21<sup>st</sup>.
- 5. Press Release/ASCO Burst:** Press office has been notified.
- 6. Action Package Preparation:** Gave to CPMS on August 25<sup>th</sup>.

7. **Approval letter:** Emailed to team on August 19<sup>th</sup>. Email to SRT on August 21<sup>st</sup>. Received SRT clearance on August 22<sup>nd</sup>.

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/s/  
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SHARON K SICKAFUSE  
08/26/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, August 15, 2014 8:21 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - CMC IR

Hi Melissa,

My CMC team has the following responses regarding your submission of August 5<sup>th</sup> in response to our July 30<sup>th</sup> IR regarding the pembrolizumab reference standard.

1. The current criterion for selecting the reference lot allows any commercial lot that meets release criteria for DS release to be acceptable as the reference standard lot. This does not meet our current expectations; the potency range implemented for the release acceptance criterion is too wide to be used to indicate acceptability of a reference standard. A lot that has a potency level that is outside a relatively narrow range relative to the clinical material, and, therefore, relative to the current reference standard, would not be considered to be sufficiently reflective of the clinical material to allow its use as a reference standard. Tighten the criterion for potency in the reference standard qualification protocol.
  - a. We would agree with an approach for setting the acceptance criterion for reference standard potency that is the equivalent to the first part of our approach as described in response 1a- assigning a potency to the new RS: “A <sup>(b)</sup><sub>(4)</sub> % confidence interval for the mean potency value determined to be of sufficient precision (3% margin of error) is computed. If the entire CI falls within the acceptance criterion of <sup>(b)</sup><sub>(4)</sub> % relative potency, the new reference standard is assigned a potency value equal to the primary reference standard.”
  - b. We do not agree with <sup>(b)</sup><sub>(4)</sub>  

2. In your response to item 4, you identified the conditions under which the current primary and secondary reference standard will be replaced. Update BLA to reflect these intentions.

3. In your proposed reference stability testing strategy it is 'assumed' that the secondary reference standard is stable during the time period it is used. It is not clear how this assumption is made. Provide confirmation that you have/will have the secondary reference standard testing data to support its stability during the time period it is used.
  
4. In your response to item 2, you indicated that the stability/recertification protocols for the primary and secondary reference standard will be updated and submitted to the Agency by September 30<sup>th</sup>. These protocols are needed sooner than the proposed time frame to allow us to complete the BLA review; therefore please submit the draft protocols or detailed description of the protocols for stability /recertification of the primary and secondary reference standard by August 27<sup>th</sup>. The recertification protocols should include tests and acceptance criteria; and testing intervals. If agreed upon, the finalized protocols should be submitted to the BLA in the first annual report.

We will need a response by August 27<sup>th</sup>. Thank you

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SHARON K SICKAFUSE  
08/15/2014



BLA 125514/0

## LABELING PMR/PMC DISCUSSION COMMENTS

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We also refer to our April 29, 2014, letter in which we notified you of our target date of September 26, 2014, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On May 23, 2014, we received your May 23, 2014, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by August 21, 2014. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Content of Labeling

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

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SHARON K SICKAFUSE  
08/13/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, August 12, 2014 11:31 AM  
**To:** 'Tice, Melissa'  
**Subject:** RE: BLA 125514/0 - carton & container labeling

Hi Melissa,

Regarding Item A6, the team finds your proposal to maintain "Single-Use" acceptable.

Moving forward, FDA is planning to publish a Draft Guidance for Appropriate Package Type Terms for Injection Drugs or Biological Products in Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM314767.pdf>.

---

**From:** Tice, Melissa [[mailto:melissa\\_tice@merck.com](mailto:melissa_tice@merck.com)]  
**Sent:** Thursday, August 07, 2014 11:49 AM  
**To:** Sickafuse, Sharon  
**Subject:** RE: BLA 125514/0 - carton & container labeling

Hi Sharon,

We would greatly appreciate feedback as soon as possible on the two comments below A2 and A6 in order to revise carton and container labeling by the due date of Aug 15<sup>th</sup>.

Thanks  
Melissa

---

**From:** Sickafuse, Sharon [<mailto:Sharon.Sickafuse@fda.hhs.gov>]  
**Sent:** Tuesday, August 05, 2014 4:18 PM  
**To:** Tice, Melissa  
**Subject:** BLA 125514/0 - carton & container labeling

Hi Melissa,

We have reviewed the revised carton and container labeling submitted on July 15, 2014, and have the following requests for additional revisions. Please submit revised carton and container labeling by August 15, 2014.

A. Carton Labeling for (b) (4) Facility

1. (b) (4)

2. (b) (4)

Merck acknowledges that the carton labeling is in compliance with federal regulations, 21 CFR 600.3(f) and 21 CFR 610.60, by listing Merck Sharp & Dohme Corp. as the manufacturer, with the appropriate US License No.

Merck proposes to retain Schering-Plough Brinny on the carton labeling as shown on the carton submitted on 15-Jul-2014 for compliance with state regulations.

**Rationale:**

Certain states, such as California, Maryland, Kentucky, Louisiana, Michigan, and Arkansas, have state regulations which require the actual site of manufacture to be shown on the packaging, differing from the definition of “manufacturer” as defined by 21 CFR 600.3(f). To maintain compliance with both state and federal regulations, Merck proposes to retain the drug product facility on the packaging.

We request Agency feedback on retaining the manufacturing information as previously presented prior to proceeding with other requested revisions.

3. Delete the statement (b) (4)
4. Revise the statements “Sterile lyophilized powder must be reconstituted with sterile water for injection. Reconstituted solution requires further preparation prior to administration.” to as follows:  
  
Sterile lyophilized powder must be reconstituted with Sterile Water for Injection, USP. Reconstituted solution requires further dilution prior to administration.  
  
Additionally, relocate this important information to the principal display panel.
5. Relocate the listing of the contents of the vial from the principal display panel to a side panel or back panel to make room for the above recommendation.
6. Revise the term “Single-use vial” to “Single-Dose vial”. Single-Dose vial is the appropriate term for this vial per United States Pharmacopeia 8/1/14 – 11/30/14 <659> Packaging and Storage Requirements.

Merck acknowledges the term “Single-Dose vial”, as noted in the United States Pharmacopeia 8/1/14 – 11/30/14 <659> Packaging and Storage Requirements, for Injectable products.

Merck proposes to retain the use of the term “single-use” in place of “single-dose”.

**Rationale:**

“Single-dose” may imply that the entire dose of KEYTRUDA may be contained in one vial, which may or may not be the case based on patient weight.

Use of the term "single-use" is consistent with many recently-approved Injectable products (Yervoy, Kadcyla, (b) (4) Perjeta, Adcetris and Benlysta) for which the entire dose may not be contained in one vial.

We request Agency feedback in retaining the use of the term “single-use” prior to proceeding with other requested revisions.

**B. Carton Labeling for US Facility**

1. See A2, A3, A4, A5, A6.

**C. Container Label**

1. See A6.

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SHARON K SICKAFUSE  
08/12/2014

**From:** Sickafuse, Sharon  
**Sent:** Monday, August 11, 2014 3:09 PM  
**To:** 'Tice, Melissa'  
**Subject:** RE: BLA 125514/0 - carton & container labeling

Hi Melissa,

Regarding A2, my team has the following response:

We find your proposal acceptable. Thus, the manufacturer information on the Carton Labeling should appear as follows:

**Carton Labeling for** (b) (4) **Facility**

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

Product of (b) (4)

**Carton Labeling for US Facility**

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

---

We are still discussing internally the single-dose versus single-use.

Could you please email me the State regulations that you mentioned regarding A2, so that we can better understand these regulations moving forward? Thank you

---

**From:** Tice, Melissa [[mailto:melissa\\_tice@merck.com](mailto:melissa_tice@merck.com)]  
**Sent:** Thursday, August 07, 2014 11:49 AM  
**To:** Sickafuse, Sharon  
**Subject:** RE: BLA 125514/0 - carton & container labeling

Hi Sharon,

We would greatly appreciate feedback as soon as possible on the two comments below **A2** and **A6** in order to revise carton and container labeling by the due date of Aug 15<sup>th</sup>.

Thanks  
Melissa

---

**From:** Sickafuse, Sharon [<mailto:Sharon.Sickafuse@fda.hhs.gov>]

**Sent:** Tuesday, August 05, 2014 4:18 PM

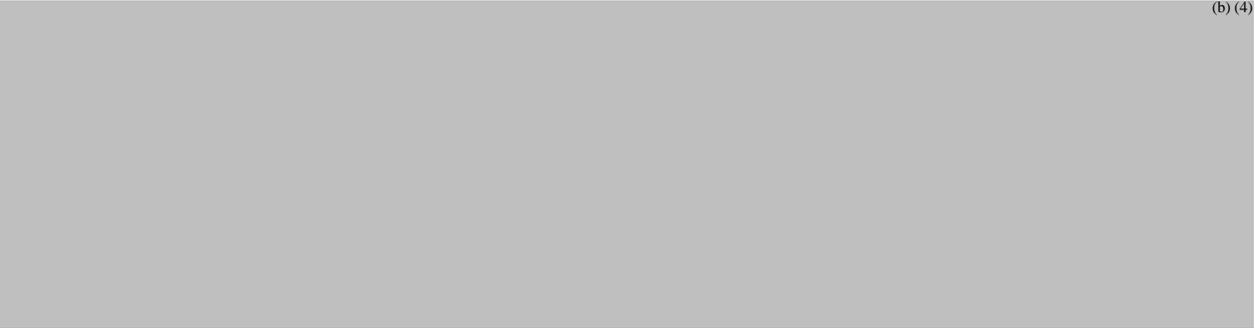
**To:** Tice, Melissa

**Subject:** BLA 125514/0 - carton & container labeling

Hi Melissa,

We have reviewed the revised carton and container labeling submitted on July 15, 2014, and have the following requests for additional revisions. Please submit revised carton and container labeling by August 15, 2014.

A. **Carton Labeling for** (b) (4) **Facility**



**Merck acknowledges that the carton labeling is in compliance with federal regulations, 21 CFR 600.3(f) and 21 CFR 610.60, by listing Merck Sharp & Dohme Corp. as the manufacturer, with the appropriate US License No.**

**Merck proposes to retain Schering-Plough Brinny on the carton labeling as shown on the carton submitted on 15-Jul-2014 for compliance with state regulations.**

**Rationale:**

**Certain states, such as California, Maryland, Kentucky, Louisiana, Michigan, and Arkansas, have state regulations which require the actual site of manufacture to be shown on the packaging, differing from the definition of “manufacturer” as defined by 21 CFR 600.3(f). To maintain compliance with both state and federal regulations, Merck proposes to retain the drug product facility on the packaging.**

**We request Agency feedback on retaining the manufacturing information as previously presented prior to proceeding with other requested revisions.**

3. Delete the statement (b) (4)

4. Revise the statements “Sterile lyophilized powder must be reconstituted with sterile water for injection. Reconstituted solution requires further preparation prior to administration.” to as follows:

Sterile lyophilized powder must be reconstituted with Sterile Water for Injection, USP. Reconstituted solution requires further dilution prior to administration.

Additionally, relocate this important information to the principal display panel.

5. Relocate the listing of the contents of the vial from the principal display panel to a side panel or back panel to make room for the above recommendation.

6. Revise the term “Single-use vial” to “Single-Dose vial”. Single-Dose vial is the appropriate term for this vial per United States Pharmacopeia 8/1/14 – 11/30/14 <659> Packaging and Storage Requirements.

**Merck acknowledges the term “Single-Dose vial”, as noted in the United States Pharmacopeia 8/1/14 – 11/30/14 <659> Packaging and Storage Requirements, for Injectable products.**

**Merck proposes to retain the use of the term “single-use” in place of “single-dose”.**

**Rationale:**

**“Single-dose” may imply that the entire dose of KEYTRUDA may be contained in one vial, which may or may not be the case based on patient weight.**

**Use of the term "single-use" is consistent with many recently-approved Injectable products (Yervoy, Kadcyła, (b) (4) Perjeta, Adcetris and Benlysta) for which the entire dose may not be contained in one vial.**

**We request Agency feedback in retaining the use of the term “single-use” prior to proceeding with other requested revisions.**

**B. Carton Labeling for US Facility**

1. See A2, A3, A4, A5, A6.

**C. Container Label**

1. See A6.

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SHARON K SICKAFUSE  
08/11/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, August 05, 2014 4:18 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - carton & container labeling

Hi Melissa,

We have reviewed the revised carton and container labeling submitted on July 15, 2014, and have the following requests for additional revisions. Please submit revised carton and container labeling by August 15, 2014.

**A. Carton Labeling for (b) (4) Facility**

1. (b) (4)
2. (b) (4)
3. Delete the statement (b) (4)
4. Revise the statements "Sterile lyophilized powder must be reconstituted with sterile water for injection. Reconstituted solution requires further preparation prior to administration." to as follows:

Sterile lyophilized powder must be reconstituted with Sterile Water for Injection, USP. Reconstituted solution requires further dilution prior to administration.

Additionally, relocate this important information to the principal display panel.

5. Relocate the listing of the contents of the vial from the principal display panel to a side panel or back panel to make room for the above recommendation.
6. Revise the term "Single-use vial" to "Single-Dose vial". Single-Dose vial is the appropriate term for this vial per United States Pharmacopeia 8/1/14 – 11/30/14 <659> Packaging and Storage Requirements.

**B. Carton Labeling for US Facility**

1. See A2, A3, A4, A5, A6.

**C. Container Label**

1. See A6.

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SHARON K SICKAFUSE  
08/05/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, August 01, 2014 2:18 PM  
**To:** melissa\_tice@merck.com  
**Subject:** FW: BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

---

**From:** Rawat, Rashmi  
**Sent:** Friday, August 01, 2014 2:09 PM  
**To:** Sickafuse, Sharon  
**Cc:** Paciga, Mark; Schmiel, Deborah  
**Subject:** RE: BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

Hi Sharon,  
Can you please send our following response to the sponsor.  
Thanks,  
Rashmi

We accept your proposed acceptance criteria for the potency assay and agree with the request to modify the (b) (4) main peak criterion to maintain (b) (4)%.  
The justification provided for the proposed potency assay stability acceptance criterion indicates a large variation in the assay, which could be indicative of problem with the potency assay. We recommend a thorough investigation of any 'OOS or OOT' potency results observed. A summary of the investigation should be submitted with the PMC study report for the re-evaluation of DS and DP specifications, if you propose to maintain the (b) (4)% acceptance criterion at the time of the PMC submission.

---

**From:** Sickafuse, Sharon  
**Sent:** Friday, August 01, 2014 12:36 PM  
**To:** Rawat, Rashmi; Paciga, Mark; Rawat, Rashmi  
**Subject:** FW: BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR  
**Importance:** High

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**From:** Tice, Melissa [[mailto:melissa\\_tice@merck.com](mailto:melissa_tice@merck.com)]  
**Sent:** Friday, August 01, 2014 10:05 AM  
**To:** Sickafuse, Sharon  
**Subject:** FW: BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR  
**Importance:** High

Hi Sharon,  
Would you please provide this response to your CMC review team. We request that the specification of the (b) (4) main peak is maintained at (b) (4)% for the number of significant digits to match our quality systems instead of (b) (4)%.

Thanks  
Melissa

---

**From:** Tice, Melissa  
**Sent:** Thursday, July 31, 2014 1:57 PM  
**To:** May, Kimberly (mrk 2)  
**Cc:** Robinson, David  
**Subject:** FW: BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

In response to response #2 sent yesterday

---

**From:** Sickafuse, Sharon [<mailto:Sharon.Sickafuse@fda.hhs.gov>]  
**Sent:** Thursday, July 31, 2014 1:56 PM  
**To:** Tice, Melissa  
**Subject:** BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

Hi Melissa,

The CMC teams agrees with Merck's proposed acceptance criteria for DS and DP release and stability specifications with the exception of the Potency Assay acceptance criteria. The proposed acceptance criteria (b) (4) %) for potency are too wide based upon your clinical experience of (b) (4) %. The potency of (b) (4) % is based upon the mean +/- 3 SD and (b) (4) TI. Provide updated potency acceptance criteria to both DS and DP release and stability specifications.

Thank you

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SHARON K SICKAFUSE  
08/04/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 31, 2014 2:48 PM  
**To:** melissa\_tice@merck.com  
**Subject:** FW: BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

Hi – the 2<sup>nd</sup> to the last sentence should read “We recommend potency of (b) (4) % based upon the mean +/- 3 SD and (b) (4) TI.”

---

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 31, 2014 1:56 PM  
**To:** [melissa\\_tice@merck.com](mailto:melissa_tice@merck.com)  
**Subject:** BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

Hi Melissa,

The CMC teams agrees with Merck’s proposed acceptance criteria for DS and DP release and stability specifications with the exception of the Potency Assay acceptance criteria. The proposed acceptance criteria ((b) (4) %) for potency are too wide based upon your clinical experience of (b) (4) %. The potency of (b) (4) % is based upon the mean +/- 3 SD and (b) (4) TI. Provide updated potency acceptance criteria to both DS and DP release and stability specifications.

Thank you

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/s/  
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SHARON K SICKAFUSE  
07/31/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 31, 2014 1:56 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - re your response to item #2 of 7-29-2014 CMC IR

Hi Melissa,

The CMC teams agrees with Merck's proposed acceptance criteria for DS and DP release and stability specifications with the exception of the Potency Assay acceptance criteria. The proposed acceptance criteria (b) (4) %) for potency are too wide based upon your clinical experience of (b) (4) %. The potency of (b) (4) % is based upon the mean +/- 3 SD and (b) (4) TI. Provide updated potency acceptance criteria to both DS and DP release and stability specifications.

Thank you

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/s/  
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SHARON K SICKAFUSE  
07/31/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 31, 2014 9:40 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - CMC IR

**Importance:** High

Hi Melissa,

My CMC team has the following IR. They would like a response by tomorrow:

1. Regarding the evaluation of potency for release of reference standard (RS):
  - a. The potency criterion for release of new primary or working RS is not acceptable. The drug substance (DS) release criterion is significantly wider than the current expectations for qualification of primary and working RS. Materials in the outer regions of this range are not reflective of the materials that were used in the pivotal clinical studies. (b) (4)  
Update the requirements to include a sufficiently narrow range(s) for potency at release to ensure that the quality of the commercial drug product (DP) does not drift from the quality of the material used during the pivotal clinical studies. Note that the (b) (4) % range for setting the primary RS to (b) (4) % potency might also be wider than recommended; implementing slightly different ranges for release of primary and working RS might be useful.
  - b. We note that it is stated in sections 3.2.S.5.1.1.2 and 3.2.S.5.1.2.2 that the acceptance criteria will be statistically derived based on assay variability as determined in analytical method validation and/or historical experience. The acceptance criteria for RS qualification and requalification should be set based on maintaining a reference that will prevent drift in product quality attributes, not on validation and historical data.
  - c. Based on Table 4 in section 3.2.S.5.1.1.2 and Table 6 in section 3.2.S.5.1.2.2, it appears that the "result," which would be the mean of the results from independent determinations, is used for one portion of the criteria and that the 95% confidence interval generated from the results is used to determine the margin of error, which the forms basis for the second acceptance criterion. However, in attachment 1 (section 3.2.S.5), Table 2 (primary reference standard) only lists the requirement for a result "achieved within a 3% margin of error," and Table 4 (secondary reference standard) appears to indicate that the "result" is the 95% confidence interval of the independent determinations. Clarify the calculations used to determine the result used to evaluate potency; if a confidence interval is used, clarify how the confidence interval range is compared to the (b) (4) % range that is currently proposed as part of the acceptance criterion (e.g., if the entire

confidence interval must be within the acceptance criterion range). Note that if a confidence interval is considered, and it is not required to be entirely within the acceptance criterion range, the acceptance criterion range is effectively widened, and this is likely to not be acceptable unless the range is quite tight around (b) (4) %.

d. (b) (4)  
Update the BLA as applicable when the potency acceptance criteria are finalized.

e. The (b) (4) acceptance criteria listed in Table 5 in section 3.2.S.5.1.1.2 include both "(b) (4) for the calculated result" and "(b) (4) for calculated result." Identify the correct criterion and correct the BLA, as appropriate.

f. It is not clear how equivalency of the primary RS sublots will be/was evaluated. If the sublots of the current primary RS are to be issued a single certificate containing the initial subplot results and used interchangeably, they should have the same potency and protein concentration. Table 3 (attachment 1) states that the "result must be within (b) (4) % of reference standard W12-MK3475P-09C(s1) in order to be reported as (b) (4) % potency." This is listed in the same row of the table as "95% confidence interval." Clarify the calculations used to determine the result used to evaluate potency; if a confidence interval, rather than the mean of the results, is used, clarify how the confidence interval range is compared to the (b) (4) % range that is currently proposed as part of the acceptance criterion (e.g., if the entire confidence interval must be within the acceptance criterion range). (b) (4)

(b) (4)  
Clarify how the "result" is evaluated with respect to assigning the same potency value to sublots s2 and s3 as was assigned to subplot s1.

2. Regarding reference standard requalification/stability:

- a. Attachment 1 (section 3.2.S.5) does not contain the "protocol for the requalification of MK-3475 primary and secondary RS." Provide the requalification/stability protocol(s) used for monitoring stability of the RS.
- b. Requalification/demonstration of stability of the primary and secondary RS is essential for appropriate evaluations of DS and drug product (DP) at release and on stability. Secondary RS stability cannot be assumed (section 3.2.S.5.1.1.3). Therefore, it is not clear how stability of the primary and secondary RS is monitored. We note that the EC50 values are included in

- the tables describing the initial certification and 2013 recertification of the current primary RS (section 3.2.S.5.1, Tables 1 and 2). Use of the EC50 values during recertification/stability testing, along with the tracking and trending of routine release and stability test data, could provide for an appropriate mechanism to evaluate the stability of the RS.
- c. The protocol provided in Attachment 1 states that the primary RS was recertified and the updated certificate "confirms the assigned potency of (b) (4) %." It is not clear how the potency was confirmed; it appears that confirmation of potency, which, in this case would be the same as requalification/recertification/stability, was not based on a secondary RS, which is the only mechanism described. Clarify how the primary RS was recertified. We note that this might be an appropriate mechanism to use for routine recertification.
  - d. It is stated in section 3.2.S.5.1 that the current reference material was "subjected to scheduled annual recertification testing for stability" and that the material will "continue to be monitored by annual re-certification testing" (p. 3). However, in section 3.2.S.5.1.1.4, it is stated that "a retest period of (b) (4) years will be set for the primary reference standard." Clarify this apparent discrepancy, and correct the BLA as appropriate. If a (b) (4) year period is proposed, provide a justification based on data that indicate the material will remain stable through this time period. In addition, provide data to demonstrate that a (b) (4) year retest period is appropriate for secondary RS(section 3.2.S.5.1.2.4).
3. In a two tiered RS system, a secondary RS should not be used to qualify another secondary RS, and a new primary RS should not be qualified against a secondary RS or against a secondary RS that was itself qualified against a secondary RS (section 3.2.S.5.1.1.3, p. 10). The acceptance criteria (most significantly the potency criterion) are not set to be applicable to such a system. The provision to qualify a primary RS or a secondary RS in this manner should be removed from the BLA. New RS should be qualified before the current RS has degraded/expired; in the event of an unforeseen occurrence, mechanisms for qualifying a new RS can be discussed with the Agency.
  4. To manage potential drift in commercial product quality attributes over time, RS should be changed only when necessary. Clarify under what conditions the primary and secondary RS will be replaced by a new RS.
  5. While it might be acceptable to blend DS batches to achieve a more representative purity/impurity profile, it is not acceptable to blend DS batches to achieve an acceptable level of potency. Confirm that any DS batch used for the manufacture of a RS will meet the RS qualification requirements.

6. The current primary RS [W12-MK3475P-09C(s)] was prepared as a number of sub-lots. Based on the procedures described in section 3.2.S.5, it appears that the practice of preparing sub-lots of RS that would be used interchangeably will no longer be an option. Confirm the Agency's understanding of the use of the preparation of sub-lots.
7. A small amount of certification and recertification data was provided for the current primary RS (section 3.2.S.5.1 Tables 2 and 3). Provide the complete qualification/certification and requalification/recertification datasets.

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/s/  
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SHARON K SICKAFUSE  
07/31/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, July 30, 2014 4:47 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 IR

**Importance:** High

Hi Melissa,

Dr. Chuk has the follow IR:

Provide tables of treatment emergent laboratory abnormalities (chemistry and hematology) by toxicity grade of abnormality (Gr1, Gr2, Gr3, G4, all grades) that exclude patients who did not have an increase in grade from baseline for:

- Part B2 by dose
- Melanoma ISS (n=411) by dose
- Melanoma ISS all doses combined

Also provide these tables as SAS or excel files. Please provide this data by COB August 5, 2014.

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SHARON K SICKAFUSE  
07/30/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, July 29, 2014 6:43 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - CMC IR

**Importance:** High

Hi Melissa,

My CMC team has the following IR which they are asking for a response by COB July 30:

1. The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 for (b) (4) and FMC and 3.2.P.8.2 for (b) (4)) do not include information regarding the intention to submit data from the stability studies. Provide commitments to submit the data from all ongoing stability studies, including the leachable study, and the data from annual stability lots in the BLA annual reports.
2. The release data provided for the drug substance (DS) and drug product (DP) lots manufactured by the (b) (4) and FMC and (b) (4) manufacturing process and for the DS and DP lots used in the clinical studies do not support the proposed acceptance criteria for select release and stability specifications. We do not agree with the proposed acceptance criteria for the specifications indicated below and have following recommendations. Submit revised DS and DP specifications and stability protocols for primary, process validation and post-approval DS and DP stability lots.

DS and DP Release Test	Release and Shelf life Acceptance Criteria for DS	Release and Shelf life Acceptance Criteria for DP
Clarity (Opalescence)	(b) (4)	(b) (4)
Appearance	Essentially free of visible particles	Essentially free of visible particles
Potency	(b) (4) %	(b) (4) %
Charge Distribution (b) (4)		

(b) (4)

(b) (4)

3. The manufacturer information listed in sections 3.2.S.2.1 and 3.2.P.3.1 (Table 1) and Form 356h indicates that analytical methods for release and stability testing of the DS and DP are performed at more than one testing site. Data to demonstrate that appropriate method transfer studies were performed and that the methods perform equally and provide sufficiently similar data at both testing sites were not included in the BLA. Provide summary reports for analytical method transfer for the methods that are performed at more than one testing site.
4. The left hand sides of Tables 54 and 84 in Section 3.2.P.2.3 (p. 115 and 175) are cut off from the page. Revise this section to include complete tables, ensuring that the batch numbers are visible.

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SHARON K SICKAFUSE  
07/29/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, July 29, 2014 10:40 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - safety IR

**Importance:** High

Hi Melissa, Please see below.

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**From:** Chuk, Meredith  
**Sent:** Tuesday, July 29, 2014 9:59 AM  
**To:** Sickafuse, Sharon  
**Subject:** RE: BLA 125514/0 - safety info submitted on July 25  
**Importance:** High

Sharon,

Here is a list of what we discussed on the call; please send this to Melissa.

1. Lab tables with data cut-off of October 18 and December 31, 2013 with the addition of hemoglobin and neutrophils in SAS.xpt or excel files.
2. Line listings of patients in Part B2 and the Melanoma ISS (N=411) with AEOSI events including patient ID number, PT, event start and stop date.
3. Vital sign tables with changes from baseline and analysis
4. Narratives for the following patients:
  - a. Patient 100042 with myasthenic syndrome
  - b. Patient 0063 with Grade 3 hemolytic anemia
  - c. Patient 0068 with Gr 3 rhabdomyolysis
  - d. Patient 0919 with Gr 5 diffuse alveolar damage
  - e. Patient 0106 with Gr 5 interstitial lung disease

Items should be submitted by Thursday noon, but earlier when possible. Preference is for items 1 to be submitted by noon tomorrow. Items can be emailed when ready and submitted as one amendment to the BLA.

Thanks.  
Meredith

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/s/  
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SHARON K SICKAFUSE  
07/29/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, July 25, 2014 1:51 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - clinical IR

Hi Melissa,

Please update and resubmit the datasets that pertain to patient demographics, e.g., ADSL, DM, MH, CM, and other affected datasets to correctly reflect the information that has been submitted in response to FDA's information requests, specifically received on March 26, March 28, May 21, May 30, June 2, June 4, June 5, and June 12, 2014.

Thank you

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SHARON K SICKAFUSE  
07/25/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, July 23, 2014 9:54 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

**Importance:** High

Hi Melissa,

Can you please email me the following document referenced in the CSR: "Summary of Laboratory Abnormality for Highest Toxicity Grade (All Patients as Treated)." The CSR states that it can be found in Section 14.4.14, but Section 14.4.13.5 is followed by Section 14.5.

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SHARON K SICKAFUSE  
07/25/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 24, 2014 6:08 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - CMC IR

Hi Melissa,

My CMC team has the following IR:

1. Revise section 3.2P.3.4 to include the proposed (b) (4) hold times for both the (b) (4).
2. Revise section 3.2.P.8 to include the stability protocols used for (b) (4) (b) (4) validation batches.
3. Provide data to support the proposed (b) (4) % overfill volume for Keytruda drug product. Specifically, provide summary data from the studies conducted demonstrating that a minimum (b) (4) % overfill is required in order to withdraw the correct dose.
4. We note that the page numbers 72 and 73 of section 3.2.P.3.5, "Process Validation for (b) (4) are missing. Update the BLA to include these missing pages.
5. Provide the anti-host cell protein (HCP) antibody qualification data to support its use in the HCP ELISA. Specifically, provide data demonstrating that the commercial kit can detect the majority of HCPs present in the production cell line. This data should include 2D SDS-PAGE gels of the range of HCPs detected by silver stain compared to the range detected by western blot analysis using the antibody employed in the commercially available ELISA kit. Include information on the approximate percent of potential HCP impurities that are recognized by the HCP antiserum.

Please submit your response by July 29. Thank you

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/s/  
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SHARON K SICKAFUSE  
07/24/2014

**From:** Pierce, Melanie  
**To:** [melissa\\_tice@merck.com](mailto:melissa_tice@merck.com)  
**Cc:** [nikhil.mehta@merck.com](mailto:nikhil.mehta@merck.com)  
**Subject:** BLA 125514 IR  
**Date:** Friday, July 18, 2014 10:43:00 AM

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Please see the attached IR for BLA 125514.

1. Please clarify patient 0021000132 in Part B1. It appears that the response for this patient was not captured in the IRO, but response was recorded by investigator. This patient was treated approximately for five months with MK-3475 and experienced grade 2 hypothyroidism according to p. 1865 of the Clinical Study Report.
2. Additionally, please provide the USUBJIDs for ipilimumab-treated patients only by treatment arm for Part B1 .

Please provide your response by COB today, Friday, July 18, 2014 or Monday morning, July 21, 2014.

Thanks,

Melanie

*Melanie B. Pierce  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research*

*Email: [Melanie.Pierce@fda.hhs.gov](mailto:Melanie.Pierce@fda.hhs.gov)  
Phone: 301-796-1273*

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/s/  
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MELANIE B PIERCE  
07/18/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 17, 2014 5:09 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

**Importance:** High

Hi Melissa,

My team has the following IR. We'll need a response by July 25. Thank you

1. Provide a narrative summary supported by data of your analyses of the safety information to determine time to onset of irAE, duration of irAE and type/amount/duration of steroid treatment for irAE for renal disorders.
2. Provide narratives for the following patients on study PN001:
  - 101820 with fatal liver failure
  - 100006 with Stevens Jonson Syndrome

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SHARON K SICKAFUSE  
07/17/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, July 17, 2014 4:50 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 qual micro IR

Hi Melissa,

My qual micro team has the following IR. We'll need a response by July 23<sup>rd</sup>. Thank you

Regarding drug substance sampling in (b) (4) (b) (4)



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SHARON K SICKAFUSE  
07/17/2014



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

Memorandum

**Date:** July 12, 2014  
**From:** Melanie Pierce, on behalf of Sharon Sickafuse DOP2/OHOP/CDER  
**Subject:** BLA 125514/0; Information Request

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Keytruda (pembrolizumab).

We are in the process of reviewing your application and have the following comments and requests for additional information:

1. We do not agree that the future changes that are managed by Merck's quality systems "include regulatory updates for all Critical Process Parameters and Key Operating Parameters" only (section 3.2.S.2.2). All process parameters and other controls that are described in sections 3.2.S.2.2 and S.2.4 and section 3.2.P.3.3 and P.3.4 are considered to be regulatory commitments. Therefore, any changes to these process parameters or controls should be reported to the Agency under the appropriate reporting category, as determined by Merck's regulatory unit upon review of the proposed changes. Update the BLA to confirm that all applicable changes will be reported.
2. To support the licensure of the Keytruda manufacturing process, revise section 3.2.S.2.2 to include the following parameters and associated operating ranges or limits along with the justification for the proposed ranges or limits:

a.

(b) (4)

b.

(b) (4)

c. (b) (4) and FMC: (b) (4)

d. (b) (4)

e. Operating temperature for downstream manufacturing steps for (b) (4) and FMC

f. (b) (4) step at FMC and (b) (4)

g. (b) (4)

h. (b) (4)

i. Formulation Step at FMC:  
• (b) (4)

j. (b) (4)

3. In response to question 13 and 14 of our May 14, 2014 IR, Merck indicated that the concurrent validation protocols for the (b) (4) steps are not yet finalized. If the (b) (4) validation protocols cannot be submitted to the BLA at this time, the provisions for (b) (4) should be removed from section 3.2.S.2.2. The BLA can be amended to include the (b) (4) validation reports are submitted to the BLA as a post-approval supplement(s).

4. Provide the concurrent lifetime validation protocols for the (b) (4).  
These protocols should include, but not be limited to, the monitoring of appropriate process parameters, in process testing, and product quality attributes and the acceptance criteria for confirming the commercial lifetime limits for the (b) (4).

5. Regarding the overall approach to qualification of replacement of WCBs, an assessment of DS release data on a sufficient number (e.g., three) of commercial scale lots of DS manufactured with the new WCB is expected for confirmation of product quality. Modify the WCB qualification protocol to include the evaluation of commercial scale DS lots.
6. The description of the (b) (4)  
[REDACTED]
7. You have used the terms (b) (4) several places in the BLA. Identify what temperature range and/or humidity these terms refer to.
8. If available, provide a "simple stability update" to support the proposed dating period for (b) (4) drug product and (b) (4) and FMC drug substance. A simple stability update is defined as the stability data and analyses performed under the same conditions and for the same drug substance and drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This stability update should use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and should not contain matrix or bracketing approaches that deviate from the stability protocol in the original BLA.

Please provide your response by COB, July 21, 2014.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/  
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MELANIE B PIERCE  
07/15/2014



BLA 125514/0

**MID-CYCLE COMMUNICATION**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We also refer to the teleconference between representatives of your firm and the FDA on June 27, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date:** June 27, 2014

**Application Number:** BLA 125514/0  
**Product Name:** Keytruda (pembrolizumab)  
**Proposed Indication:** Indicated for the treatment of unresectable or metastatic melanoma in patients who progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor.

**Applicant Name:** Merck Sharp and Dohme Corp. (Merck)

**Meeting Chair:** Marc Theoret  
**Meeting Recorder:** Sharon Sickafuse

**FDA ATTENDEES**

**Office of Hematology and Oncology Products**

Division of Oncology Products 2

Jennie Chang, PharmD

Sharon Sickafuse, M.S.

Marc Theoret, M.D.

Division of Hematology Oncology Toxicology

Whitney Helms, Ph.D.

Shawna Weis, Ph.D.

**Office of Clinical Pharmacology**

Division V

Hong Zhao, Ph.D.

Pharmacometrics

Liang Zhao

**Office of Scientific Investigations**

Lauren Iacono-Connor

**Office of Biotechnology Products**

Division of Monoclonal Antibodies

Mark Paciga, Ph.D.

Rashmi Rawat, Ph.D.

Deborah Schmiel, Ph.D.

**Office of Manufacturing and Product Quality**

Division of Good Manufacturing Practice Assessment  
Biotech Manufacturing Assessment Branch  
Maria Reyes Candau-Chacon, Ph.D.  
Kalavati Suvarna, Ph.D.

**Office of Medication Error Prevention and Risk Management**

Division of Risk Management  
Carolyn Yancey, M.D.

**Office of Medical Policy Initiatives**

Division of Medical Policy Programs  
Patient Labeling Team  
Sharon Mills

**APPLICANT ATTENDEES**

Global Regulatory Affairs  
Dennis Erb, Ph.D., Senior Vice President  
Nikhil Mehta, Ph.D., Vice President Oncology & Immunology  
Melissa Tice, Ph.D., Executive Director-Oncology  
David Robinson, Ph.D., Executive Director- Biologics/Vaccines  
Kimberly May, Ph.D., Director –Biologics/Vaccines

(b) (4)

(b) (4)

Project Leadership & Management  
Alise Reicin, M.D., Vice President

Clinical Research-Oncology  
Eric Rubin, M.D., Vice President  
Robert Iannone, M.D., MSCE Executive Director  
Scot Ebbinghaus, M.D., Executive Director  
Peter Kang, M.D., Director  
Jill Lindia, Clinical Scientist

Clinical Project Management  
Cathy Doherty, Associate Director

Clinical Operations  
Debra Reisinger, Executive Director

Clinical Safety and Risk Management  
Mary Frances Schubert, M.D., Executive Director  
Amy Sun, M.D., Director

Preclinical Pharmacology  
Beth Hutchins, Ph.D., Director

Safety Assessment & Toxicology  
Frederique Poulet, D.V.M, Ph.D., Senior Principal Scientist - Pathology

Bioanalytics Biologics & Vaccine Formulation  
Frank van Aarle, Principal Scientist

Biostatistics  
Cong Chen, Ph.D. Director  
Nicole Li, Ph.D., Associate Principal Scientist

Worldwide Product Labeling  
Tina Marks, Associate Director  
Jill Holzer, Director

Clinical Imaging  
Andrea Perrone, M.D., Executive Director, Imaging Oncology

Pharmacokinetics Pharmacology, & Drug Metabolism  
Dinesh De Alwis, Ph.D., Executive Director  
Rik de Greef, MSc., Director

Clinical Pharmacology  
David Cutler, M.D., Executive Director

Clinical Data Management  
Bernadette Frye, Director

Merck Manufacturing Division  
Parimal Desai, Ph.D., Assistant Vice president  
Gargi Maheshwari, Ph.D., Director

## **1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

### Clinical

1. Based upon FDA Office of Scientific Investigations preliminary clinical site inspection observations, the CSR safety datasets submitted in the BLA are missing adverse events for at least 7 subjects. These adverse events occurred prior to the data cut-off for date for Study PN001. The extent of missing data and potential impact on the safety evaluation of pembrolizumab is yet to be determined.

#### Discussion:

FDA acknowledged receipt of Merck's amendment of June 27, 2014, which addresses this issue. Merck stated that they agree that there is an issue regarding under-reporting of adverse events with site #19, but does not believe that there is a wide-spread issue. The issue with site #19 should not compromise the safety data. FDA asked what differences in monitoring would be included in the ongoing registration trials (PN002 and PN006). Merck noted that an automated randomizer is in place [to select visits to be source document verified] and a review of 100% investigator visit reports would be conducted.

2. Lack of information in the BLA, including specific details with respect to management and outcome of immune-related adverse events (irAEs) with corticosteroids, to provide evidence-based recommendations for treatment of these adverse events.

#### Discussion:

FDA stated that they are discussing internally how to best communicate to physicians the management of irAEs. FDA requested that Merck submit version 1 of the MK-3475 events of clinical interest document. FDA also stated that Merck should expect, in the next week, additional information requests concerning use of corticosteroids for immune-related adverse events.

3. Potential need for a medication guide in order to communicate safety information and mitigate risk of serious complications of immune-related adverse events of pembrolizumab.

#### Discussion:

Merck stated that they are supportive of a Medication Guide if warranted.

### Nonclinical

4. Potential nonclinical postmarketing studies are under consideration to further characterize the pharmacological effects of pembrolizumab on the immune response to vaccines and chronic infection.

#### Discussion:

FDA noted a concern about the effect MK-3475 could have on the safety of administered vaccines and attainment of immunity in the context of an altered TH phenotype. This might be of particular concern in pediatric populations.

Merck noted patients that had received live vaccines were excluded from trials.

FDA also expressed concern about the effect of MK-3475 on the response to chronic infections (such as tuberculosis). FDA specifically cited the literature on the severity of tuberculosis in PD-1 deficient mice.

5. Consistent with its known abortifacient risks and unknown teratogenic risks, including those on the developing immune system, FDA considers pembrolizumab a Pregnancy Category D [REDACTED] (b) (4).

Discussion:

Merck inquired on the rationale for the FDA proposal for Pregnancy Category D when no positive evidence of fetal risk exists based on experience in humans. FDA noted that many other oncology products are assigned a Pregnancy Category D without human data based on the drug's mechanism of action. FDA stated that a warning about the risk of embryofetal toxicity was warranted as Merck relied on published data on fetal death in mice following disruption of the PD-1 pathway to support the pregnancy labeling, rather than conducting an embryofetal study with pembrolizumab to directly assess its teratogenic potential.

Clinical pharmacology

6. A potential PMR to re-assess anti-drug antibody (ADA) response to pembrolizumab using validated assays with improved drug tolerance (refer to CMC section for issues with immunogenicity assays), as current assays used in detecting ADA response may be interfered by the presence of pembrolizumab in the patient serum samples, resulting in more than 60% of patients with an inconclusive ADA status.

Discussion:

Merck stated that for patients receiving pembrolizumab at 2 mg/kg, which is the proposed recommended dose, can provide conclusive ADA data on 60% of the patients. For patients receiving 10 mg/kg pembrolizumab, Merck is having problems collecting ADA data.

The current ADA assay has 25 µg of drug tolerance. FDA stated that Merck can either improve the ADA assay to have a greater drug tolerance, or they can collect patient samples at a longer time point after receiving pembrolizumab. Merck stated that the current ADA assay already contains [REDACTED] (b) (4) step to provide better drug tolerance; therefore, it is difficult for them to further improve the drug tolerance limit of the assay. FDA acknowledged Merck's concern and advised that if Merck believes they have performed due diligence in developing the ADA assays and the potential for assay improvement is minimal, then Merck should submit their justification with supporting

data as soon as possible. Merck should work with FDA in developing potential PMRs regarding immunogenicity re-testing. Merck acknowledged FDA's position.

### CMC

7. The ADA assay validation data and the levels of pembrolizumab in subject samples indicate that the drug tolerance of the current immunogenicity assay is not sufficient. Therefore a PMR to develop a validated, sensitive, and accurate assay, with sufficient capacity for pembrolizumab levels expected in patient serum at the time of sampling might be required.

#### Discussion:

See further discussion under item #6.

### **3.0 INFORMATION REQUESTS**

#### Quality microbiology

8. Information requests pertaining to low endotoxin recovery and storage of diluted drug product are pending.

#### Discussion:

Merck stated that the will submit a response by July 7, 2014.

9. Merck's response to FDA's June 5, 2014, quality microbiology information request received on June 18, 2014, is currently under review. An additional information request will be sent regarding (b) (4), maximum (b) (4) (b) (4) hold times, and low endotoxin recovery studies of drug substance.

### **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

FDA is considering requesting a medication guide in order to communicate safety information and mitigate risk of serious complications of AEs from pembrolizumab. There is no need for a REMS.

### **5.0 ADVISORY COMMITTEE MEETING**

There are no plans at this time for an advisory committee meeting.

### **6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

A late cycle meeting is scheduled for August 11, 2014. Revised labeling and request for PMRs/PMCs is due to Merck by September 26, 2014.

### **7.0 OTHER ISSUES**

Regarding Merck's Pre-Launch Activities Importation Request (PLAIR) which was denied by the Office of Compliance because it was submitted too early (i.e., more than 60 days before the action date), FDA stated that if they decide to take an early action, they will notify the Office of Compliance.

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/s/  
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MELANIE B PIERCE  
07/11/2014



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

Memorandum

**Date:** July 3, 2014  
**From:** Melanie Pierce, on behalf of Sharon Sickafuse DOP2/OHOP/CDER  
**Subject:** BLA 125514/0; Information Request-Carton/Container label

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Keytruda (pembrolizumab).

We also refer to your May 23, 2014 amendment containing updated carton and container labeling.

We completed our review of your May 23, 2014 amendment and have the following comments and requests for additional information:

**General Comments**

1. Revise the manufacturer information [REDACTED] (b) (4)

[REDACTED]

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.*

2. The revised USP standard on labeling and cap overseals was implemented on December 1, 2013. Provide an explanation for any text on the ferrule and cap overseal, if

applicable. Further information on the USP standard can be found at:  
[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)

### **Carton Labeling**

3. Add the statement “No U.S. standard of potency” to the carton labeling to comply with 21CFR 610.61(r).
4. Revise the dosage form ‘Injection’ 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.
5. 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.
6. Revise the storage statement [REDACTED] (b) (4) [REDACTED] to read as follows:  
“Store vial refrigerated at 2°C - 8°C (36°F - 46°F).”

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

### **Container Label**

7. Clarify if there is 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) when the label is affixed to the container.
8. Reference comments 4, 5, and 6.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/  
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MELANIE B PIERCE  
07/03/2014



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

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Memorandum

**Date:** July 3, 2014  
**From:** Melanie Pierce, on behalf of Sharon Sickafuse DOP2/OHOP/CDER  
**Subject:** BLA 125514/0; Information Request

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Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Supplemental Biologics License Application (sBLA), submitted under section 351 of the Public Health Service Act for Keytruda (pembrolizumab).

We also refer to the teleconference between representatives of your firm and the FDA on June 27, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

As a follow up to our June 27, 2014 teleconference, we have the following requests for additional information:

1. Clarify when version 1 of the MK-3475 Event of Clinical Interest Guidance document was provided to PN001 investigators.
2. Clarify when PN001 instituted CRFs for use by the investigator to designate AEs as an immune-related adverse event (irAE) and/or Event of Clinical Interest.
3. Provide a narrative summary supported by data of your analyses of the safety information to determine time to onset of irAEs, duration of irAEs, and type/amount/duration of steroid treatment for each irAE including pneumonitis, hypophysitis, colitis, hepatitis and hyperthyroidism/hypothyroidism, to inform prescribers in product labeling of appropriate management of side effects to promote safe and effective use of MK-3475.
  - When providing information related to the duration of an irAE, please consider the event as ongoing if the patient died with symptoms still present. Many events are listed as resolved at the time of patient death and it is not clear if the event was still ongoing or the event was listed as resolved as a result of patient death.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/  
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MELANIE B PIERCE  
07/03/2014

**From:** Sickafuse, Sharon  
**Sent:** Monday, June 30, 2014 4:09 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 Qual Micro IR re DS

Hi Melissa,

My team has the following information request regarding your submission of June 9, 2014:

**Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Downstream Manufacturing Process and Process Controls**

1. Regarding your response to item 2a, the new sampling steps are adequate. Please amend the BLA by July 14 to include the new sampling steps.

**Process Validation and/or Evaluation – Validation Batches**

2. Regarding your response to items 4a and 4b, microbial quality results from the PPQ (b) (4) are acceptable. Submit action limits by July 14 for (b) (4); those action limits should not exceed the limits for the corresponding (b) (4).

**Process Validation and/or Evaluation – (b) (4) Validation**

3. Regarding your response to items 4a and 4b, it appears that microbial quality results from the PPQ batches were used to validate the maximum (b) (4) hold times. Validated maximum (b) (4) hold times should be conducted in triplicates and should be the shortest of the three longest runs. In addition, the maximum hold determined in hours should not be rounded to days, unless hold lasted 24 hours or longer. According to the data in your response, the maximum hold times (b) (4). Therefore, the (b) (4) until additional results are available.
4. Regarding your response to item 18d, the updated BLA should include the microbial quality results in support of the newly validated hold times. Indicate if the results will be part of the July 2014 update or if the study will be conducted post-approval.

**Control of Drug Substance – Validation of Analytical Procedures (Endotoxin)**

5. Regarding your response to item 23c, provide preliminary results for the LER study by July 25. The study should include endotoxin recovery results of undiluted formulated drug substance spiked with known amounts of control

standard endotoxin (CSE) and naturally occurring endotoxin (NOE) held for the maximum holding time [REDACTED] (b) (4)

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SHARON K SICKAFUSE  
06/30/2014

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

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Memorandum

**Date:** June 13, 2014

**From:** Sharon Sickafuse, RPM

**BLA:** 125514/0

**Product:** Keytruda (pembrolizumab)

**Applicant:** Merck Sharp and Dohme, Corp. (Merck)

**Subject:** Mid-Cycle Review Meeting

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Major Findings/Issues:

1. FDA recommends pregnancy category D.
2. FDA determined that there is a positive risk-benefit assessment for Keytruda in a patient population with an unmet medical need. An internal goal date for regulatory action earlier than the PDUFA date was discussed, targeting the end of August 2014.
3. FDA will request confirmation of clinical benefit (survival) from ongoing trials.

Merck is conducting the following confirmatory studies:

**PN002**

- Treatment line: ipilimumab-refractory melanoma
- Randomization: 1:1:1, n=510
  - MK-3475 2 mg/kg Q3W vs. 10 mg/kg Q3W vs. chemotherapy
- Primary: PFS and OS using RECIST 1.1 by IRC

**PN006**

- Treatment line: first-line advanced melanoma
- Randomization: 1:1:1, n=645
  - MK-3475 10 mg/kg Q2W vs. 10 mg/kg Q3W vs. ipilimumab 3 mg/kg Q3W x 4
- Primary: PFS and OS using RECIST 1.1 by IRC

4. FDA will request additional safety data on immune-related events and renal impairment from ongoing controlled studies.

Status of OSI Inspections:

A total of 4 sites were inspected – 2 in the U.S., 1 in Canada, and the Merck site. All site inspections are completed. One U.S. site (Memorial Sloan Kettering Cancer Center) had an issue of under-reporting of adverse events prior to the data cut-off of October 2013. OSI and the clinical team are having internal discussion about the course of action.

Status of Facility Inspections:

The MedImmune, Frederick, MD drug substance facility was inspected in April 2014. The initial classification from the Biologics Manufacturing Assessment Branch (BMAB) was VAI (Voluntary Action Indicated) and Acceptable. The final recommendation by the Office of Compliance is pending.

The (b) (4) drug substance facility is being inspected (b) (4).

The drug product facility is Schering Plough Brinny Co., Ireland. The last GMP inspection occurred in Jan. 28-Feb. 5, 2013 and was classified NAI (Acceptable), therefore the inspection of this facility for the BLA was waived.

Labeling Meetings Scheduled:

July 24, 2014	Indications & Usage Dosage & Administration Dosage Forms & Strengths Use in Specific Populations/Pediatric Use Use In Specific Populations/Geriatric Use Description How Supplied
August 4, 2014	Use in Specific Populations/Pregnancy Use in Specific Populations/Nursing Mothers Nonclinical Toxicology Patient Counseling Information
August 25, 2014	Drug Interactions Use in Specific Populations/Renal Impairment Use in Specific Populations/Hepatic Impairment Clinical Pharmacology
September 11, 2014	Clinical Studies Warnings & Precautions

September 15, 2014 Finish Warnings & Precautions  
Adverse Events  
Highlights

Labeling needs to be sent to Merck by September 26, 2014.

Status of PMRs/PMCs:

1. Clinical will request a PMR for a confirmatory study for accelerated approval.
2. Nonclinical may request a PMR for a nonclinical study to further characterize the pharmacological effects of Keytruda on the immune response to vaccines and chronic infection.
3. Clin pharm may request a PMR to re-assess anti-drug antibody (ADA) response to pembrolizumab using the validated assays with improved drug tolerance as the current assays used in detecting ADA response may be interfered by the presence of pembrolizumab in the patient serum samples, resulting in a high percent of patients with an inconclusive ADA status.
4. CMC may request a PMR to develop a validated, sensitive, and accurate assay, with sufficient capacity for Keytruda levels expected in patient serum at the time of sampling.
5. Quality micro requested 2 PMCs regarding endotoxin in a June 20, 2014, information request.

REMS:

At this point, the team does not anticipate that a REMS will be needed.

Review Due Dates:

Primary reviews: August 2, 2014  
Secondary reviews: August 5, 2014  
CDTL review: September 30, 2014  
Division Director Review: October 16, 2014  
Office Director Review: October 28, 2014

Upcoming Meetings:

MidCycle Communication with Merck	June 27, 2014
Internal for Late Cycle Meeting (LCM)	July 22, 2014
[LCM package due July 30, 2014]	
LCM	August 11, 2014
Wrap-Up meeting	September 18, 2014

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SHARON K SICKAFUSE  
06/25/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, June 20, 2014 1:46 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - qual micro IR

Hi Melissa,

My qual micro team has the following IR:

1. Microbiological studies in support of the storage time of diluted pembrolizumab DP have not been provided. Please provide a report from studies showing that adventitious microorganisms do not grow under the storage conditions (room temperature and 2°C to 8°C) for the diluted pembrolizumab DP. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution and storage. It is generally accepted that growth is evident when the population increases more than 0.5 Log<sub>10</sub>. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3 times the label's recommended storage period and using the label recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.
2. The low endotoxin recovery studies submitted to the BLA suggests a masking effect on endotoxin recovery of pembrolizumab. We have the following comments:
  - a. Please limit the sample storage time to a time point where (b) (4) % endotoxin recovery is observed using sample spiked with reference standard.
  - b. As a postmarketing commitment, please conduct a study using 3 lots of formulated bulk and/or DP spiked with endotoxin (5 EU/mL and 10 EU/mL) and assess the endotoxin recovery at various time points using LAL assay. The study should compare the LAL results with rabbit pyrogen test. Please submit a timeline for submission of the final study report. .
  - c. As a postmarketing commitment, please conduct studies to evaluate the factors that impact low endotoxin recovery and develop an endotoxin detection assay to overcome the low endotoxin recovery observed with pembrolizumab. Please submit a timeline for submission of the final study report.

Please submit your response by July 7<sup>th</sup>. Thank you

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SHARON K SICKAFUSE  
06/20/2014

**From:** Patel, Mona  
**Sent:** 6/18/2014 11:47:32 AM  
**To:** 'nikhil.mehta@merck.com'  
**CC:** Sickafuse, Sharon  
**Subject:** FDA Request: BLA 125514/0  
**Signed By:**

Nikhil,

Based upon FDA Office of Scientific Investigations preliminary clinical site inspection observations it appears that there are AEs for at least 7 subjects enrolled in Study MK-3475-P001 that have one or more AEs that occurred prior to the data cut-off date for the study but were not reported in the CSR data sets. These 6 subjects were enrolled at site 19.

1. Please provide an explanation for these omissions and a corrective action plan that will be implemented for this and all study sites to ensure this is not an ongoing problem.
2. Provide details concerning site monitoring performed during Trial PN001 and identify any deficiencies that led to the missing data from Site 19 in the BLA. Provide your plan for determining whether missing AE data was a more wide-spread issue that would call into question the data integrity of this application. Whether the extent of the missing data, including AE data from Site 19 and any other affected sites, requires corrected datasets, clearly identifying the new information, will be a review issue. Additionally, if the missing information is substantial, you may need to repeat the sponsor safety analyses.

Please provide a response by June 25, 2014 via email followed by a formal submission.

Please acknowledge receipt.

Mona

Mona Patel, PharmD | LCDR, USPHS | Regulatory Project Manager | Division of Oncology Products 2, Office of Hematology & Oncology Products, CDER, FDA | White Oak Complex, (b) (6) | 10903 New Hampshire Avenue | Silver Spring, MD 20993  
☎ 301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)



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/s/  
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MONA G PATEL  
06/18/2014

**From:** Sickafuse, Sharon  
**Sent:** Monday, June 09, 2014 4:48 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

Hi Melissa, My team has the following IR for which they would like a response by noon on Wednesday, June 11<sup>th</sup>:

1. For patient 0023000402, the best overall response by IRO is CR; however, the percent change from baseline at day 84 (6/12/2013) is -57.7%. Adjudication comment provided in ADJDCTN.xpt provides the justification for CR, but the response is not reflected in the percent change from baseline with regard to sum of diameters. Please clarify.
2. Additionally, because all patients underwent a double-read for radiological response, please explain which set of lesion measurements were chosen by the adjudicator to be included in the BLA submission. If no adjudication was performed, please also explain which set of measurements were included in the BLA submission.

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SHARON K SICKAFUSE  
06/09/2014



BLA 125514/0

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We have reviewed your May 12, 2014, submission which contained a response to our April 16, 2014, information request letter and have the following information requests. We request a written response by June 18, 2014, in order to continue our evaluation of your BLA.

Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Downstream Manufacturing Process and Process Controls

1.  (b) (4)

2. Regarding your response to item 2f, clarify if  (b) (4).

Process Validation and/or Evaluation – Validation Batches

3. Regarding your response to items 4a and 4b,  (b) (4)

Process Validation and/or Evaluation – (b) (4)

4. Regarding your response to item 6, indicate which (b) (4)

Justification of Bioburden Specification

5. Regarding your response to item 12, Section 3.2.P.3.3 shows a (b) (4) (step 3.2.2.5 and Figure 1 of section 3.2.P.3.3; refer also to Table 2 of section 3.2.P.3.4). Clarify at which (b) (4)

Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Upstream Manufacturing Process and Process Controls

6. Regarding your response to item 14, monitor (b) (4)

Process Validation and/or Evaluation – (b) (4) Validation

7. Regarding your response to item 18b:
- Table 64 of Section 3.2.S.2.5 includes hold times (b) (4)
  - Maximum hold times (b) (4) converted from hours to days should be rounded to the shortest number of days; if manufacturing hold times are monitored in hours, the conversion from hours to days is not necessary as long as maximum hold times are established in hours.
  - Establish maximum hold time for (b) (4) maximum hold time should be based on microbial quality results. Amend the BLA to include the microbial quality results and the validated maximum time.
8. Regarding your response to item 18d, include (b) (4) is not consistent with bioburden acceptance criterion at the same step in Table 17.3; correct the discrepancy in the BLA if it is due to an error or justify any relaxation in the acceptance criterion.

Control of Drug Substance – Validation of Analytical Procedures (Bioburden)

9. Regarding your response to item 22a, the information in the (b) (4) qualification report is insufficient. Indicate what solution was used as control for the product inhibition test, what other negative controls were used, if samples were tested in duplicates, and if unspiked product was tested. Indicate if the only acceptance criterion for the qualification was % recovery from the sample between (b) (4) %.

Control of Drug Substance – Validation of Analytical Procedures (Endotoxin)

10. Regarding your response to item 23c:
- a. Clarify if the rabbit endotoxin test was conducted with drug product spiked with endotoxin.
  - b. Your response includes a summary study conducted using the Kinetic Turbidimetric Method; however, the drug substance release test at MedImmune, LLC Frederick Manufacturing Center is conducted using the Kinetic Chromogenic Method (refer to Section 3.2.S.4.2.26 of the BLA). Please repeat the LER study for formulated drug substance in representative containers using the Kinetic Chromogenic Method. The formulated pool should be spiked with concentrated endotoxin (CSE or RSE) and held for the maximum hold time, including the maximum allowed time between sampling and testing.

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

Sincerely,

*{See appended electronic signature page}*

Patricia Hughes-Troost  
Team Lead  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA F HUGHES TROOST  
06/05/2014



BLA 125514/0

## INFORMATION REQUEST

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We have the following information requests:

1. Please explain the following discrepancies between the CSR analysis and AE.xpt datasets and CRFs for the following patients and confirm whether drug was discontinued or only delayed for the listed adverse events:
  - a. Patient 3475-001\_0001000284 is listed in the CSR and AE.xpt as having discontinued pembrolizumab for an adverse event of fatigue. The information in the CRF and DS.xpt lists her as still on therapy; drug was only interrupted for this adverse event.
  - b. Patient 3475-001\_0015000406 is listed in the CSR and AE.xpt as having discontinued pembrolizumab for an adverse event of sepsis. The information in the CRF lists this patient as still on therapy.
  - c. Patient 3475-001\_0024000110 is listed in the CSR and AE.xpt as having discontinued pembrolizumab for an adverse event of myositis beginning June 15, 2012, with resolution 150 days later. The information in the CRF lists this patient as on therapy until November 12, 2012 and after the resolution of the adverse event.
  - d. Patient 3475-001\_0010000265 is listed in the CSR and AE.xpt as having discontinued pembrolizumab for an adverse event of pneumonitis beginning on

May 20, 2013; however, the last dose of drug is listed as May 2, 2013, and the reason for treatment discontinuation (subject status- end of treatment CRF) listed in the CRF is progression of disease.

2. Please clarify the dose of ipilimumab administered and the total number of doses given for the patients below:

STUDYID	USUBJID	CMENDTC	QVAL	CMDOSE	CMDOSU	CMDOSTOT
3475-001	3475-001_0008000317	2012-07-30	2012-08-27	1920	mg/kg	1920
3475-001	3475-001_0019000258	2011-11-25	2012-05-04	260	mg/kg	260
3475-001	3475-001_0019000270	2011-07-26	2011-09-19	300	mg/kg	300
3475-001	3475-001_0019000347	2012-08-07	2012-11-19	1000	mg/kg	1000
3475-001	3475-001_0019000356	2011-10-21	2012-02-03	620	mg/kg	620
3475-001	3475-001_0019000365	2012-12-13	2013-01-02	290	mg/kg	290
3475-001	3475-001_0020000400	2012-08-17	2012-08-31	840	mg/kg	840
3475-001	3475-001_0020000427	2012-10-24	2013-03-11	1036	mg/kg	1036
3475-001	3475-001_0021000277	2011-10-28	2011-11-29	750	mg/kg	750
3475-001	3475-001_0021000388	2010-09-27	2010-12-13	760	mg/kg	760
3475-001	3475-001_0021000388	2011-03-21	2011-05-23	760	mg/kg	760
3475-001	3475-001_0023000269	2012-05-04	2012-05-23	800	mg/kg	800
3475-001	3475-001_0023000280	2012-04-19	2012-07-02	3600	mg/kg	3600

3. We appreciate your responses to the information requests regarding prior ipilimumab treatment; however, to have a more clearer understanding as to the protocol-defined refractoriness of the patients in Part B2, given the data discrepancies, please provide information on the following requirements for patients with ipilimumab-refractory-melanoma. Please indicate how many patients met each requirement. For patients that did not meet the criterion, please provide USUBJID, corresponding to the arm below. Patient 0008000421 was randomized to the 2 mg/kg Q3W but received MK-3475 at the 10 mg/kg Q3W dose instead. Please assign this patient to the 2 mg/kg arm.

Table 1. Protocol requirements for ipilimumab-refractory melanoma

Requirement	2 mg/kg Q3W N=90 (%)	10 mg/kg Q3W N=83 (%)	Comment
Received at least two doses of ipilimumab (minimum dose of 3 mg/kg).	If no, USUBJID, continue with same convention throughout table.	If no, USUBJID, continue with same convention throughout table.	
Progressive disease after ipilimumab will be defined according to irRC. The initial evidence of PD is to be confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression (this evaluation is based on investigator assessment; Sponsor will collect imaging scans for retrospective analysis). Once PD is confirmed, initial date of PD documentation will be considered as the date of disease progression.			
Documented disease progression within 24 weeks of the last dose of ipilimumab. Patients who were re-treated with ipilimumab and patients who were on maintenance ipilimumab will be allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with ipilimumab).			
Resolution of ipilimumab related AEs (including irAEs) back to Grade 0-1 and $\leq 10$ mg/day prednisone or equivalent dose for irAEs for at least two weeks prior to			

first dose of study drug.			
No history of severe irAEs from ipilimumab CTCAE Grade 4 requiring steroid treatment.			
No history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment (>10 mg/day prednisone or equivalent dose) >12 weeks.			
Minimum of four weeks (wash out period) from the last dose of ipilimumab.			
Patients with BRAF V600mutant melanoma must have had a prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors.			
Patient must have progressive disease after the most recent treatment regimen.			

4. Please submit all CRFs (investigator and IRO) for the following patients, unless otherwise noted for investigator CRFs:

3475-001\_0019000279  
3475-001\_0010000253 (have inv CRFs)  
3475-001\_0019000380  
3475-001\_0011000307 (have inv CRFs)  
3475-001\_0021000287  
3475-001\_0021000369 (have inv CRFs)  
3475-001\_0015000271 (have inv CRFs)  
3475-001\_0021000324  
3475-001\_0019000338  
3475-001\_0019000381  
3475-001\_0011000315 (have inv CRFs)  
3475-001\_0020000400  
3475-001\_0020000318  
3475-001\_0015000349 (have inv CRFs)  
3475-001\_0016000408

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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SHARON K SICKAFUSE  
06/05/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, June 03, 2014 1:48 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR re prior ipilimumab treatment

Hi Melissa,

My clinical reviewer has reviewed your submission of May 30<sup>th</sup> which was a response to items #1 and #3 of our May 9<sup>th</sup> IR. We have the following IR:

0015000336	date of last dose of ipi
0010000285	dose of ipi as third-line
0015000314	dose of ipi for last dose given on 8/31/2012 (treatment was listed as first-line twice)
0019000258	clarify ipi dose, listed as 260 mg/kg.
0019000270	clarify ipi dose, listed as 300 mg/kg
0019000347	clarify ipi dose, listed as 1000 mg/kg
0021000312	clarify ipi dose given as fifth line or greater
0021000323	dose of ipi
0021000324	dose of ipi
0021000388	clarify ipi dose, listed as 760 mg/kg x 2
0023000269	clarify ipi dose, listed as 800 mg/kg
0023000280	clarify ipi dose, listed as 3600 mg/kg
0001000284	CMENDTC (2012-09-24) occurs after QVAL when QNAM=CNCDPDT (2012-09-21). Please clarify.
0010000267	CMENDTC (2012-06) occurs after QVAL when QNAM=CNCDPDT (2012-01-23). Please clarify.
0019000348	CMENDTC (2012-02) occurs after QVAL when QNAM=CNCDPDT (2012-01-12). Please clarify.

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SHARON K SICKAFUSE  
06/03/2014



BLA 125514/0

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

Please see table below in reference to the following questions. MH.xpt and SUPPMH.xpt were used.

1. Does MHCAT indicate the classification of melanoma at time of initial diagnosis and does MHSCAT indicate the disease at time of study enrollment?
2. Some patients that were classified as M0 appear to have metastatic disease under QVAL, as shown below. Please clarify.

STUDYID	DOMAIN	USUBJID	MHSEQ	MHGRPID	MHTERM	MHCAT	MHSCAT	QVAL	Me con
3475-001	MH	3475-001_0001000284	1478646792	DISEASE HISTORY	MELANOMA	IV	TX N2a M0	lymph nodes	
3475-001	MH	3475-001_0001000344	1478646802	DISEASE HISTORY	MELANOMA	IIIC		lymph node	
3475-001	MH	3475-001_0003000286	1478646912	DISEASE HISTORY	MELANOMA	IV		liver, lung, lymph node	
3475-001	MH	3475-001_0008000403	1478643842	DISEASE HISTORY	MELANOMA	IIIB	T2a N2a M0	left groin	
3475-001	MH	3475-001_0010000251	1478642622	DISEASE HISTORY	MELANOMA	IIIC	T4b N2a M0		
3475-001	MH	3475-001_0010000268	1478642692	DISEASE HISTORY	MELANOMA	IIIC	T2a N3 M0	left axillary	

								lymph node	
3475-001	MH	3475-001_0011000289	1478643072	DISEASE HISTORY	MELANOMA	IIIC	T4a N3 M0	No mets at primary diagnosis	
3475-001	MH	3475-001_0011000291	1478643082	DISEASE HISTORY	MELANOMA	IIC	T4b N0 M0	none	
3475-001	MH	3475-001_0011000307	1478646232	DISEASE HISTORY	MELANOMA	IIA	T3a N0 M0	none	
3475-001	MH	3475-001_0011000315	1478643092	DISEASE HISTORY	MELANOMA	IB	T1b N0 M0	No mets at primary diagnosis	
3475-001	MH	3475-001_0011000410	1478646252	DISEASE HISTORY	MELANOMA				
3475-001	MH	3475-001_0011000413	1478644012	DISEASE HISTORY	MELANOMA	IB		Skin	
3475-001	MH	3475-001_0012000305	1478643312	DISEASE HISTORY	MELANOMA	IIB	T4a N0 M0	Lymph Nodes, Soft Tissues	
3475-001	MH	3475-001_0012000425	1478647662	DISEASE HISTORY	MELANOMA	IIIC	TX N1a M0	Lymph Nodes, Soft tissue	
3475-001	MH	3475-001_0013000275	1478643382	DISEASE HISTORY	MELANOMA	IIIB	T4a N0 M0	skin: intransit metastases not amendable to surgery	
3475-001	MH	3475-001_0013000296	1478643392	DISEASE HISTORY	MELANOMA	IIIC	T3b N3 M0	lymph nodes	
3475-001	MH	3475-001_0015000336	1478644282	DISEASE HISTORY	MELANOMA	IIIC	T4b N3 M0	soft tissue of right lower extremity, including right hip	
3475-001	MH	3475-001_0015000414	1478643852	DISEASE HISTORY	MELANOMA	IIIB	T3b N1a M0	Lung	
3475-001	MH	3475-001_0016000408	1478644172	DISEASE HISTORY	MELANOMA	IIIC	T3b N3 M0	pelvis	
3475-001	MH	3475-001_0019000347	1478646512	DISEASE HISTORY	MELANOMA	IIIC	T4b N3 M0	left calf	
3475-001	MH	3475-001_0019000348	1478644212	DISEASE HISTORY	MELANOMA	IV	TX N0 M0	head and neck, soft tissue, lymph nodes	
3475-001	MH	3475-001_0019000350	1478644042	DISEASE HISTORY	MELANOMA	IIIA	T2a N1a M0	Scalp, Liver	
3475-001	MH	3475-001_0019000356	1478649302	DISEASE HISTORY	MELANOMA	IIA	T2b N0 M0	Lung	
3475-001	MH	3475-001_0019000367	1478649382	DISEASE HISTORY	MELANOMA	IB	T2a N0 M0	Lung	

3475-001	MH	3475-001_0019000380	1478643982	DISEASE HISTORY	MELANOMA	IIC	T3b N0 M0	lymph nodes	
3475-001	MH	3475-001_0020000290	1478645032	DISEASE HISTORY	MELANOMA	IV	T4b N0 M0	Lymph Nodes, abdomen, pelvic deposits, chest wall.	
3475-001	MH	3475-001_0020000427	1478649242	DISEASE HISTORY	MELANOMA	IIA	T3a N0 M0	Lung	
3475-001	MH	3475-001_0023000397	1478645872	DISEASE HISTORY	MELANOMA	IA	T1a N0 M0	Multiple mets, in the subcut. right thigh, bowel, adrenal, soft tissue behind right adrenal	

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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SHARON K SICKAFUSE  
06/02/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, May 29, 2014 8:48 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 Clin pharm IR

Hi Melissa,

My clin pharm team has the following IR regarding the updated immunogenicity data report (data cutoff of December 31, 2013) submitted on April 30<sup>th</sup>:

Please submit the updated immunogenicity/PK datasets (presented as [Appendix I](#) and [II](#) in the report) in XPT format by June 2, 2014. Please add two new variables to all the datasets in [Appendix II](#) (from Table All-1 to Table All-12): one is for “ADA confirm” and the other one is for differentiation between the original and the updated data.

Thank you

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SHARON K SICKAFUSE  
05/29/2014



BLA 125514/0

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We are reviewing the quality microbiology section of your submission and have the following comments and information requests. We request a written response by June 9, 2014, in order to continue our evaluation of your BLA.

1. Provide bioburden data from samples collected after the (b) (4) step for all drug product lots (b) (4) prepared using drug substance manufactured at the (b) (4) site. Include investigations into atypical bioburden results obtained during PPQ (b) (4) (Table 52). A bioburden action limit should be implemented at the (b) (4) step prior to the (b) (4) step.
2. The established hold time at controlled room temperature for the (b) (4) step of (b) (4) should be based on data obtained from three commercial scale lots (shortest of three longest hold times).
3. Provide (b) (4) validation data for the (b) (4) assemblies. If such information is available in a drug master file (DMF), provide a letter of authorization to the DMF with details of where this information can be found within the DMF (page number, volume number, and date).
4. Provide the protocol and summary validation data (b) (4) validation studies.



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

Sincerely,

*{See appended electronic signature page}*

Patricia Hughes-Troost  
Team Lead  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA F HUGHES TROOST  
05/28/2014

## Boyd, Karen

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**From:** Boyd, Karen  
**Sent:** Friday, May 23, 2014 10:30 AM  
**To:** melissa\_tice@merck.com  
**Cc:** Sickafuse, Sharon  
**Subject:** BLA 125514/0: Clinical Information Request

**Importance:** High

Hi Melissa,

On behalf of Sharon Sickafuse and the BLA 125514 review team, please see below for a clinical information request for BLA 125514/0. Please respond via email to Sharon Sickafuse ([Sharon.sickafuse@fda.hhs.gov](mailto:Sharon.sickafuse@fda.hhs.gov)) by COB May 29, 2014, followed by a formal submission to the BLA.

**Clinical Information Request:**

1. Per p. 248 of the Clinical Study Report in Table 11-20, 21 patients in Part B2 of the study, 10 in the 2 mg/kg arm and 11 in the 10 mg/kg arm had no assessment of response by investigator. Please provide reasons as to why no response assessments were done for each of the 21 patients.

**Please confirm receipt.**

Thanks,  
Karen

Karen Boyd, M.S.  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: [Karen.Boyd@fda.hhs.gov](mailto:Karen.Boyd@fda.hhs.gov)  
Phone: 301-796-7032  
Fax: 301-796-9849

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/s/  
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KAREN C BOYD  
05/23/2014

## Boyd, Karen

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**From:** Boyd, Karen  
**Sent:** Wednesday, May 21, 2014 6:04 PM  
**To:** 'melissa\_tice@merck.com'  
**Cc:** Sickafuse, Sharon  
**Subject:** BLA 125514/0: Clinical Information Request

**Importance:** High

Hi Melissa,

On behalf of Sharon Sickafuse and the BLA 125514 review team, please see below for a clinical information request for BLA 125514/0. Please respond via email to Sharon Sickafuse ([Sharon.sickafuse@fda.hhs.gov](mailto:Sharon.sickafuse@fda.hhs.gov)) by COB May 27, 2014, followed by a formal submission to the BLA.

**Clinical Information Request:**

1. Please update Tables 1 and 2 "Listing of Patients with Systemic and Topical Steroid Use and Possible AE Prompting Use" to include columns for start and stop date for each dose of steroids, start and stop date for AE with corresponding toxicity Grade, and outcome of AE with date. Please submit this data as an excel file.

If you have any questions or concerns between now and May 27<sup>th</sup> when Sharon is back in the office, please contact me.

**Please confirm receipt.**

Thanks,  
Karen

Karen Boyd, M.S.  
Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: [Karen.Boyd@fda.hhs.gov](mailto:Karen.Boyd@fda.hhs.gov)  
Phone: 301-796-7032  
Fax: 301-796-9849

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/s/  
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KAREN C BOYD  
05/21/2014

## Boyd, Karen

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**From:** Boyd, Karen  
**Sent:** Wednesday, May 21, 2014 11:25 AM  
**To:** 'melissa\_tice@merck.com'  
**Cc:** Sickafuse, Sharon  
**Subject:** BLA 125514/0: Clinical Information Request

**Importance:** High

Hi Melissa,

On behalf of Sharon Sickafuse and the review team, please see below for a clinical information request for BLA 125514/0. Please respond via email to Sharon Sickafuse ([Sharon.sickafuse@fda.hhs.gov](mailto:Sharon.sickafuse@fda.hhs.gov)) by COB May 27, 2014, followed by a formal submission to the BLA.

### **Clinical Information Request:**

1. In regard to the screen failures for PN001, can you please provide in which cohorts these screen failures occurred? This information does not appear to be captured in the CRF.
2. The Independent Review Charter, version 3.0, under Section 2.F. "Lesions with Prior Local Treatment," on p. 30 states:  
"The independent radiologists will not receive the information about the sites of previous irradiation. All anatomical sites are valid for selection of target lesions. The independent radiologist will exercise caution before selecting soft tissue lesions that may have been previously irradiated. If the independent radiologist observes radiographic evidence of prior radiotherapy he/she will avoid selection of target lesions in such areas. If an irradiated lesion is selected as target lesion Merck may choose to censor this subject."  
  
Were any patients censored based on this?
3. As a follow-up to your response on May 8, 2014, to the Division's information request, dated May 1, 2014, pertaining to single vs. double read for the independent radiology review, please provide an explanation for conducting a double read for cohorts B1, B2, and D.
4. Thank you for the ADJDCTN.xpt that provides the comments for the adjudication for the independent radiology review. Would it be possible to separate which comments were related to tumor response using RECIST for Part B2, given that this is the primary endpoint? It appears that some of the comments relate to tumor response using irRC.
5. In the ADJDCTN.xpt, for patients 0013000084 and 0019000252, the adjudicator mentions lesions related to the skin. Please clarify given that this is a radiology review.

If you have any questions or concerns between now and May 27<sup>th</sup> when Sharon is back in the office, please contact me.

**Please confirm receipt.**

Thanks,  
Karen

Karen Boyd, M.S.

Senior Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: [Karen.Boyd@fda.hhs.gov](mailto:Karen.Boyd@fda.hhs.gov)  
Phone: 301-796-7032  
Fax: 301-796-9849

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KAREN C BOYD  
05/21/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, May 14, 2014 9:40 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - May 12th response to May 6th clinical IR

Hi Melissa,

My clinical team has the following request:

Thank you for the clarification pertaining to the screen failures. One additional question for clarification, please explain the difference in the number of patients for the ie.xpt (n=118) versus ds.xpt when DSDECOD=SCREEN FAILURE (n=115). It appears the reasons for screen failure as captured on p. 11 of the annotated CRF are in the ie.xpt. Page 128 of the CSR states that 130 patients were screen failures; however, it appears either 115 or 118 were.

Additionally, please explain the difference in the three additional patients in the ADSL.xpt and dm.xpt (n=609), compared to the ds.xpt (n=606). The following three patients were not captured in the ds.xpt:

0015S00103  
0015S00126  
0015S00132

Thank you

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/s/  
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SHARON K SICKAFUSE  
05/14/2014



BLA 125514/0

## INFORMATION REQUEST

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by June 1, 2014, in order to continue our evaluation of your BLA.

### Drug Substance

1. Provide information on the action(s) taken when the target ranges (NOR and PAR) for process parameters are not met (e.g., CPP, KOP, and non-critical or non-key parameters).
2. We note that for the (b) (4) and FMC drug substance (DS) manufacturing processes, prior large scale manufacturing experience or data from developmental batches were used to justify the proposed proven acceptable ranges (PAR) for several process parameters; however no supporting data are provided in the submission. Provide the relevant data from large scale and/or developmental manufacturing lots to support the proposed PARs for these process parameters. In addition to the operating ranges observed for these parameters during the manufacturing of these lots; these data should also include the operating ranges for other critical/key process parameters that were used to control manufacturing at those specific steps, to allow for an assessment of the adequacy of the supporting data.
3. We note that the proposed control strategy for several of the upstream process steps only consists (b) (4) . (b) (4)  
Provide

justification with available supporting data and risk assessments for the proposed control strategy for the following process steps:

- a. [REDACTED] (b) (4)
- b. [REDACTED]
4. Provide the non-key or non-critical process parameters and operating ranges that are used in the pembrolizumab DS manufacturing processes at both [REDACTED] (b) (4) and FMC.
5. Provide summary information on the preliminary risk assessments performed to select the process parameters to be studied further in the process characterization studies. This information should be provided for all upstream and downstream unit operations for the [REDACTED] (b) (4) and FMC manufacturing processes.
6. Provide information on how process yield is [REDACTED] (b) (4) [REDACTED] (b) (4) s for the [REDACTED] (b) (4) and FMC processes.
7. Add a control for [REDACTED] (b) (4) [REDACTED]
8. In our experience, the WCB [REDACTED] (b) (4) [REDACTED] Alternatively, provide a justification, supported by data, that the current control strategy provides an appropriate level of control.
9. The characterization range [REDACTED] (b) (4) [REDACTED] and it appears that even within this range, there are effects on product quality parameters. Therefore, it appears that this parameter should be included in the control strategies for the [REDACTED] (b) (4) and FMC processes to ensure an adequate level of control. Update the control strategy or provide additional justification for the current strategy.
10. [REDACTED] (b) (4) [REDACTED] We note that no control is provided over this parameter during [REDACTED] (b) (4) and FMC manufacturing processes. Address [REDACTED] (b) (4) [REDACTED] the ranges for this parameter should be supported by the ranges used in the viral clearance studies.
11. We note that Section 3.2.S.2.2 states that [REDACTED] (b) (4) [REDACTED]

- related impurity levels, but also product quality in the (b) (4), clarify the control strategy for (b) (4).
12. Update the process performance qualification (PPQ) data in Section S.2.2.5 to report the results of non-key and non-critical process parameters for (b) (4) PPQ batches and FMC prospective and retrospective PPQ batches.
  13. (b) (4) step is expected to be validated at the commercial scale. Provide (b) (4) validation protocols that include, but are not limited to, the conditions for (b) (4).  
Additionally provide a commitment to include the first (b) (4) DS batch in the long term DS stability program for both the (b) (4) and FMC manufacturing processes.
  14. (b) (4) step is expected to be validated at the commercial scale. Provide the (b) (4) protocol for the FMC and (b) (4) DS. The protocol should include, but not be limited to, the conditions for (b) (4).  
Additionally provide a commitment to include the first (b) (4) DS batch in the long term DS stability program for both the (b) (4) and FMC manufacturing processes.
  15. Provide acceptance criteria for the product quality attributes for the (b) (4) studies performed for the FMC manufacturing process.
  16. Provide information on the type of containers that are used to (b) (4) (b) (4) in the commercial (b) (4) manufacturing process. Confirm that the containers used in the (b) (4) scale process (b) (4) hold time studies were fully representative of the containers used in commercial (b) (4) manufacturing process.
  17. We note that the (b) (4) hold time stability data for the (b) (4) is used to support the stability of the (b) (4). This approach is not acceptable because the product pool at each step is processed differently and can differ with respect to the process-related impurity (including leachables) profile. These differences can potentially affect the stability of the product in (b) (4). Therefore, a separate study should be conducted for the (b) (4). Provide all available data to support a hold of the (b) (4).
  18. Provide detailed information on (b) (4).

19. We note that for the (b) (4) and FMC processes, (b) (4) (b) (4) were created for each process. Clarify why (b) (4) (b) (4) were generated for each process. Please note that the (b) (4) and FMC production (b) (4) for which genetic stability testing was performed. Please comment on your strategy for (b) (4) generation and testing.
20. We note that the mean target copy number by PCR in the (b) (4) produced at (b) (4) is (b) (4). The submission indicates that these differences are due to assay variability. Provide data to support that the differences observed are due to the assay variability and not because of the stability of the MK-3475 construct.
21. Provide a detailed MCB and WCB stability protocol. Include information on, but not limited to, the cell culture conditions and duration that will be used for the stability assessment and the acceptance criteria that will be used for cell growth and viability. WCB stability can generally be assessed using regular trend analysis of cell bank performance during normal manufacture. If this is to be done for the pembrolizumab process, provide the trend analysis criteria that will be used to assess stability. The protocol should also include steps that will be taken to assess WCB stability if production is not initiated on a yearly basis.

### Drug Product

22. Per 21 CFR 610.14, identity testing on the final drug product (DP) shall be performed after all labeling operations have been completed. It is unclear if the identity testing for DP is performed after final labeling operations. Clarify the timing of sampling for the identity test, including a summary description of the labeling operations. Update the BLA as applicable to identify that this testing meets the CFR requirements.
23. The authorization letters for the DP container closure system (vials and stoppers) references master files that were submitted to CBER. If you are also in possession of letters of authorization to reference drug master files that were submitted to CDER, please submit these letters to the BLA.

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

Sincerely,

*{See appended electronic signature page}*

Rashmi Rawat, Ph.D.  
Team Leader  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Center for Drug Evaluation and Research

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/s/  
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RASHMI RAWAT  
05/14/2014

MEMORANDUM

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

**DATE:** May 12, 2014

**SUBJECT:** Team Meeting Minutes

Status of the reviews:

Clinical efficacy & statistics – review ongoing. FDA agrees with Merck’s efficacy results.

Clinical safety – review ongoing. Nothing major to report.

Nonclinical – no issues

Clinical pharmacology/pharmacometrics – review ongoing. Merck has satisfactorily responded to all information requests.

Product – will have an information request for Merck

Quality microbiology – April 16, 2014, information request is due to be submitted today.

Inspection of MedImmune facility which is one of the drug substance (DS) manufacturing sites is completed and classified “VAI”. The major problems are mislabeling of the bulk DS and protocol deviations due to human error. MedImmune is in the process of correcting the issues.

(b) (4) The drug product review is ongoing.

Upcoming meetings:

Midcycle meeting: June 13, 2014. Dr. Theoret asked that for those disciplines which will be giving a presentation to send him the slides 1 week before the meeting.

Midcycle communication with Merck: June 27, 2014

Internal meeting to prepare for Late Cycle Meeting: July 22, 2014

Late Cycle Meeting: August 11, 2014

Labeling meetings: TBD

DRISK presentation of the safety data: See attached

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/s/  
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SHARON K SICKAFUSE  
05/12/2014



BLA 125514/0

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We are reviewing the clinical section of your submission and have the following information requests.

1. The following patients are missing information regarding their prior ipilimumab treatment. Please provide the information or an explanation in the column below.

<b>Patient number</b>	<b>Treatment arm</b>	<b>Finding</b>	<b>Explanation</b>
0001000364	MK-3475 10 mg/kg Q3W	Ipilimumab dose unknown, # of doses unknown, dates of first and last dose unknown, date of progression unknown	
0001000394	MK-3475 2 mg/kg Q3W	Ipilimumab dose unknown	
0008000308*	MK-3475 2 mg/kg Q3W	Received less than 3 mg/kg of ipilimumab; BRAF mutation (+) but no BRAF or MEK inhibitor	
0008000403	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	

0008000412	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0008000426	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose	
0010000250	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose , # of doses unknown, date of progression unknown	
0010000253	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose , # of doses unknown, date of progression unknown	
0010000254	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose , # of doses unknown, dates of first and last dose unknown, date of progression unknown	
0010000255*	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose , date of progression unknown for last treatment unknown, treated three times with ipi	
0010000266	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose , # of doses unknown	
0010000267	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose , date of progression unknown	
0010000268	MK-3475 2 mg/kg Q3W	Received ipi treatment twice, date of progression for last treatment unknown	
0010000285	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0010000339*	MK-3475 10 mg/kg Q3W	Date of progression unknown	
0010000340	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose	
0010000341	MK-3475 2 mg/kg Q3W	Date of progression unknown	
0010000343	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose , date of progression unknown	
0010000374	MK-3475 10 mg/kg Q3W	Date of progression unknown	
0011000396	MK-3475 10 mg/kg Q3W	Date of progression unknown	

0012000386	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0013000275	MK-3475 10 mg/kg Q3W	BRAF mutation (+) but no BRAF or MEK inhibitor	
0015000299*	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose , missing record	
0015000414	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0018000281	MK-3475 10 mg/kg Q3W	Received less than 3 mg/kg of ipilimumab, date of progression unknown	
0018000301	MK-3475 2 mg/kg Q3W	Date of progression unknown	
0019000328	MK-3475 2 mg/kg Q3W	Date of progression unknown	
0019000381	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0020000424	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0021000288	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0021000357	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0021000369	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose	
0021000370*	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0021000375	MK-3475 10 mg/kg Q3W	Unknown ipilimumab dose	
0023000320	MK-3475 2 mg/kg Q3W	Unknown ipilimumab dose	

2. According to the case report form (CRF), patient 0010000340 received third-line ipilimumab as induction and maintenance; however, the dates of treatment and date of disease progression do not appear to be captured in CM.xpt (CMCAT) and SUPPCM.xpt (CONCDPDT)). Additionally, ipilimumab appears to be captured as second-line, not third-line treatment. Please clarify.

3. Please provide a dataset to capture the dates of progression for prior ipilimumab treatment in a tabular format for all Part B2 patients (n=173) as follows:

USUBJID	TRT01P	Treatment phase [SUPPCM:QVAL] where QNAM=PRDFLAG*	CONCDPDT*	Date of second assessment <sup>1</sup>	Date of baseline tumor imaging	Date of randomization [DS:DSSTDTC]

\*For patients retreated with ipilimumab, use progression date that corresponds to last treatment date with ipilimumab, per protocol.

<sup>1</sup> This is according to protocol definition for ipilimumab-refractory patients, in the absence of rapid clinical progression, on page 76 of 001-08.

4. For survival status as provided on page 93 of the annotated CRF, it appears that not all patients (n=130) in Part B2 had this form completed. Please clarify and provide the survival status for all patients (n=173) in Part B2.
5. Please explain the difference in how deaths were recorded on page 93, "Survival" and page 106, "Death Report" of the annotated CRF.

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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SHARON K SICKAFUSE  
05/08/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, May 06, 2014 12:17 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

Hi Melissa,

My clinical team has the following IR:

1. According to DS.xpt, 130 patients were screen failures in PN001. Please provide the reasons for screen failures as a separate dataset. The exact reasons were not included in the ds.xpt.
2. Please provide a dataset for the scan/imaging (tumor imaging) with the date of images taken *at time of screening* as provided on p. 61 of Annotated CRF. On p. 61, it states, "Entire CRF not in xpt."

Thanks

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/s/  
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SHARON K SICKAFUSE  
05/06/2014

**From:** Sickafuse, Sharon  
**Sent:** Thursday, May 01, 2014 2:39 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

Hi Melissa,

My clinical team has the following IR:

1. Please confirm the information in the CSR in the narrative for patient 000422 (SAE/Death): narrative states that on [REDACTED] <sup>(b) (6)</sup> the patient was admitted with shock with a hemoglobin of 2.6 gm/dL and Hct of 7.1%. Please verify the location of the information from this hospitalization in the CRF and in the lab datasets and provide rationale why this level of anemia was not considered a SAE. Also provide information on whether any further workup was done to establish an etiology for the anemia and to rule out an autoimmune component. Please also provide accurate data on the WBC (listed in CSR as 28000 and 2800) and platelet count (listed in CSR as unavailable) at the time of admission. Also, clarify what is meant by the "WBC count continued to get worse" in the narrative.
2. Please confirm the definition of SAE for this study as it differs in the protocol and CSR sections 9.5.1.6.1 and 12.8 and ISS.
3. Please confirm that the Treatment Emergent Flag=Y in the SUPPAE dataset represents AEs from the first day of MK-3475 to 30 days after the last dose and SAEs from the first dose to 90 days after the last dose of MK-3475 and that this was the data used in the analyses for the submission.
4. For patient 0313 with Gr 3 hypoxia, please provide chest imaging results from this patient in order to further characterize the event. The AE pneumonitis was deleted from the CRF and it is unclear why this was the case as the patient was treated with and reportedly improved on steroids and was removed from therapy due to this event. Please provide your assessment of this event in your response.
5. For patient 0423 with Grade 3 renal failure, confirm the creatinine values in the narrative as it is stated that the peak creatinine was 1.58mg/dL and baseline was 1.47 mg/dL.
6. For patient 0326 with Gr 3 encephalopathy, please confirm whether an MRI was performed and provide these results; only CT results are given and this event is not well characterized.
7. According to the Independent Review Charter (IRC), patients underwent a single radiology review by an independent radiologist, unless otherwise directed by Merck. Please provide a list of patients that underwent a single read or a double

read. Please explain how the determination was made for a single versus double read.

8. The IRC states that a certified project team member will identify the target lesions at baseline for the independent radiologist. Please provide the qualifications and certification for the certified project team member. Was this individual blinded to the treatment arms and results? Was this project team member present throughout the independent radiology review? How were lesions identified for the radiologist?
9. Please provide the CRFs, including the radiology and oncology review, per the IRC for subject 0010000253.

Thank you

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SHARON K SICKAFUSE  
05/01/2014



BLA 125514/0

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We also refer to your amendments dated March 21, 26, 27, 28, and 31(2) and April 1(2), 2, 3(2), 15 (2), 16, 22, and 23, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is October 28, 2014.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 26, 2014. In addition, the planned date for our internal mid-cycle review meeting is June 13, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified potential review issues with respect to the quality microbiology section of your application including manufacturing process and process controls of your drug substance and drug product. The potential review issues were communicated to you in our April 16, 2014, letter which is attached

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

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we identified the following labeling issues:

1. Revise the product title from “KEYTRUDA® (pembrolizumab) for intravenous infusion” to “KEYTRUDA® (pembrolizumab) injection, for intravenous infusion.”
2. Replace “single-dose vial” with “single-use vial”.
3. As currently presented, Section 2.3 (Preparation and Administration) of the Full Prescribing Information describes a process for the preparation of one vial of Keytruda. It does not provide [REDACTED] (b) (4) The [REDACTED] (b) (4) recommended dose of the product is 2 mg/kg. [REDACTED] (b) (4) .
  - a. Change the statement, [REDACTED] (b) (4) [REDACTED] to: “Determine the number of KEYTRUDA vials to be reconstituted and remove from the refrigerator. Allow the vial(s) to reach room temperature prior to reconstitution.”
  - b. Insert a new bullet “Calculate the volume of 25 mg/mL reconstituted Keytruda solution needed” before the bulleted statement that begins with, “Withdraw the required volume...”

- c. Change the following statement, (b) (4)  
  
to:  
“Withdraw the required volume from the KEYTRUDA vial(s) and transfer into an IV bag containing 0.9% Sodium Chloride Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion.”
4. Although Section 2.3 indicates that the reconstituted product should be visually inspected for discoloration prior to administration, there is no description of the expected general appearance of the reconstituted drug product. Include a description of the ‘general appearance’ of the reconstituted drug product e.g., opalescence and color in addition to the visible particulates for visual inspection.
5. See attached draft labeling for additional comments concerning issues with content and format in Sections 1, 2.2, 2.3, 3, 5, 6.1, 8.7, 11, 13.1, 13.2, and 14.1 of the Full Prescribing Information.

We request that you resubmit labeling (in Microsoft Word format for the package insert) that addresses these issues by May 27, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with format items in regulations and guidances.

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

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

### **PROMOTIONAL MATERIAL**

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

Sincerely,

*{See appended electronic signature page}*

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

Attachments:

April 16, 2014, quality microbiology information request  
Revised draft package insert



BLA 125514/0

**INFORMATION REQUEST**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated February 27, 2014, received February 27, 2014, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab).

We are reviewing the quality microbiology section of your submission and have the following comments and information requests. We request a written response by May 12, 2014, in order to continue our evaluation of your BLA.

Regarding the drug substance (DS) manufactured at  (b) (4)

1. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Upstream Manufacturing Process and Process Controls

- a.
- b.
- c.
- d.



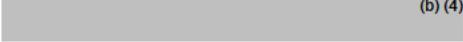
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Regarding the DS manufactured at MedImmune, LLC Frederick Manufacturing Center (FMC):

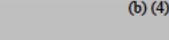
14. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Upstream Manufacturing Process and Process Controls

- a.  (b) (4)
- b. 

15. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Downstream Manufacturing Process and Process Controls

- a. Bioburden samples should be representative of worst-case bioburden conditions  (b) (4)
  - 1) Justify taking bioburden samples  (b) (4).
  - 2) Conduct sampling for bioburden for all  (b) (4)  


- b.  (b) (4)

16. Control of Critical Steps and  (b) (4)

- a.  (b) (4)
- b. 
- c. 
- d. 
- e. 

17. Process Validation and/or Evaluation – Validation Batches

a.

b.

c.



18. Process Validation and/or Evaluation –  Validation

a.

b.

c.

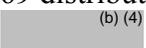
d.



19. Process Validation and/or Evaluation – 

Submit information describing microbial quality limits .

20. Process Validation and/or Evaluation – Shipping Validation

a. Indicate which ASTM D4169 distribution cycles were conducted for the shock and vibration testing of the .

- b. Submit the shipping validation report for the (b) (4) qualification in the laboratory setting and for the performance qualification study using real life conditions.
- c. Submit a diagram showing the shipper with maximum or minimum load; indicate the location of (b) (4), and temperature monitors for each type of loads.
- d. Describe the routine shipping of the bulk DS to the DP manufacturing facility.

21. Control of Drug Substance – Analytical Procedures

- a.
- b.
- c.



22. Control of Drug Substance – Validation of Analytical Procedures (Bioburden)

- a.
- b.



23. Control of Drug Substance – Validation of Analytical Procedures (Endotoxin)

- a.



b.

(b) (4)

c.

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

Sincerely,

*{See appended electronic signature page}*

Patricia Hughes-Troost  
Team Lead  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality  
Center for Drug Evaluation and Research

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/s/  
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PATRICIA F HUGHES TROOST  
04/16/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, April 15, 2014 10:30 AM  
**To:** Engel, Steven (steven.engel@merck.com)  
**Cc:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - clin pharm IR

Hi Steven,

My clinical pharmacology/pharmacometrics team is still having difficulty reproducing some of Merck's analysis results based on the resubmitted datasets and control streams dated March 27th, 2014. We are requesting four revised PK-PD datasets and a new dataset for further exposure-response analysis. Please respond to the following information request within two weeks.

1. Translational PKPD: Resubmit the original dataset "MousePKPD\_3832.csv" associated with report "03v4kh.pdf". Dataset "MousePKPD\_3832.csv" as referred to in the output file "pkpd-run6-1st-out.txt" is still missing and the two resubmitted datasets "p001pkpdmouse383201.csv" and "p001tvmouse383201.csv" cannot be used to reproduce the result.
2. Exposure-Response (Safety) Analysis: Resubmit the original datasets and programs associated with output files "run3007.ctf.lst" and "run3011.ctf.lst" in the analysis report "03tlcn.pdf". The output files cannot be reproduced by FDA.
3. Exposure-Response (Efficacy) Analysis: Submit a new dataset for Part B2 of Study P001. Include the following variables:

AN (NONMEM ID), USUBJID (unique subject identifiers), TREATMENT, DOSE, AUC\_Tau\_ss, Cmax\_ss, Cmin\_ss, ORR (yes or no), PFS\_Week24 (yes or no), OS\_Month6 (yes or no), Corticosteroid Use (yes or no), along with all the AE variables as listed in Table 2.7.4: 21 of "Summary of Clinical Safety.pdf", Page 62-66) such as Anemia (yes or no), Leukocytosis (yes or no), Atrial Fibrillation (yes or no), etc.

4. Resubmit the 4 PKPD datasets (p001pkdm012c.xpt, p001pkada009c.xpt, p001pkparametersparta.xpt and p001pkparametersparta2.xpt) including (1) USUBJID as used in the clinical datasets in Study P001 and (2) another variable differentiating the sub-cohort IDs (ie, A, A1, A2, B1 and B2) as the sub-cohort IDs are missing in the current variable PART.

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/s/  
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SHARON K SICKAFUSE  
04/15/2014

**From:** Sickafuse, Sharon  
**Sent:** Monday, April 14, 2014 8:38 AM  
**To:** Engel, Steven (steven.engel@merck.com)  
**Cc:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 IR

Hi Steve,

My clinical team has the following IR:

Please provide the document entitled "MK-3475 Event of Clinical Interest and Immune-Related Adverse Event Guidance Document" that was provided to the investigators. It is referenced in Section 9.5.1.6.3 of the CSR, but there is no link and although the CSR states it is located in 16.1.10, this seems to be documents related to laboratory testing and imaging.

Thank you

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/s/  
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SHARON K SICKAFUSE  
04/14/2014

## Biable, Missiratch (Mimi)

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**From:** Biable, Missiratch (Mimi)  
**Sent:** Thursday, April 10, 2014 5:04 PM  
**To:** Tice, Melissa (melissa\_tice@merck.com)  
**Cc:** Sickafuse, Sharon  
**Subject:** BLA 125514/0 Stat IR

**Importance:** High

Dear Melissa,

I am sending you the following on behalf of Ms. Sharon Sickafuse.

Our Stats team has the following information request .

1. Submit the data monitoring committee meeting minutes.
2. Some patients lesion records are missing the flags indicating the type of assessment ( IRO or IRC or INV). Re-submit the related datasets with complete information of the assessments.
3. Please provide the SAS programs for derivations from raw data to derived data with necessary documentation of the algorithms. In particular, the SAS codes should show how CR, PR, and SD were derived.
4. In the raw lesion data set, the variable “visit name” does not have a uniform coding scheme as the values are recorded in cycles or weeks. Please submit the dataset with a uniform coding scheme.
5. Please clarify how the visit dates were calculated for the lesion data. In particular, the date of lesion measurement as it did not always correspond to the correct cycle of the study. For example, Subject 0003000066 had a visit at cycle 5 but the day of lesion measurement is recorded as 85. So factoring the +/- 7 day measurement window, the subject’s lesion measurement should have been  $21 * 5 = 105$ . This means the measurement should have been taken from day 98 to 113, instead it was taken on day 85.
6. Please clarify the length of the screening period and if it is defined in the study protocol. Most subjects were screened within the first 21 days; however some subjects exceeded this screening period. For example, Subject 0011000075 was screened on Day 30.

Please provide the requested information for items 1 and 2 by **COB Tuesday, April 15, 2014** and provide your response for times 3-6 by **COB Monday, April 21, 2014** .

If you have any questions, please contact me and kindly respond to confirm receipt of this communication.

Regards,

Missiratch (Mimi) Biable  
Regulatory Health Project Manager  
Division of Oncology Products 2

Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Email: [Missiratch.biable@fda.hhs.gov](mailto:Missiratch.biable@fda.hhs.gov)

Phone: 301-796-0154

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/s/  
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MISSIRATCH BIABLE  
04/10/2014

## **BLA 125514/0: Review Plan Overview**

Product: Keytruda (pembrolizumab)  
Submission Date: February 27, 2014  
Received Date: February 27, 2014  
**Sponsor:** Merck Sharp and Dohme Corp.

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

### **Review Team/Collaborators for BLA 125514/0:**

Patricia Keegan, M.D., Director DOP2  
*Sharon Sickafuse, M.S., Lead Regulatory Health Project Manager*  
Jennie Chang, PharmD., Medical Officer  
Meredith Chuk, M.D., Medical Officer  
Marc Theoret, M.D., Medical Officer (TL and CDTL)  
Emmanuel Sampene, Ph.D., Statistics  
Kun He, Ph.D., Statistics (TL)  
Runyan Jin, Ph.D., Clinical Pharmacology  
Hong Zhao, Ph.D., Clinical Pharmacology (TL)  
Hongshan Li, Ph.D., Pharmacometrics  
Jingyu Yu, Ph.D., Pharmacometrics  
Liang Zhao, Ph.D., Pharmacometrics (TL)  
Shawna Weis, Ph.D., Non-Clinical  
Whitney Helms, Ph.D., Non-Clinical (TL)  
*Lyndsay Hennessey, OBP RPM*  
Mark Paciga, Ph.D., Product  
Deborah Schmiel, Ph.D., Product  
Rashmi Rawat, Ph.D., Product (TL)  
Maria Candauchacon, Ph.D., Quality Micro DS  
Kalavati Suvarna, Ph.D., Quality Micro DP  
Patricia Hughes, Ph.D., Quality Micro (TL)  
*Sue Kang, OSE RPM*  
Otto Townsend, OSE/DMEPA  
Chi-Ming (Alice) Tu, OSE/DMEPA (TL)  
Carolyn Yancy, OSE/DRISK  
Cynthia LaCivita, OSE/DRISK (TL)  
Lauren Iacono-Connor, OSI  
*Olga Salis, OPDP RPM*  
Quynh-Van Tran, OPDB  
Sharon Mills, Patient Labeling  
Barbara Fuller, Patient Labeling (TL)

### **Review Status:**

- Priority Review requested, team agreed to a 8 month review as outlined below.
- Categorical Exclusion requested
- Has Orphan Drug designation, so PREA doesn't apply.
- The clinical development of pembrolizumab for melanoma has been conducted under IND 110080

**1. Dates for Milestones and for When Letters Must Issue:**

<b>Milestone</b>	<b>Due</b>
<b>Acknowledgment Letter</b>	Issued 3-5-2014
<b>Filing Action Letter</b>	<b>4-28-2014</b>
<b>Deficiencies Identified Letter (74 Day Letter)</b>	<b>5-12-2014</b>
<b>Send proposed labeling/PMR/PMC/REMS to applicant</b>	9-28-2014
<b>Review Target Due Dates:</b>	
<i>Primary Review Due</i>	8-1-2014
<i>Secondary Review Due</i>	8-5-2014
<i>CDTL Review Due</i>	9-30-2014
<i>Division Director Review Due</i>	10-16-2014
<i>Office Director Review Due/Sign-Off</i>	10-28-2014
<b>Compile and circulate Action Letter and Action Package</b>	10-7-2014
<b>FINAL Action Letter Due</b>	10-28-2014

**2. Consults/Collaborative Reviewers:**

OPDP	Olga Salis – RPM Quynh-Van Tran
OSE	Sue Kang - OSE RPM Carolyn Yancy - DRISK Otto Townsend - DMEPA
Quality Micro/OMPQ	Kala Suvarna - DP Maria Candauchacon - DS
QT-IRT	Consult sent 3-25-2014
OSI	Lauren Iacono-Connor assigned, sites selection in progress.

Pediatric Page/PeRC	Pediatric Page in DARRTS: 3-4-2014
SGEs or Patient Representatives	
Patient labeling	Sharon Mills

**1. ODAC Presentation??:**

Practice sessions TBD

**2. Upcoming Internal Team Meetings:**

**Applicant Orientation Presentation:** Held on March 24, 2014.

**Planning Meeting** held on: March 28, 2014

**Filing Meeting** scheduled for: April 10, 2014

**Team Meeting** scheduled for: May 12, 2014

**Mid-Cycle Meeting** scheduled for: June 13, 2014

Midcycle communication (telecon) to sponsor:  
Scheduled for: June 27, 2014

Labeling meetings

PMR/PMC meeting, if needed

Internal meeting for Late Cycle Meeting

Late Cycle Meeting

Wrap-up Meeting

**3. Anything else**

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/s/  
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SHARON K SICKAFUSE  
03/28/2014

**From:** Sickafuse, Sharon  
**Sent:** Friday, March 28, 2014 12:13 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - OSI IR  
**Attachments:** i110080\_Oct13\_preBLA & slides.pdf

**Importance:** High

Hi Melissa,

OSI has the following IR:

1. Please provide all elements of OSI request Part II as conveyed to you during the October 25, 2013, preBLA meeting as it pertains to the clinical sites in the registration study.
2. For those OSI PART II requests, if any, that you have already included in the BLA, provide the exact location of those site-specific data listings in the format requested. We are unable to find any data listings organized in the format requested.
3. Please provide the exact location and point of contact for the IRC function covered by [REDACTED] <sup>(b) (4)</sup>). They are not listed in the document called Trial Administrative Structure for the pivotal study. We did find the charter for the IRC but it is unclear as to the location where the work was done.
4. Please identify the specific location where the study documentation resides.

Thank you

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SHARON K SICKAFUSE  
03/28/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, March 26, 2014 6:01 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clinical IR

Hi Melissa,

My clinical team has the following request:

1. Please submit a list of major and minor protocol deviations by number, type, and site and also a definitions for what constituted a major or minor protocol deviation.
2. An AE dataset and analysis for Grade 3-5 AEs occurring from days 30-90 after the last dose of drug with flags for those considered serious AEs.
3. A tabular listing of patients initiating steroids on study that includes the adverse event which prompted use of steroids, toxicity severity grade, the specific steroid administered, the dose(s) of the steroid administered, the route of administration of the steroid, and the duration of steroid administration at each dose.

Please submit these items a BLA amendment(s). Thank you

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SHARON K SICKAFUSE  
03/26/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, March 25, 2014 12:25 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - clinical IR

Hi Melissa,

My clinical team has the following IR:

Please refer to FDA comment in the table below and clarify the dates of disease progression following treatment with ipilimumab for the patients below:

USUBJID	CMSTDTC	CMENDTC	QVAL of Subset of SUPPCM 3	QLABEL of Subset of SUPPCM 3	FDA comment	Merck explanation
3475-001_0008000319	2012-04-12	2012-08-27	2012-03-15	Date of progression after TX phase	Date of PD is before ipi tx	
3475-001_0012000305	2012-06-19	2012-09-04	2011-08-23	Date of progression after TX phase	Date of PD is before ipi tx	
3475-001_0012000379	2011-08-29	2011-10-10	2011-10-09	Date of progression after TX phase	Date of PD is before ipi tx	
3475-001_0021000370	2011-11	2012-04	2011-08-31	Date of progression after TX phase	Date of PD is before ipi tx	

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/s/  
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SHARON K SICKAFUSE  
03/25/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, March 25, 2014 12:10 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 clin pharm IR

Hi Melissa,

My clin pharm team has the following IR:

Based on the following xpt files submitted for Section 5.3.5.3 "Reports of Analyses of Data from More Than One Study", your output files cannot be reproduced by your NONMEM or R programs included in the submission:

1. "NonMDataAnalP001poppk.xpt" and "NonMDataAnalP001poppkFinal.xpt" associated with Report "03tlc8 (M&S analysis report of Population PK of MK-3475)".
2. "p001pkqtc009d.xpt" associated with Report "03tlcf (PK/QTc Report MK-3475)".
3. "p001pkaes05.xpt", "p001pkaeosi05.xpt", and "p001pkaegra05.xpt" associated with Report "03tlcn (M&S report MK-3475 – PK-AE)".
4. "p001pkest.xpt" and "p001pkiddiam08.xpt" associated with Report "03tlcv (M&S analysis report MK-3475)".
5. "MousePK\_M32\_M46.xpt" and "MousePKPD\_3832.xpt" associated with Report "03v4kh (M&S analysis report MK-3475 – Translational PKPD)".

Please resubmit runnable XPT datasets that match the associated NONMEM control streams or the R script by Friday, March 28<sup>th</sup>.

The two datasets associated with Report 03tlc9 (M&S report MK-3475 – Pop PK and PK/PD) did reproduce your output files.

Thank you

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SHARON K SICKAFUSE  
03/25/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, March 19, 2014 8:15 AM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 - dataset issues for March 20 telecon

Hi Melissa,

The following are data deficiencies and nonstandard use of CDISC and MedDRA terms that impair efficient analysis of data:.

1. Specific Deficiencies

- a. Oncology Efficacy domain—cannot link datasets for tumor response (RS), Tumor identification (TU) and tumor lesion (LS). Links in RELREC domain do not exist and this prevents traceability from tumor response back to lesion measurements.
- b. Widespread use of non-standard lab terminology in (LBTESTCD)
- c. Missing values for LBSTRESC when LBORRES is provided for about 25% of the data
- d. Define.xml file did not provide sufficient detail:
  - i. No references to specific CRF pages from where data was collected
  - ii. Comments that are not explained: e.g. BR022\_AE\_DURATION, BR37
  - iii. Sponsor-specific codelists (e.g. ARMCD) are missing
- e. ARM/ARMCD values to not match trial arms (TA) data in several cases which could impact the denominators in analysis if populations are not clear. e.g.. ARMCD value of UNALLOC is not a standard CDISC term. Is this SCRNFALL or NOT ASSIGN? Use of this nonstandard term prevents proper analysis.
- f. Several terms under AEDECOD are not valid MedDRA terms for version 16 (Candida infection, neutrophilic dermatosis, ophthalmic herpes zoster, bacillus bacteraemia)
- g. 4 AETERM values with no corresponding AEDECOD
- h. Study day of start of medication (CMSTDY) is after Study day end of medication (CMENDY) in several cases. Suspect many are caused by

imputations of missing dates? Estimate that CMSTDY is imputed in the majority of cases.

2. Clarifications/Discussion

- a. Please clarify what constitutes a protocol deviation for inclusion in report labeled MK-3475-001\_Identification of Protocol Deviators\_Dec Interim Analysis\_FINAL\_16Jan2014\_ Version 2
- b. 145 subjects do not have a reference end date (RFENDTC). Are these patients still on therapy?
- c. Many of the issues should have been addressed in the Reviewer's Guide

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SHARON K SICKAFUSE  
03/19/2014

**From:** Sickafuse, Sharon  
**Sent:** Tuesday, March 18, 2014 4:20 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 Information Request for pharmacovigilance plan

Hi Melissa,

My team has the following information request:

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with pembrolizumab following market approval. Guidance for pharmacovigilance planning is included in the attached FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please submit it.  
Thanks



FDA Guidance.E2E  
PV Planning.2...



FDA  
Guidance.Good...

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/s/  
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SHARON K SICKAFUSE  
03/18/2014

**From:** [Biable, Missiratch \(Mimi\)](#)  
**To:** "[melissa\\_tice@merck.com](mailto:melissa_tice@merck.com)"  
**Cc:** [Sickafuse, Sharon](#)  
**Subject:** BLA 125514/0 Clinical Information Request  
**Date:** Friday, March 14, 2014 3:46:43 PM  
**Importance:** High

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Hi Melissa,

Our Clinical team has the following IR. Please provide the following by COB Wednesday, March 19, 2014.

1. Copy of the independent review charter that was used by (b) (4) for the independent radiology and oncology response evaluations, as this could not be located in the BLA submission. If the most recent one differs from Version 3.0, dated August 5, 2013 in IND 110080, please provide a track changes, red-line version.
2. CRFs for the following patients:
  - a. 0012000257
  - b. 0019000353
3. List of patients that underwent adjudication radiology review in the independent review, or indicate where this is located in the datasets.
4. Using ADIRC, a dataset which provides the percent change from baseline of tumor (PCHGBL) and nadir (PCHGNAD) by radiology assessment corresponding to ADY for AVALC.

If you have any questions, please contact me and kindly respond to confirm receipt of this communication.

Regards,

Missiratch (Mimi) Biable

Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: [Missiratch.biable@fda.hhs.gov](mailto:Missiratch.biable@fda.hhs.gov)

Phone: 301-796-0154

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MISSIRATCH BIABLE

03/14/2014



BLA 125514/0

**BLA ACKNOWLEDGEMENT**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

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

**Name of Biological Product:** Keytruda (pembrolizumab)

**Date of Application:** February 27, 2014

**Date of Receipt:** February 27, 2014

**Proposed Use:** Treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

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

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

*{See appended electronic signature page}*

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

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SHARON K SICKAFUSE  
03/05/2014

**From:** Sickafuse, Sharon  
**Sent:** Wednesday, February 26, 2014 3:47 PM  
**To:** melissa\_tice@merck.com  
**Subject:** BLA 125514/0 nonclinical IR

**Importance:** High

Hi Melissa,

My nonclinical team has the following IR:

Study TT #11-1084, the 6 month toxicology study of cynomolgus monkeys treated with MK-3475, appears to include insufficient histopathology data based on the known targets of the drug and findings noted in an earlier 1 month study at similar dose levels. Based on the Investigator's Brochure for MK-3475 and the recent pediatric ODAC presentation, the following target organs that have been identified either in patients treated with MK-3475 or in previous animal studies: skin, lymphoid organs, lung, liver, thyroid, adrenals, kidney, brain/meninges, pituitary, pancreas, and GI tract. Perform additional histological analysis of all suspected target organs in animals. Due to the idiosyncratic nature of autoinflammatory lesions and the target saturation of PD-1 at all dose levels used in this study, this analysis should include animals from all MK-3475 dose groups included in Study 11-1084. In addition, we note that the histopathology summary tables provided for this study suggest that there was significantly less inflammatory infiltration of tissues in the 6 month study compared to the 1 month study at the same dose levels. Following the additional histological assessments, provide a finalized pathology report reflecting the new histological analysis as soon as possible to facilitate timely review of the data.

This difference between the 1 month and 6 month studies is unexpected, as based on its mechanism of action, a PD-1 inhibitor is likely to exacerbate any background pathological processes that are inflammatory in nature. Please explain this discrepancy.

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SHARON K SICKAFUSE  
02/26/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 125514/0

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp.  
126 E. Lincoln Avenue, RY33-200  
P.O. Box 2000  
Rahway, NJ 07065-0900

ATTENTION: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs

Dear Dr. Tice:

Please refer to your Biologics License Application (BLA) dated November 22, 2013, received November 22, 2013, submitted under section 351(a) of the Public Health Service Act, for Pembrolizumab, 50 mg/vial.

We also refer to your January 8, 2014, correspondence, received January 8, 2014, requesting review of your proposed proprietary name, Keytruda. We have completed our review of the proposed proprietary name, Keytruda and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 8, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Sharon Sickafuse, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1462.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
01/27/2014



BLA 125514/0

**BLA PRESUBMISSION ACKNOWLEDGEMENT**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

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

Name of Biological Product: KEYTRUDA (MK-3475)

Date of Submission: November 22, 2013

Date of Receipt: November 22, 2013

Our Reference Number: BLA 125514/0

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

The BLA Secondary Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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SHARON K SICKAFUSE  
11/27/2013



IND 110080

**MEETING MINUTES**

Merck Sharp and Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Worldwide Regulatory Affairs  
126 East Lincoln Ave.  
P.O. Box 2000 MS RY33-200  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "MK-3475."

We also refer to the meeting between representatives of your firm and the FDA on October 25, 2013. The purpose of the meeting was to discuss the content and format of a proposed BLA for the treatment of melanoma.

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

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** preBLA

**Meeting Date:** October 25, 2013

**Application Number:** IND 110080  
**Product Name:** MK-3475  
**Indication:** Treatment of melanoma  
**Sponsor/Applicant Name:** Merck Sharp and Dohme Corp. (Merck)

**Meeting Chair:** Marc Theoret  
**Meeting Recorder:** Sharon Sickafuse

**FDA ATTENDEES:**

**Office of Hematology and Oncology Products**  
Jonathan Jarow, M.D.

**Division of Oncology Products 2**

Mimi Biable  
Meredith Chuk, M.D.  
Joseph Gottenberg, M.D.  
Jennie Chang, M.D.  
Sharon Sickafuse, M.S.  
Marc Theoret, M.D.

**Division of Hematology Oncology Toxicology**

Emily Fox, Ph.D.  
Whitney Helms, Ph.D.  
Shawna Weis, Ph.D.

**Office of Biostatistics**

**Division V**

Jade Chen, Ph.D.  
Kun He, Ph.D.

**Office of Clinical Pharmacology**

**Division V**

Ruby Leong, Ph.D.  
Hong Zhao, Ph.D.

Meeting Minutes  
Type B

**Office of Biotechnology Products  
Division of Monoclonal Antibodies**

Lyndsay Hennessey  
Sarah Kennett, Ph.D.  
Mark Paciga, Ph.D.  
Rashmi Rawat, Ph.D.

**Office of Surveillance and Epidemiology  
Division of Risk Management**

Cynthia LaCivita

**Division of Medication Error Prevention and Analysis**

Chi-Ming (Alice) Tu

**Office of Scientific Investigations**

Kassa Ayalew  
Lauren Iacono-Connors

**Office of Planning and Informatics**

Kimberly Taylor

**Center for Device and Radiological Health  
Office of In Vitro Diagnostics and Radiological Health**

Elizabeth Mansfield, Ph.D.

**EASTERN RESEARCH GROUP ATTENDEES**

Christopher Sese, Independent Assessor

**SPONSOR ATTENDEES**

Cong Chen, Ph.D., Director, Biostatistics  
Parimal Desai, Ph.D., AVP, Vaccines Manufacturing Sciences  
Scot Ebbinghaus, M.D., Executive Director, Clinical Research Oncology  
Dennis Erb, Ph.D., Sr. Vice President, Global Regulatory Affairs  
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Peter Kang, M.D., Associate Director, Clinical Research Oncology  
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Eric Rubin, M.D., Vice President, Clinical Research Oncology  
Melissa Tice, Ph.D., Executive Director, Regulatory Affairs

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Type B**BACKGROUND**

MK-3475 is a human monoclonal IgG4 antibody that directly blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. Merck states that this blockade facilitates tumor regression and ultimately, immune rejection. The proposed indications are for the treatment of melanoma (b) (4)

On August 21, 2012, a meeting was held to discuss whether the efficacy and safety results from expanded cohorts of melanoma patients in PN001 could support review under accelerated approval regulations. Merck proposed two confirmatory trials, PN002 and PN006, to provide confirmatory evidence of therapeutic benefit. FDA stated that a BLA submission for accelerated approval of MK-3475 primarily based on the proposed endpoint, landmark analysis of objective response rates (ORR) determined at 12 weeks with confirmation at 16 weeks, would likely not provide substantial evidence establishing a MK-3475 treatment effect that is reasonably likely to predict clinical benefit. In design of the expansion cohorts of PN001 to support a BLA for MK-3475, FDA advised Merck to target a confirmed ORR (RECIST 1.1) effect size that, in adequate and well-controlled trial(s), is of sufficient magnitude and duration to be reasonably likely to predict clinical benefit. Merck proposed a data package which would include up to 80 ipilimumab (IPI)-refractory patients with a projected follow-up of 7 months and an estimated ORR of 30% in the high-dose arm. FDA stated that, in the absence of the actual trial results, it could not determine whether the package would suffice to support the request for accelerated approval.

On January 17, 2013, Breakthrough Therapy designation was granted to MK-3475 for the treatment of unresectable or metastatic melanoma that is refractory to ipilimumab treatment, and for the treatment of unresectable or metastatic melanoma in patients who have not received prior ipilimumab therapy. In support of Breakthrough Therapy designation of MK-3475, Merck provided data in 85 patients with advanced melanoma, including IPI-naïve (n=58) and IPI-treated (n=27) patients, demonstrating a confirmed ORR (RECIST 1.1) of 40% [95% confidence interval (CI): 29%, 51%] with a median duration of response that was not reached but ranged from 28 weeks to at least 240 weeks (responses were ongoing). A meeting was held on April 22, 2013, to discuss the nonclinical, clinical pharmacology and clinical development programs as a result of the Breakthrough Therapy designation. A meeting to discuss the product and manufacturing program as a result of the Breakthrough Therapy designation was held on April 2, 2013. Additional CMC meetings were held on June 11 and August 27, 2013.

On August 20, 2013, Merck submitted a request (SDN 300) for a preBLA meeting to discuss the format and content of the proposed BLA for MK-3475 for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab. The meeting package was submitted on September 26, 2013 (SDN 339). A meeting to discuss the CMC portion of the BLA was held on October 24, 2013.

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Type B**Proposed Indication:**

According to the Background Package, data from Part B2 of PN001 form the potential basis for the efficacy portion of the BLA submission in support the following proposed indication:

“[MK-3475] is indicated for the treatment of unresectable or metastatic melanoma in patients who have been treated previously treated with ipilimumab.”

Merck proposes the recommended dose and schedule of administration of MK-3475 as 2 mg/kg administered intravenously once every three weeks.

**CMC**

During the development program of MK-3475, clinical materials from two Drug Substance (DS) facilities ( (b) (4) and FMC) and two Drug Product (DP) facilities ( (b) (4) and Brinny) supply chains have been used.

*Drug Substance:*

(b) (4) DS:  
(b) (4)

## FMC DS:

Clinical/ (intended) commercial DS facility at (b) (4) scale in Frederick, MD

*Drug Product*

(b) (4) DP:  
(b) (4)

(b) (4) DP:

Clinical and intended commercial DP manufactured at Brinny, Ireland using (b) (4) DS

(b) (4) DP:

Clinical and intended commercial DP manufactured at Brinny using FMC DS

At the initiation of PN001, patients received (b) (4) (b) (4) DS/ (b) (4) DP) and based on the demonstration of analytical comparability data reviewed by the FDA, new enrolling patients received (b) (4). At the time of the projected BLA submission in December 2013, 393 of 411 melanoma patients enrolled in PN001 will be treated with (b) (4) and 20 patients in PN001 Part B2 will be treated with (b) (4) ( (b) (4) DS, Brinny DP). As of September 2013, approximately 200 patients in the ongoing PN001 Part B3 (melanoma) and 110 patients in PN001 Part F (non-small cell lung cancer) have been treated with (b) (4). In the ongoing PN002 study in IPI-refractory melanoma patients, a total of 397 patients have been randomized to date and 177 of these patients have received (b) (4). Although the efficacy data from

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PN001 Parts B3 and F and PN002 will not be included in the BLA submission, serious adverse event data will be provided from the ongoing clinical studies.

**Table 1 Manufacturing of MK-3475 DS and DP**

	(b) (4)	(b) (4)	(b) (4)
Drug Substance	(b) (4)	(b) (4)	FMC (b) (4)
Drug Product	(b) (4) 50 mg lyophilized vial	Brinny 50 mg lyophilized vial	Brinny 50 mg lyophilized vial
Formulation	Identical final formulation (b) (4) reconstituted in water for injection)		
Planned usage in clinical studies	PN001, PN002	PN001, PN002, confirmatory trial and additional indications	Confirmatory PN006 trial
Patients dosed in PN001 and PN002	613	591	N/A
Planned Commercial Usage	N/A	Initial (US) Product Launch	Initial (US) Product Launch

The MK-3475 DS/DP planned for commercial use will include two DS supply chains ((b) (4) DS and FMC DS) and one DP facility in Brinny Ireland. Both DS supply chains will be manufactured into commercial DP at the Brinny facility resulting in two comparable lyophilized DPs: (b) (4) (b) (4) DS, Brinny DP) and (b) (4) (b) (4) (FMC DS, Brinny DP).

Merck states that they have demonstrated analytical comparability of (b) (4) (b) (4) and these data have been submitted to IND 110080. FDA has concurred with the acceptability of comparability between (b) (4). The comparability data between (b) (4) are under FDA review. Merck estimates that a limited number of patients (approximately 34) will have been exposed to (b) (4) at the time of the BLA submission based on their plan to introduce (b) (4) into the clinic in mid-October 2013.

### **Clinical Data**

In the BLA, Merck intends to submit data from PN001, entitled “Phase 1 Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma.” This trial is an open-label, multicenter trial of MK-3475

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in patients with progressive locally advanced or metastatic carcinomas, including cohorts limited to patients with melanoma or NSCLC, conducted in several parts:

**Part A:** Dose escalation trial of MK-3475 (cohorts at 1, 3, 10 mg/kg) in patients with advanced solid tumors (N=30)

- Part A1: MK-3475 at maximum dose of 10 mg/kg Q2W (N=6)
- Part A2: expansion cohort (N=12)

**Part B:** Activity-estimating and safety in advanced melanoma

- **Part B1:** Single-arm trial in patients with advanced melanoma, IPI-naïve and IPI-treated (N= 135)
- **Part B2:** Randomized trial of MK-3475 2 mg/kg Q3W or MK-3475 10 mg/kg Q3W in patients with IPI-refractory advanced melanoma patients (N = 173)
- **Part B3:** Randomized trial of MK-3475 administered at 10 mg/kg Q2W or 10 mg/kg Q3W in patients with IPI-naïve, IPI-treated, or IPI-refractory advanced melanoma (enrollment ongoing, approximately 200 patients at cutoff date)

**Part C:** Single-arm trial of MK-3475 10 mg/kg Q3W in patients with advanced NSCLC after two prior therapies (N= 38)

**Part D:** Randomized trial of MK-3475 2 mg/kg Q3W or MK-3475 10 mg/kg Q3W in patients with IPI-naïve advanced melanoma (N= 103)

**Part F:** Randomized trial of MK-3475 10 mg/kg Q2W or MK-3475 10 mg/kg Q3W in patients with non-squamous NSCLC patients (enrollment ongoing, approximately 110 patients at cutoff date)

The efficacy data from Part B2 (IPI-refractory advanced melanoma patients) are the primary data intended to support the proposed label indication. The BLA will also contain efficacy data from PN001 Parts A, B1, D, as well as safety data from PN001 Parts A, B1, B2, C, and D. For the efficacy portion, the data cut-off date for Part B2 will be July 26, 2013; however, Merck proposed that an Efficacy Update Report based on a data cutoff date of October 18, 2013, be submitted within 60 days of the initial BLA submission. This amendment will contain updated efficacy data from Part B2 as well as updated survival data from Parts B1, B2, and D. Additionally, a Safety Update Report based on a data cutoff date of October 18, 2013, will be submitted within 60 days of the initial submission. This amendment will also include data from a dedicated QTc evaluation of approximately 50 patients.

### ***Primary Efficacy Data Intended to Support Accelerated Approval of MK-3475***

#### ***Part B2 Design***

Part B2 of PN001 is an open-label, multicenter, randomized (1:1) trial of MK-3475 in 173 patients with unresectable or metastatic melanoma refractory to ipilimumab treatment, and, if BRAF V600 mutation-positive, to BRAF inhibitor and/or MEK inhibitor treatment. The primary objective of Part B2 is to evaluate the anti-tumor activity (per RECIST 1.1) of MK-3475 in patients with melanoma previously treated with ipilimumab. Secondary objectives are to

evaluate the response rate of patients with melanoma refractory to ipilimumab per immune-related response criteria (irRC). Key eligibility criteria for IPI-refractory patients are:

- Prior treatment with at least two doses of ipilimumab (minimum dose of 3 mg/kg)
- Documented disease progression (per irRC) within 24 weeks of the last dose of ipilimumab

Note: patients who were re-treated with ipilimumab and patients who were on maintenance ipilimumab will be allowed to enter the trial as long as there is documented progressive disease (PD) within 24 weeks of the last treatment date (with ipilimumab).

- Resolution of ipilimumab related adverse events (AEs), including immune-related AEs (irAEs) back to Grade 0-1 and requiring 10 mg/day or less of prednisone or equivalent dose for irAEs for at least two weeks prior to first dose of study drug
- Prior treatment with BRAF inhibitor and/or MEK inhibitor therapy in patients with BRAF V600 mutation positive melanoma
- Progressive disease after the most recent treatment regimen
- Adequate organ function

Patients were randomized to receive MK-3475 2 mg/kg intravenously Q3W or MK-3475 10 mg/kg intravenously Q3W until disease progression per RECIST 1.1 or intolerable toxicity. Stratification factors for randomization were ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated), and BRAF mutation status (wild-type vs. mutant V600E or V600K)

The original design of Part B2 in Amendment 5, submitted on August 13, 2012, was a randomized (2:1) trial of MK-3475 administered at two doses to 60 patients (40 patients at a dose of 2 mg/kg Q3W and 20 patients at a dose of 10 mg/kg Q3W). In Amendment 6, submitted on November 20, 2012, the randomization schema was modified to achieve a final 1:1 randomization and the sample size in Part B2 was increased to add 100 IPI-refractory patients (total of 160 patients).

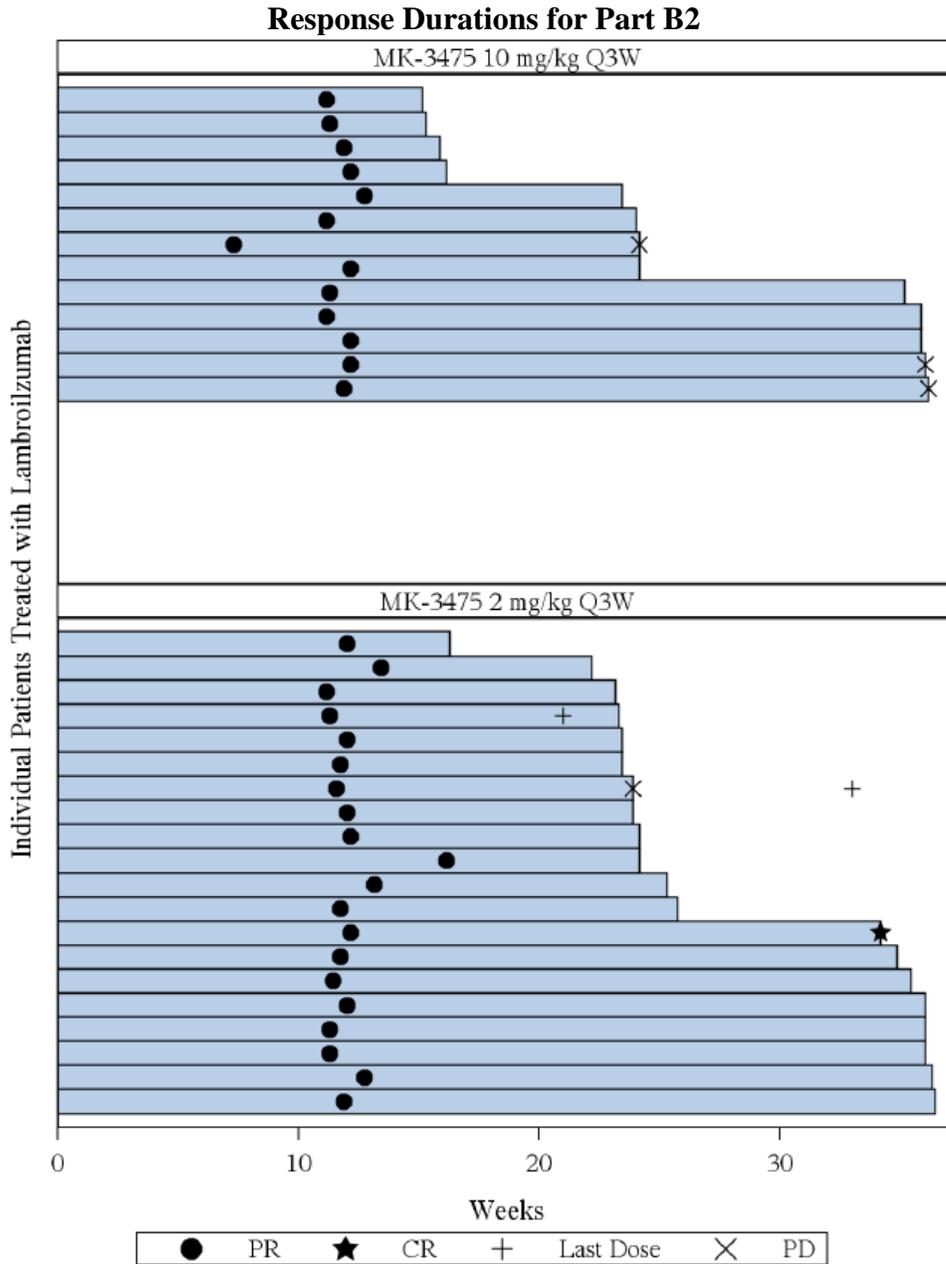
For Part B2, the primary endpoint is confirmed ORR [complete response (CR) plus partial response (PR)] per RECIST 1.1 as assessed by blinded central reviewers. With 80 IPI-refractory patients at each dose level, Part B2 has approximately 85% power to detect a 15% difference in response rate between the two doses at the 10% type I error rate (one-sided) assuming an ORR of 10% in the inferior arm. A p-value of 10% approximately corresponds to a 7% empirical difference in response rate.

### *Part B2 Results*

A total of 173 patients received at least one dose of MK-3475 in Part B2, 89 patients in the MK-3475 2 mg/kg arm and 84 patients in the MK-3475 10 mg/kg arm. The objective response data are based on the full analysis set (FAS) population which consists of patients who had at least

one measurable lesion at baseline by independent central review, i.e., 79 patients on the MK-3475 2 mg/kg arm and 74 patients on the MK-3475 10 mg/kg arm.

Merck states that the initial BLA submission will contain 28-weeks of follow-up for 47 (59%) of the 79 patients in the MK-3475 2 mg/kg arm and for 26 (35%) of the 74 patients in the MK-3475 10 mg/kg arm. All patients in Part B2 were followed for a minimum of 16 weeks. The confirmed ORR as assessed by independent central review was 25% (95% CI: 16-36%) in the MK-3475 2 mg/kg arm and 18% (95% CI: 15-29%) in the MK-3475 10 mg/kg arm. On the MK-3475 2 mg/kg arm, there were 20 partial responses (PRs) with median duration of response that was not reached (range 4+ to 25+ weeks). On the MK-3475 10 mg/kg arm, there were 13 PRs with a median duration of response of 24 weeks (range 4+, 25+) weeks. Twenty-nine of the 33 PRs were ongoing. There were no complete responses (CRs) in either arm. The following Figure presents the duration of responses in Part B2.



Database Cutoff Date: 26JUL2013

Source: Merck October 18, 2013, response to an FDA information request dated October 17, 2013.

Merck states that responses to MK-3475, like other immunotherapies, can be delayed. Initial analyses of results from Part B1 suggested that approximately 70% of objective responses were first identified by independent central review by Week 12, over 90% of responses were first identified by Week 24, and occasionally very late responses were first identified beyond Week 24 (for example, approximately Week 48). Merck states that, for this reason, an analysis of responses that would be first detected at Week 12 and confirmed at Week 16 would underestimate the true rate of response to MK-3475.

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The response rates based on independent central review assessments for patients with at least 28-week follow-up are 34% (95% CI: 21-49%) of the IPI-refractory patients treated at 2 mg/kg Q3W and 27% (95% CI: 12-48%) of patients treated at the 10 mg/kg Q3W dose.

***Additional Efficacy Data Intended to Support Accelerated Approval of MK-3475***

**Objective Response Rate and Duration of Response Across Part B1, Part B2, and Part D**

Parts B1 and D will be submitted as supportive efficacy data. Part B1 consists of 48 additional IPI-treated melanoma patients. The overall response rate for the IPI-treated patients in Part B1 was 27% (95% CI: 12-48%) for patients who received the 10 mg/kg Q3W dose. Part D consists of all IPI-naïve patients and the overall response rate was 40% at 2 mg/kg Q3W, 37% at 10 mg/kg Q3W, and 49% at 10 mg/kg Q2W.

The following Tables summarize the response rates and duration of responses of MK-3475 in advanced melanoma patients in Parts B1, B2, and D.

**Summary of Overall Response Rates (ORR) for MK-3475 in Advanced Melanoma Patients Receiving 2 or 10 mg/kg every 3 weeks**

Study Population	2 mg/kg Q3W		10 mg/kg Q3W		Total	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
<b>IPI-EXPOSED PATIENTS</b>						
IPI-refractory, Part B2 all FAS*	<b>79</b>	<b>25 (16, 36)</b>	74	18 (10, 28)	153	22 (15, 29)
IPI-refractory, Part B2 with 28 weeks of follow-up	47	34 (21, 49)	26	27 (12, 48)	73	32 (21, 43)
IPI-treated, Part B1	0	--	26	27 (12, 48)	26	27 (12, 48)
<b>IPI-NAÏVE PATIENTS (all patients followed for &gt;28 weeks)</b>						
IPI-naïve, Part D	45	33 (20, 49)	47	36 (23, 52)	92	35 (25, 45)
IPI-naïve, Part B1	20	40 (19, 64)	19	37 (16, 62)	39	38 (23, 55)

\*FAS: Full Analysis Set

Note: Primary efficacy population in support of accelerated approval is bolded and highlighted

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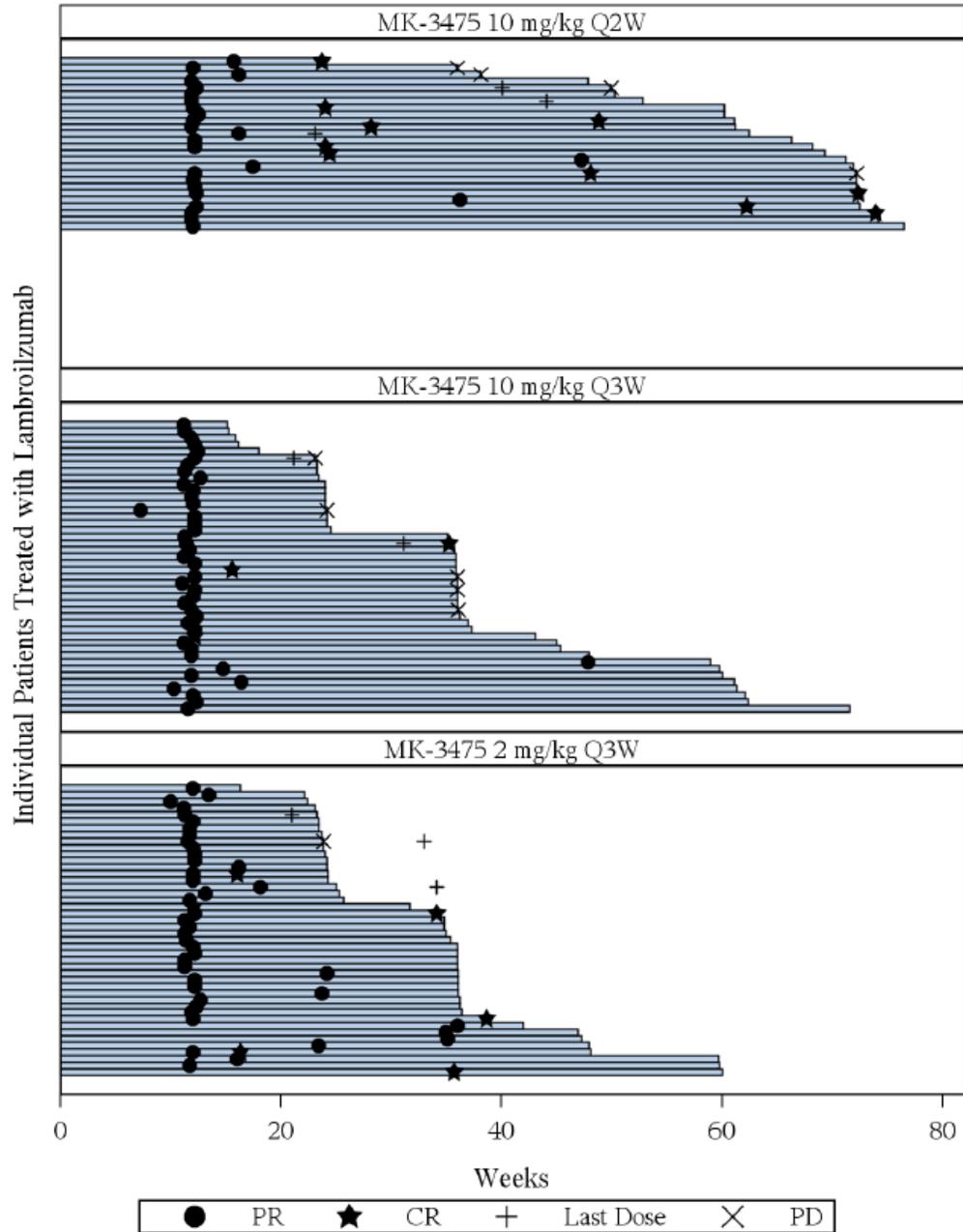
Study Population	Response Duration (weeks)		Confirmed ORR, N	PD events N	Response Ongoing (%)
	Median	Range			
<b>IPI-EXPOSED PATIENTS</b>					
IPI-refractory, Part B2 all FAS (N=153)	NR	4+-25+	33(22%)	4	88%
<b>IPI-refractory, Part B2 at 2 mg/kg Q3W dose (N=79)</b>	<b>NR</b>	<b>4+-25+</b>	<b>20(25%)</b>	<b>1</b>	<b>95%</b>
IPI-refractory, Part B2 with 28 weeks (N=73)	NR	8+-25+	23(32%)	4	83%
<b>IPI-refractory, Part B2 with 28 weeks at 2 mg/kg Q3W dose (N=47)</b>	<b>NR</b>	<b>8+-25+</b>	<b>16(34%)</b>	<b>1</b>	<b>94%</b>
IPI-treated, Part B1 (N=40)	NR	12+-62+	15(38%)	1	93%
<b>IPI-NAÏVE PATIENTS (ALL PATIENTS FOLLOWED FOR &gt;28 WEEKS)</b>					
IPI-naïve, Part D (N=92)	NR	6+-27+	32(35%)	2	94%
IPI-naïve, Part B1 (N=76)	NR	8+-65+	33(43%)	5	85%
<b>POOLED DATA</b>					
All melanoma patients in FAS population (N=361)	Not done	4+ - 65+	113	12	89%
All melanoma patients with >28 weeks follow-up (N=281)	Not done	8+ - 65+	103	12	88%

Abbreviations in table: Ipi, ipilimumab; NR, not reached

Note: Primary efficacy population in support of accelerated approval is bolded and highlighted

The duration of responses, displayed in the following bar graph, were submitted separately on October 18, 2013, in response to an FDA information request dated October 17, 2013

**Response Durations for Parts B1, B2, and D Combined**



Database Cutoff Date: 26JUL2013

Source: Merck October 18, 2013, response to an FDA information request dated October 17, 2013.

**Safety**

Merck plans to summarize safety from 411 patients with an average of 182 days on study (1-596 days) which includes IPI-refractory (B2, N=173), IPI-treated (Part B1, N=48), and IPI-naïve (Part D, N=103; Part B1, N=87). The safety population of Part B2 includes 173 IPI-refractory

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patients (randomized by dose) with an average of 136 days on treatment (range 1 to 337). Supportive safety results from Parts A, B1, B2, C, and D, as well as integrated across the cohorts, will be included in the BLA submission. The Table below summarizes the adverse events in Part B2:

**Adverse Event Summary for Part B2 Patients (All Patients as Treated)**

	MK-3475 2 mg/kg Q3W		MK-3475 10 mg/kg Q3W		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	89		84		173	
with one or more adverse events	87	(97.8)	79	(94.0)	166	(96.0)
with no adverse event	2	(2.2)	5	(6.0)	7	(4.0)
with drug-related <sup>†</sup> adverse events	70	(78.7)	61	(72.6)	131	(75.7)
with serious adverse events	23	(25.8)	21	(25.0)	44	(25.4)
with serious drug-related adverse events	7	(7.9)	2	(2.4)	9	(5.2)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued <sup>‡</sup> due to an adverse event	4	(4.5)	6	(7.1)	10	(5.8)
discontinued due to a drug-related adverse event	3	(3.4)	1	(1.2)	4	(2.3)
discontinued due to a serious adverse event	3	(3.4)	4	(4.8)	7	(4.0)
discontinued due to a serious drug-related adverse event	3	(3.4)	1	(1.2)	4	(2.3)

*Confirmatory Trials*

Merck is conducting the following confirmatory trials:

- PN002 is a randomized (1:1:1) Phase 2 trial comparing two dose levels (2 mg/kg and 10 mg/kg Q3W) of MK-3475 to physician's choice chemotherapy in 510 patients with unresectable and metastatic (advanced) melanoma who have progressed after previous treatment with IPI, including patients also treated with a BRAF or MEK inhibitor, if indicated. The primary objectives are to compare progression-free survival (PFS) and overall survival (OS) of MK-3475 versus chemotherapy.
- PN006 is a randomized (1:1:1), active-controlled, open-label, three-arm Phase 3 trial comparing MK-3475 10 mg/kg Q2W, MK-3475 10 mg/kg Q3W, and IPI 3 mg/kg Q3W for four doses, in 645 patients with advanced melanoma who have not been previously treated with IPI. The co-primary endpoints of the trial are PFS and OS.

FDA preliminary comments were emailed to Merck on October 23, 2013. Merck notified FDA via email on October 24, 2013, that they wanted to discuss Questions 3, 4, 5, 11, 13, 15 and 17.

**SPONSOR QUESTIONS AND FDA RESPONSES****Nonclinical**

1. *During discussions with the Agency on December 18, 2012, and April 22, 2013, the Agency indicated that the non-clinical package (pharmacology, pharmacokinetics, and toxicology) was adequate to support licensure of a marketing application for MK-3475 in patients with advanced malignancies. Further, the Agency concurred that a Developmental and Reproductive Toxicity (DART) study was not required for registration of MK-3475 based on the risk on reproductive function. Based on the feedback previously obtained from the Agency, Merck proposes that the non-clinical package (pharmacology, pharmacokinetics, and toxicology) is adequate to support the marketing application for MK-3475. Does the Agency concur?*

**FDA Response:**

The nonclinical package described (demonstration species-specificity to support the relevance of the chosen toxicological model; toxicological assessment with demonstrated maintenance of pharmacokinetic and/or toxicokinetic exposure through at least 3 months) would be sufficient to support registration of MK-3475. It should be noted, however, that the adequacy of the data to support a marketing application for MK-3475 will be made following a review of the reports submitted in the BLA.

Due to its mechanism of action and the assessment that Merck provided previously, MK-3475 is expected to induce spontaneous abortion in pregnant animals and humans, and this risk will be communicated in the label. For the proposed indication, FDA agrees that an embryo-fetal study is not required prior to submission of the BLA. If MK-3475 is developed in other therapeutic areas, or if clinical safety data suggest a need to further elucidate the effect of MK-3475 in the developing fetus, an embryo-fetal development study may be requested as a post-marketing requirement.

**Discussion:**

Merck did not have any questions or comments.

**Clinical Pharmacology**

2. *Does the Agency agree that the available electrocardiograms (ECG) data at the time of the initial BLA submission and the additional ECG data from the Part F patients at the time of the Safety Update Report are adequate to evaluate the potential of MK-3475 to significantly prolong the QTc interval and to support the filing and registration of MK-3475?*

**FDA Response:**

Yes, we agree.

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Merck did not have any questions or comments.

**Clinical**

*Merck proposes to submit a BLA for MK-3475 in late December 2013, for the proposed indication in melanoma patients previously treated with IPI, based predominantly on results of Part B2 in study PN001. Part B2 includes 173 IPI-refractory melanoma patients randomized to receive treatment with MK-3475 at either 2 or 10mg/kg Q3W with a minimum follow-up of 16 weeks, with approximately half of the cohort followed for 28 weeks or more. Merck proposes to submit an efficacy update in February 2014 (data cutoff of October 18, 2013) of the 173 patient Part B2, when all patients will have at least 28 weeks of follow-up.*

3. *Does the Agency agree that the planned organization and presentation of the safety and efficacy results from the MK-3475 clinical development program are adequate to support the filing and review of MK-3475 for the treatment of melanoma patients previously treated with IPI?*

FDA Response:

FDA does not agree with Merck's proposal. See FDA's response to Question 4.

Although the design and reported results of PN001 based predominantly on Part B2, with the proposed supportive data, appear sufficient to support the filing of the BLA from a clinical perspective, the proposal to present only partial efficacy results from Part B2, the "key patient population to support the proposed label indication", in the initial BLA submission would not allow for a comprehensive review and decision on the application.

Additionally, the proposal to organize the BLA and present the BLA efficacy data based on primary efficacy analyses using the full analysis set population (N=361) which is a heterogeneous population—e.g., patients with IPI-naïve, IPI-treated, and IPI-refractory melanoma and who received MK-3475 at two dose levels (2 mg/kg or 10 mg/kg) and on two dose schedules (every 2 or 3 weeks)—is not an adequate organization and presentation of the data to permit an expedited review.

In general, the organization of the BLA, including the clinical study report, integrated summaries of efficacy and safety, and trial datasets, should primarily focus on presentation and discussion of the data from the patient population that supports the indication.

However, include integrated (side-by-side) and/or pooled analyses of the data from Parts B1 and Part D of PN001, and a thoughtful discussion of the results within the integrated summaries of efficacy and safety, to support the conclusion that data from Part B2

represents substantial evidence of a MK-3475 treatment effect that is reasonably likely to predict clinical benefit.

Furthermore, the primary analysis for ORR should be performed based on the modified intent-to-treat population defined as all patients treated with MK-3475.

Discussion:

FDA stated that data from the patient population in Part B2 in PN001 with a data cutoff of October 18, 2013, for both efficacy and safety, will serve as the primary basis of the clinical review for the proposed indication. However, FDA stated that it was acceptable for Merck to submit a Clinical Study Report (CSR) in Module 5 with a data cut-off of July 26, 2013, for Parts B1, B2, D, as the initial clinical portion of the rolling BLA. Merck will then submit an updated CSR with an appendix for updated data from Part B2 with a data cut-off of October 18, 2013.

For the last clinical portion of the rolling BLA, Merck will submit Sections 2.5, 2.7.1, 2.7.2, 2.7.3, and 2.7.4 in Module 2 and an Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) in Module 5 with data cutoffs of July 26, 2013, for Parts B1, and D, and October 18, 2013, for Part B2, to include side-by-side and pooled analyses. FDA agreed to this approach.

Merck proposed that the primary efficacy analysis of ORR be performed in the Full Analysis Set (FAS) population who are patients who have centrally measurable disease. The FAS population includes 88% of the study population. FDA stated that Merck may provide an analysis of ORR based on the FAS population; however, FDA's primary analysis of ORR will be based on the modified ITT population.

See also discussion for Question 15.

4. *Does the Agency agree with Merck's proposal to update the efficacy results (ORR) from Part B2, as well as provide updated overall survival data from Parts B1, B2, and D in February 2014?*

FDA Response:

No. Under the PDUFA V program, FDA cannot agree to accept an application that does not contain all the information to allow a comprehensive review and decision on the application, with the exception of required safety and stability updates.

Per the meeting package, only 47/79 (59%) patients in the 2 mg/kg every three weeks cohort will have evaluable response data at 28 weeks at the time of the proposed BLA submission in late December 2013. FDA notes that the statistical analysis plan in Protocol Amendment 8 states that the efficacy analysis will be based on patients with at least 28 weeks of follow-up. Therefore, the final results from the data cut-off of October 18, 2013, will form the basis of the efficacy review for the BLA submission.

However, please consider the following options to accelerate the timeline for submitting an application for MK-3475 that is complete at the time of the initial submission, i.e., efficacy results based on the October 18, 2013, data cutoff date:

- Proceed with an initial BLA submission of MK-3475 in December 2013, but present the data based on an October 18, 2013, data cutoff.
- Submit the BLA components under Rolling Review with the final efficacy data submitted in February 2014.

Discussion:

Merck agreed that the final Part B2 efficacy and safety addendum with a data cutoff date of October 18, 2013, will be the final portion of the rolling BLA and will start the review clock.

See discussion for Question 15.

5. *Does the Agency agree with Merck's proposal to submit the Safety Update Report with data cutoff of October 18, 2013, in February 2014?*

FDA Response:

See FDA responses to Questions 3 and 4.

Discussion:

Merck stated the Safety Update Report with a data cut-off of December 31, 2013, for Parts B1, B2, and D will be submitted 60 days after the final portion of the rolling BLA is submitted. FDA stated that this was acceptable.

6. *The preBLA background document discussion is focused on the unmet medical need of metastatic melanoma patients who have been previously treated with IPI. However, our current data indicate similar clinical benefit in the IPI-naïve patient population as well (including similar response rates, durability of response and preliminary survival data compared to the IPI-refractory population). Does the Agency agree that the result observed in the IPI-naïve population would support a broader indication given the unmet medical need in 1L/2L metastatic melanoma patients?*

FDA Response:

PN001 appears inadequate in design to support a broad indication which includes patients who have not received standard therapy i.e., IPI-naïve patients.

In the absence of additional evidence from a randomized trial, such as PN006, a randomized, active-controlled, multicenter trial evaluating MK-3475 compared to ipilimumab, FDA does not agree with the following rationale provided for Merck's

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conclusion that results from PN001 provide substantial evidence that MK-3475 addresses an unmet medical need in the IPI-naïve patient population (where there is available therapy): MK-3475 provides “efficacy similar to those of available therapy, while avoiding serious toxicity that occurs with available therapy” and MK-3475 is “a drug with a novel mechanism of action (but comparable safety and effectiveness).”

Discussion:

Merck did not have any questions or comments.

7. *Foreign clinical data from global clinical sites will be included in support of this filing without a formal ethnic sensitivity report. Does the Agency concur with Merck’s proposal that an ethnic sensitivity report is not required to support the filing and registration of MK-3475?*

FDA Response:

Yes.

Discussion:

Merck did not have any questions or comments.

## Safety

8. *Does the Agency agree with Merck’s approach to describing adverse events that are potentially immune-related?*

FDA Response:

The approach to describing adverse events is acceptable. Additionally, the BLA submission should provide the list of MedDRA Preferred Terms mapped to the HLT, HLTG, and SOC, similar to what Merck provided in Appendix 3 of the meeting package.

Discussion:

Merck did not have any questions or comments.

9. *Based on the current data, the safety profile of the product appears to be acceptable relative to current cytotoxic or immune therapies for melanoma. Therefore, Merck proposes not to prepare a REMS or submit an RMP. Does the Agency agree that a REMS and/or RMP would not be required in the BLA?*

FDA Response:

Based on the information provided in the meeting package, FDA agrees with Merck’s proposal not to include a REMS in the initial BLA submission. Please note that during the review of the BLA, FDA may identify safety information that would require Merck to prepare a REMS, if necessary to ensure that the benefits of the drug outweigh the risks.

Discussion:

Merck did not have any questions or comments.

**Imaging**

10. Merck has retained an imaging core lab, (b) (4) to manage the independent radiology and oncology review for study PN001. The imaging reads are performed under an Imaging Review Charter (IRC) which was previously submitted with the IND. The radiology review is intended to determine the following endpoints for each subject:

- Best Overall Response
- Time point of Best Overall Response
- Time point of Best Overall Response Confirmation
- Time point of Progression

Following the independent radiology review, a clinical review is conducted by an independent oncologist. The same endpoints listed above are determined by the independent oncologist as an integrated response of both the radiology assessment and pre-specified clinical data. These results will be used for the response assessments to support the primary efficacy endpoints using RECIST 1.1.

Merck will adhere to the guidance from the FDA regarding data format and content following the April 22, 2013, meeting. Specifically, Merck is planning to submit imaging data sets for Lesion assessment/Response to include:

- Investigator (INV) per RECIST 1.1 criteria for Cohort A only, per protocol
- INV per irRC criteria for other cohorts
- Independent Review based on independent radiologist and oncologist (IRO) per RECIST 1.1
- Independent Review based on global IRO per RECIST 1.1

In addition, Merck will provide the raw lesion assessment datasets and include the following:

- Unique patient identifier
- Scheduled/unscheduled visits (visit number, visit data, reviewer ID)
- Type of lesion [target or non-target (unequivocal progression and equivocal progression, disappear)]
- Lesion organ, location, longest diameter (with unit), method of assessment (CT, MRI, photographic), criteria (RECIST 1.1 or irRC), target lesion, target lymph

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*node shortest axis, target lymph node shortest axis <10 mm, type of new lesions (unequivocal or equivocal), and evaluator*

*Merck proposes to not submit the images with the BLA. During review of the BLA, upon Agency request, the Sponsor/ (b) (4) will provide requested images and data along with relevant computer systems and support from the imaging vendor to view these images. Alternatively, the Sponsor/ (b) (4) can provide requested images of a subset of patients on a laptop or CD with the BLA.*

*Does the Agency agree with this proposal?*

FDA Response:

Yes. Please note that the raw data used by the independent oncologist in the determination of the integrated response assessment must be captured and submitted in the BLA efficacy datasets. For example, if the independent oncologist uses measurements of subcutaneous tumors in the integrated assessment of tumor response, these measurements must be provided in the datasets at each tumor response evaluation time point.

Discussion:

Merck did not have any questions or comments.

**Office of Scientific Investigations (OSI)**

11. *Merck plans to provide site level datasets in the BLA to aid OSI in identifying clinical trial sites for inspections for the MK-3475 trial. This information will be consistent with the FDA document “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” with two exceptions:*

- *Financial disclosure information will not be included in the summary level dataset since this information is sensitive and has extremely limited distribution within Merck. Note that this information is provided by a separate group within Merck and will be available within a section of the BLA.*
- *Once OSI has selected sites for inspection and informed Merck, Merck will submit site specific individual data listings.*

*Does the Agency agree that the proposal regarding OSI with no financial disclosure information provided will satisfy OSI requirements?*

FDA Response:

It is acceptable to exclude the financial disclosure information in this dataset and note that this information is provided within another section of the BLA. Of note,

ALL other variables described in the draft Guidance are needed in order for the submitted dataset to be utilized in CDER's Clinical Site Selection Tool.

OSI requests that the items in Attachment 1 be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe the location or provide a link to the requested information.

Site-specific individual data listings for the pivotal study may be submitted prior to the submission of the BLA, but no later than the final component, of the BLA, for all clinical study sites that enrolled subjects in the pivotal study. Provision of complete information as requested in Parts I and II will facilitate, and more importantly accelerate, development of clinical investigator and sponsor/monitor/CRO inspection assignments and the preparation of the inspection-supporting background packages. In order for the application to be considered complete at submission, it should contain elements that fully address Part I (General Study Related Information and Comprehensive Clinical Investigator Information) and Part II (Subject Level Data Listings by Site) of the OSI Pre-NDA/BLA Request (See Attachment 1).

Part III of the OSI Pre-NDA/BLA Request (Attachment 1) offers an opportunity for Merck to also provide an electronic submission of Site Level Dataset on or prior to the complete submission of the BLA. This Site Level Dataset is used in CDER's Clinical Site Selection Tool. Electronic submission of the Site Level Dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application review process. If Merck wishes to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning," available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> for the structure and format of this dataset.

Attachment 2 provides instructions for where OSI requested items should be placed within an eCTD submission.

Discussion:

Merck stated that all data in the Request for Subject Level Data Listings by Site in OSI Attachment 1 will be included in the SAS transport file. Merck asked if OSI can directly use the SAS transport files to find subject level data listing or is it sufficient to provide a Clinical Site Data Elements Summary Listing (DE)?

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FDA stated that the Subject Level Data Listings by Site need to be segregated by site and provided in PDF format. Merck can submit this information before the BLA submission if they wish.

### Datasets

12. *Does the Agency agree with the proposed file formats and the approach regarding the SDTM data sets?*

FDA Response:

Yes.

Discussion:

Merck did not have any questions or comments.

### Statistics

13. *Does the Agency agree that the proposed Statistical Review Aid is adequate to support the BLA submission?*

FDA Response:

Yes. In addition, please provide a Define.pdf file which contains data definitions of the STDM tabulate data sets and variables.

Discussion:

Merck asked if FDA wanted Merck to provide a Define.xml file as they normally do, or both Define.xml and Define.pdf? FDA stated that both Define.xml and Define.pdf are needed.

### Case Report Forms

14. *Does the Agency concur with the submission plans for CRFs?*

FDA Response:

No. Case report forms should be provided for all deaths occurring within 90 days of last study medication, all serious adverse events, and all study discontinuations for reasons other than disease progression.

Discussion:

Merck did not have any questions or comments.

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15. *Based on the proposed schedule to file the BLA on December 23, 2013, would the FDA agree to accept a rolling BLA submission?*

**Table 14 Rolling Submission Timeline of Reviewable Units**

Reviewable Units [eCTD Module(s)]	Expected Submission Date
Nonclinical Toxicology Reviewable Unit <ul style="list-style-type: none"> <li>Module 4 (Nonclinical Study Reports) including Nonclinical Overview (Section 2.4) and Nonclinical Written and Tabulated Summaries (Section 2.6)</li> </ul>	November 1, 2013
Chemistry, Manufacturing and Controls Reviewable Unit Clinical Reviewable Unit and Administrative Information <ul style="list-style-type: none"> <li>Module 1 (Administrative Information)</li> <li>Module 3 (Quality) and Quality Overall Summary (Section 2.3)</li> <li>Module 5 (Clinical Study Reports) and Clinical Overview (Section 2.5) and Clinical Summary (Section 2.7)</li> </ul>	December 23, 2013
Chemistry, Manufacturing and Controls Process Performance Qualifications for one Prospective batch	January 23, 2014
Efficacy update including Part B2 follow-up efficacy data and survival data from parts B1, B2, and D Safety Update Report – includes QT study report	February 23, 2014

**FDA Response:**

FDA does not object to the proposed submission dates; however, FDA considers the application complete upon receipt of the last component necessary to conduct a substantive review of the application which is February 2014. See FDA responses to Questions 3 and 4.

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Discussion items are in red.

**Proposal for BLA Rolling Submission (slide 3 of Merck's presentation)**

Reviewable Units [eCTD Module(s)]	Expected Submission Date
Nonclinical Toxicology Reviewable Unit <ul style="list-style-type: none"> <li>Module 4 (Nonclinical Study Reports) including Nonclinical Overview (Section 2.4) and Nonclinical Written and Tabulated Summaries (Section 2.6)</li> </ul>	November 1, 2013
Chemistry, Manufacturing and Controls Reviewable Unit Clinical Reviewable Unit and Administrative Information <ul style="list-style-type: none"> <li>Module 1 (Administrative Information)</li> <li>Module 3 (Quality) and Quality Overall Summary (Section 2.3)</li> <li>Module 5 Clinical Study Reports – July 26, 2013 cutoff</li> </ul>	December 23, 2013
Chemistry, Manufacturing and Controls Process Performance Qualifications for one Prospective batch Module 5 CSR Final B2 Efficacy & Safety Addendum – October 18, 2013, cut-off	Late January 2014 New proposal to submit Part B2 with Oct. 18, 2013, data cutoff date prior to submission of Section 2 summaries
Sections 2.5, 2.7.1, 2.7.2, 2.7.3, & 2.7.4, ISS, ISE (July 26 cutoff other cohorts, Oct. 18 cutoff B2 cohort, pooled from July 26, side by side comparison with Oct. 18 B2 vs. other cohorts July 26)  QT study report  Additional scenario – provide CSR with B2 + all cohorts with Oct. 18 cut-off. Module 2 summaries with all Oct. 18 data.	TBD – this last piece will start the PDUFA clock
120 day Safety Update – December 31, 2013 cut-off	TBD

FDA advised Merck to submit a proposed schedule as an IND amendment and that FDA would respond to Merck's proposal in writing. Therefore, the proposed November 1, 2013, submission of the nonclinical module is not acceptable as the schedule must be agreed to before Merck can

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submit any component of the BLA. Merck expressed understanding and said that they would submit a proposal.

16. *In alignment with breakthrough designation, Merck will request a priority review for MK-3475, however based on the proposed content of the BLA which includes a single efficacy CSR, would the Agency be able to provide an estimated review timeline and if an advisory committee meeting would be needed?*

FDA Response:

The review timeline (priority vs. standard) and need for an advisory committee meeting will be determined during review of the BLA submission. Please refer to 21<sup>st</sup> Century Review Process which can be accessed at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf>.

Discussion:

Merck did not have any questions or comments.

## **ADDITIONAL FDA COMMENTS**

### **Clinical**

17. Provide a list of clinical investigators who participated in Parts B1, B2, and D of PN001 as an IND amendment. Include contact information (address and telephone number).

### **Clinical Pharmacology**

18. Address the following clinical pharmacology related questions in the Summary of Clinical Pharmacology Studies in Module 2 of the BLA submission:
- a. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
  - b. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
  - c. What are the exposure-response relationships (dose-response, exposure-response) for safety?
  - d. What are the pharmacokinetic characteristics of MK-3475?

- e. What influence do the intrinsic factors (as listed below but not limited to) have on MK-3475 exposure and its pharmacodynamic responses? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
  - 1) gender
  - 2) race
  - 3) weight
  - 4) disease
  - 5) genetic polymorphism
- f. What influence do the extrinsic factors (e.g., concomitant medications, etc.) have on MK-3475 exposure and its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- h. What is the impact of immunogenicity on MK-3475 exposure and its pharmacodynamic response? What is their clinical impact?

Discussion:

Merck did not have any questions or comments.

19. Regarding the format and content related to clinical pharmacology sections of the BLA submission:
- a. Submit bioanalytical method(s) and validation reports for clinical pharmacology studies.
  - b. Submit the methods and validation reports for assays used for the detection of anti-product antibodies.
  - c. Provide complete datasets for clinical pharmacology studies. The datasets should not be limited to pharmacokinetics (PK) and pharmacodynamics (PD). For example, domains related to safety (e.g., adverse events) and efficacy, demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.
  - d. Provide all concentration-time and derived PK parameter datasets as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- e. Present the PK parameter data as geometric mean with coefficient of variation (and mean  $\pm$  standard deviation) and median with range as appropriate in the study reports.
- f. Provide a table listing of patients with renal or hepatic impairment who have received MK-3475, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLcr calculated by the Cockcroft Gault equation or eGFR calculated by MDRD, AST/ALT, or total bilirubin for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.
- g. Submit the following datasets to support the population PK analysis:
  - 1) SAS transport files (\*.xpt) for all datasets used for model development and validation.
  - 2) Description of each data item provided in a Define.pdf file (any concentrations and subjects that have been excluded from the analysis should be flagged and maintained in the datasets).
  - 3) Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (submit these files as ASCII text files with \*.txt extension [e.g., myfile\_ctl.txt, myfile\_out.txt]).
  - 4) Model development decision tree and/or table which gives an overview of modeling steps.
- h. For the population analysis reports, submit:
  - a. Standard model diagnostic plots.
  - b. Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line.
  - c. Model parameter names and units in tables [for example, oral clearance should be presented as CL/F (L/h) and not as THETA(1)].
  - d. Summary of the report describing the clinical application of modeling results.

For more information, refer to the following pharmacometric data and models submission guidelines at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

- i. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for MK-3475 and include the results of this exploratory analysis in the BLA submission.

For more information, refer to the FDA Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

- j. Submit the following items for QTc study/assessment:
  - 1) QT/QTc study protocol
  - 2) Investigator's Brochure
  - 3) Annotated CRF
  - 4) Define file which describes the contents of the electronic data sets
  - 5) Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
  - 6) ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
  - 7) Highlights of Clinical Pharmacology Table

Discussion:

Merck stated that they plan to provide the requested information in Module 2.7.2. FDA agreed to this approach.

20. Provide adequate justification in the BLA to support the proposed weight-based dosing regimen.

Discussion:

Merck did not have any questions or comments.

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Type B**ADDITIONAL DISCUSSION ITEM**

21. FDA asked if Merck could launch based on (b) (4) supply alone, and Merck noted that in order to support launch and continuous supply both (b) (4) were needed. Merck committed to provide supply information regarding the potential shortages and supply needs for (b) (4) to support launch. Merck agreed to provide the SAE line listings from PN006 to support (b) (4) patient safety. See slides 15 and 16 from Merck's presentation.

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.

Merck will submit a proposed schedule for a rolling BLA.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that based on the information provided in the meeting package, FDA agrees with Merck's proposal not to include a REMS in the initial BLA submission. Please note that during the review of the BLA, FDA may identify safety information that would require Merck to prepare a REMS, if necessary to ensure that the benefits of the drug outweigh the risks.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Merck stated its intent to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, FDA notes that a CMC pre-submission meeting was held on October 24, 2013. FDA refers Merck to the minutes of that meeting for any additional agreements that may have been reached.

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, Merck is exempt from these requirements. If there are any changes to the development plans that would cause the application to trigger PREA, Merck's exempt status would change.

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In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

**ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Submit a letter to the IND of the proposed rolling BLA schedule	Merck	Submitted 11-13-2013
Provide a list of clinical investigators who participated in Parts B1, B2, and D of PN001 as an IND amendment. Include contact information (address and telephone number).	Merck	TBD

**ATTACHMENTS AND HANDOUTS**

OSI Attachment 1  
OSI Attachment 2  
Merck's Presentation

## Office of Scientific Investigations Attachment 1

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

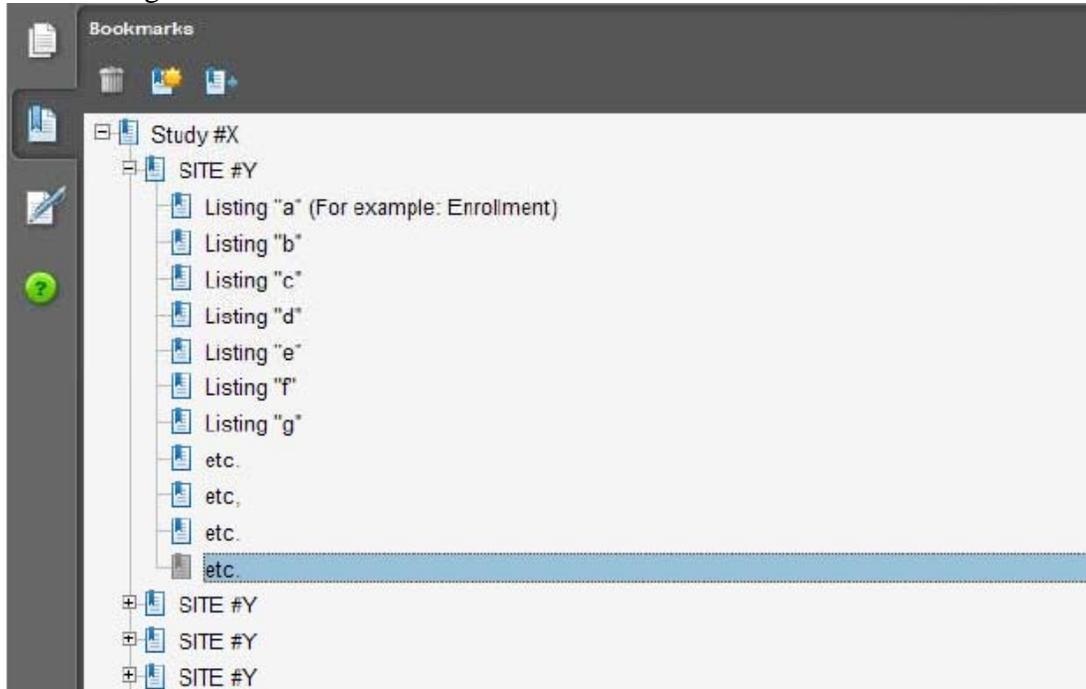
1. Please include the following information in a tabular format in the original BLA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original BLA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the BA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

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

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



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” available at

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> for the structure and format of this data set.

## Office of Scientific Investigations Attachment 2

### Technical Instructions:

### Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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



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

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

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References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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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  
11/19/2013



IND 110080

**MEETING MINUTES**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Worldwide Regulatory Affairs  
126 E. Lincoln Avenue, RY33-227  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-3475.

We also refer to the meeting between representatives of your firm and the FDA on October 24, 2013. The purpose of the meeting was to discuss the CMC specific content and format of the planned BLA submission and the overall clinical and commercial supply strategy for the program.

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

If you have any questions, call Lyndsay Hennessey, Regulatory Project Manager, at (240) 402-3746.

Sincerely,

*{See appended electronic signature page}*

Rashmi Rawat, Ph.D.  
Team Leader  
Division of Monoclonal Antibodies  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** CMC pre-BLA

**Meeting Date and Time:** October 24, 2013 from 1-2 P.M. Eastern Standard Time (EST)  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 21, Conference Room: 1537  
Silver Spring, Maryland 20903

**Application Number:** 110080  
**Product Name:** MK-3475  
**Indication:** Neoplasm malignancy  
**Sponsor/Applicant Name:** Merck Sharp & Dohme Corp.

**Meeting Chair:** Rashmi Rawat, Ph.D.  
**Meeting Recorder:** Lyndsay Hennessey

**FDA ATTENDEES**

Sarah Kennett, Ph.D.	Review Chief, DMA
Rashmi Rawat, Ph.D.	Team Lead, DMA
Mark Paciga, Ph.D.	Product Quality Reviewer, DMA
Lyndsay Hennessey	Regulatory Project Manager, OBP
Patricia Hughes, Ph.D.	Team Lead, BMAB
Reyes Candau-Chacon, Ph.D.	Microbiology Reviewer, BMAB
Patricia Keegan, M.D.	Division Director, DOPII
Marc Theoret, M.D.	Team Lead, DOPII
Jennie Chang, M.D.	Clinical Reviewer, DOPII
Meredith Chuk, M.D.	Clinical Reviewer, DOPII

## **SPONSOR ATTENDEES**

Nikhil Mehta, Ph.D.	Vice President, Worldwide Regulatory Affairs
Andrew Robertson, Ph.D., J.D.	Director of Regulatory Policy
Heimen Kooy, MSc	Associate Director CMC Regulatory, Biologics
Kimberly May, Ph.D.	Director, Bioprocess Development
Gargi Maheshwari, Ph.D.	Director, Project Leadership, Biologics Mfg. Sci. & Comm.
Ronald Smulders, Ph.D.	Executive Director Analytical Development and Validation Department
Marc Bastiaansen, Ph.D.	Director, Program Management
Scott W. Hooper, Ph.D.	Associate Director, Engineering
Parimal Desai, Ph.D.	Associate Vice President, Engineering
Colleen S. Hutter	Director, Engineering, Packaging Technology
Ann Niland	Director, Quality Assurance
David Robinson, Ph.D.	Executive Director, Regulatory Affairs/Biologics & Vaccines
Maureen D. Skowronek	Vice President, Quality Control
Carolyn Wightman, Ph.D.	Director, Supply Chain Management

## **1.0 BACKGROUND**

- (i) Purpose of meeting: to discuss the CMC specific content and format of the planned BLA submission and the overall clinical and commercial supply strategy for the program
- (ii) Names of drug: MK-3475
- (iii) Brief history of events: three previous CMC meetings were held for MK-3475:
  - a. April 2, 2013 Type B: to discuss the manufacturing strategy with respect to comparability of the results and bridging data
  - b. June 11, 2013 Type A: to discuss the comparability and stability plans
  - c. August 27, 2013 Type C: to discuss the Fab-arm exchange data, analytical strategy for HCP and potency assay, viral clearance strategy, process performance qualification for Drug Substance and Drug Product, and reference material strategy
  - d. An interdisciplinary pre-BLA Meeting is scheduled for October 25, 2013
- (iv) Product development: MK-3475 has been designated breakthrough therapy
- (v) Expected outcome for the meeting: To gain concurrence from the Agency on the CMC-specific content and format of the planned BLA submission

## 2.0 DISCUSSION

### 2.1. Comparability of [REDACTED] (b) (4)

**Question 1:** Based on the Agency's review of the analytical comparability results submitted, and assuming that the results to be included in the BLA remain supportive, does the Agency agree that the results adequately demonstrate comparability of [REDACTED] (b) (4) as well as [REDACTED] (b) (4) to support licensure of [REDACTED] (b) (4) FMC, and Brinny?

**FDA Response to Question 1:** No, we don't agree. The comparability data recently submitted to the IND (July 23 and August 23, 2013) were reviewed for the purpose of introduction of the [REDACTED] (b) (4) into the ongoing clinical study. The analytical comparability data that were provided to the IND and any additional data submitted to the BLA will be reviewed for the purpose of supporting licensure during the time of the BLA review. Input from the non-clinical and clinical disciplines will also contribute to the assessment of comparability in support of licensure.

**Discussion:** *The sponsor provided a response to the Agency's comment (please see attached presentation). The Agency stated that the comparability plan appeared sufficient. The Agency clarified that there may have been confusion regarding the concept of "supporting filing" versus "supporting licensure." The information provided in the package appears to be sufficient to support filing. In response to the sponsor's question regarding what should be addressed in the BLA, the Agency indicated that the major outstanding concern with the lack of stability data from commercial scale production batches.*

*The Agency asked the sponsor if microbial control data will be available for the BLA. The sponsor responded "yes."*

### 2.2. FMC DS Process Performance Qualification Data Submission Proposal

**Question 2a:** As committed during the Type C meeting held on 27-August-2013, a summary report of the investigations at FMC into the [REDACTED] (b) (4) Microbial Ingress was provided. Extensive reports on the investigation will be available for inspection on-site at PAI. Does the Agency agree that based on this information, the retrospective analysis approach in a PPQ format as discussed during the same Type C meeting and detailed further in questions Q2b and Q2c below can be used to support process robustness at FMC in the BLA?

**Question 2b:** Does the Agency agree with the proposal of including retrospective analysis of 3 commercial-scale batches in a PPQ format for the FMC Drug Substance in the BLA as discussed in the Type C meeting on 27-August-2013 and outlined in the company position below?

**FDA Response to Questions 2a and 2b:** Based on the information provided in the briefing packages and the previous meetings, the retrospective PPQ analysis can be used as one component of the development and validation package process to support process licensure of FMC; however, the initial BLA submission should include prospective process validation results from at least one process validation batch that is fully representative of the proposed commercial process. The results should include data, including testing results and process operating data, and information on any deviations (all events, including OOT/OOS) associated with this manufacturing run. We note a high contamination rate in the production (b) (4) at FMC, and successful completion of this validation batch and the additional planned post-correction manufacturing runs will provide evidence that the problems leading to the (b) (4) contaminations were identified and adequately corrected. The complete PPQ report, including the remaining intended process validation runs, should be available for review at the time of the PAI, and submission of this report to the BLA may be included in an information request during the course of the review. The investigations into the production (b) (4) contaminations and the corrective actions implemented will also be reviewed during the PAI.

The PPQ batches should include data demonstrating microbial monitoring at critical points in the manufacturing process and microbial control during hold times. Samples should be collected (b) (4) Bioburden and endotoxin limits should be established for (b) (4) and storage during lifetime at scale and should be monitored on a routine basis to verify continued microbial control. The protocol with the established limits and monitoring points and frequency should be submitted to the BLA and the results obtained will be reviewed during the inspection.

Additionally the BLA should contain detailed process development information, including any DoE studies performed to establish process parameters, to support the commercial FMC process.

From the information provided, it is not clear that the critical quality attributes and acceptance criteria provided in appendix 1 will be considered acceptable.

**Discussion:** *The sponsor stated they would provide major deviations that would affect product quality only. The Agency agreed this would be acceptable if a brief statement of what is considered a major or minor deviation is also provided. The sponsor agreed that they would include a definition of the major and minor changes.*

**Question 2c:** Does the Agency agree with the proposal of providing data from one PPQ batch executed under a prospective PPQ protocol for FMC DS within 30 days of submission of the BLA? The complete PPQ report will be available for review by the Agency during PAI.

**FDA Response to Question 2c:** No, under the PDUFA V program, FDA cannot agree to accept an application that does not contain complete information to allow for a

comprehensive review of and decision on the application, with exception of the required safety update. The PPQ data are considered a major component of the BLA as they are integral to the manufacturing process review and the determination that the manufacturing process can provide a consistent supply of MK-3475 of acceptable quality.

Therefore, please consider the following options for submitting the BLA for MK-3475:

- Proceed with an initial BLA submission for MK-3475 that contains a complete CMC package, including data from one PPQ batch, in December 2013.
- Submit the BLA components under Rolling Review with the data from the initial PPQ batch submitted in January/February 2014 as the final CMC component of a complete BLA.

***Discussion:*** *The Agency agreed that from a CMC standpoint, it would be reasonable to propose a rolling submission that includes the submission of a complete CMC reviewable unit in late December 2013 and submission of a second reviewable unit, which would include PPQ data from one FMC batch and a shipping validation section, in January 2014.*

### **2.3. Stability Data to be Provided in the BLA and during Assessment of the BLA**

***Question 3a:*** Does the Agency agree that the available pivotal stability data will be sufficient for filing the BLA?

***FDA Response to Question 3a:*** The proposed pivotal stability data for the (b) (4) DS and DP are sufficient for filing. However, in general, the Agency interprets a complete CMC package to include a minimum of six months of stability data, as described in ICH Q5C. If the analytical data provided in the BLA, including rates and pathways of degradation for (b) (4) and FMC materials, demonstrate comparability, the stability data from the (b) (4) DP batches may be considered as fully representative of the FMC material and support that the stability data from the FMC batches are sufficient for filing. Additional data regarding the changes in the FMC process for manufacturing of commercial product will also be evaluated. The Agency considers several factors when evaluating supporting stability data for the commercial shelf life of a product, including the adequacy of the stability protocols; the strength of the analytical methods; the range of product attributes covered and the demonstrated stability-indicating potential of the methods; comparison of rates and pathways of degradation under long term, accelerated, and stress conditions; and the actual results of the stability studies, including whether the data are sufficiently comparable.

***Discussion:*** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

**Question 3b:** Does the Agency agree that the stability update to support the initial shelf life claim can be submitted during BLA review, as a simple stability update no later than 14-March-2014?

**FDA Response to Question 3b:** Under PDUFA V, data should not be submitted more than 30 days after the submission of the original application unless it is requested by the Agency. The Agency may include a comment regarding the submission of a “simple stability update” in an information request during the review period. “Simple stability updates” are defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Furthermore, the “simple stability update” will use the same tabular presentation as in the original submission, as well as the same mathematical or statistical analysis methods (if any), and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA/NDA. This type of “simple stability update” submitted up to month 4 for a priority submission may be reviewed and considered in shelf life determinations.

**Discussion:** *The sponsor accepted FDA’s response (please see attached presentation); no discussion occurred.*

**Question 3c:** Does the Agency agree with the proposal to extrapolate the shelf life using the principles laid out in ICH Q1E as discussed during the 11-June-2013 CMC Type A Meeting and as laid out in Table 6 and Table 7?

**FDA Response to Question 3c:** It is acceptable to propose an initial shelf life that is beyond the current coverage of the real time data. The acceptability of such a shelf life will depend on the data provided and the level of product knowledge demonstrated. Note that ICH Q1E states that for drug substances (b) (4), the shelf life should be based on long-term data. The final determination on the shelf life is a BLA review issue.

**Discussion:** *The sponsor accepted FDA’s response (please see attached presentation); no discussion occurred.*

**Question 3d:** Does the Agency agree with the proposal to extend the shelf life using the same principles as outlined under Question 3c using a protocol and with the submission of updated stability in the annual report as discussed during the 2-April-2013 CMC Type B Meeting?

**FDA Response to Question 3d:** No. Extension of the expiry period post-licensure should be based on real-time stability data from the approved stability protocol. Data from an approved protocol can be submitted in the annual report.

***Discussion:*** *The sponsor provided a response to the Agency's comment (please see attached presentation). The Agency stated that this is not an agreement that could be made at this time. The Agency noted that this is not standard practice, but stated that any justification and supporting data submitted in the BLA would be considered.*

***Question 3e:*** Does the Agency agree to the post-approval stability commitment?

***FDA Response to Question 3e:*** There is insufficient information provided to allow for agreement with a stability commitment; for example, the stability studies that are part of this commitment will be reviewed after submission of the BLA. However, the general "company position" appears to be appropriate.

***Discussion:*** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

#### 2.4. Container Closure Integrity Method Validation

***Question 4:*** Does Agency concur that the sponsor's strategy on container closure integrity testing on drug product vials is sufficient to demonstrate system integrity?

***FDA Response to Question 4:*** The BLA should include data on the sensitivity of the CCIT using known defect sizes, as stated in the package. Please ensure the vials capped under the worst-case capping parameters are tested for CCIT. The microbial ingress method should be correlated to dye ingress method.

***Discussion:*** *The sponsor and Agency agreed that a protocol of the correlation between dye ingress and microbial ingress test method will be submitted in the BLA. In addition, the sponsor agreed to provide a schedule of when the tests are to be completed.*

#### 2.5. Shipping Qualification Strategy for Drug Substance and Drug Product

***Question 5a:*** Does the Agency agree the DS and DP shipping qualification strategy are sufficient to demonstrate control of DS and DP in the supply chain?

***FDA Response to Question 5a:*** Shipping studies should include an evaluation of the impact of shipping on product quality attributes, most significantly for shipping of the (b) (4) DS; the integrity of the lyophilized DP cake should also be evaluated. The BLA should include information on the effects of min and max loads on temperature control during shipment and, for the passive (b) (4) container, on effects of seasonal variation on the maintenance of temperature. The BLA should also include information on the acceptable excursion limits during shipment. PQ data should be submitted to the BLA. Bioburden testing of pooled samples (b) (4) will not assess impact of shipping and storage on microbiological properties of DS.

***Discussion:*** *The sponsor provided a response to the Agency's comment (please see attached presentation). The sponsor and Agency agreed that all available information pertaining to the (b) (4) will be submitted in January 2014 (see Question 2c discussion). Further agreement was made that a summary update would be provided for pending (b) (4) data in the January 2014 submission and the final data will be available at PAI.*

***Question 5b:*** Does the Agency agree with the sponsor's proposal to add additional (b) (4) through similar qualification practices and internal change control in the future with notification via annual report?

***FDA Response to Question 5b:*** A protocol describing the shipping qualification standards should be submitted for approval in the BLA. Any shipping improvements that meet acceptance criteria described in the BLA could be reported in an annual report.

***Discussion:*** *The sponsor provided a response to the Agency's comment (please see attached presentation). The Agency stated that whether a Quality Manual in place of a qualification protocol was sufficient would be a review issue. The Agency stated that the Quality Manual should be placed in the Drug Product section of the application and referenced in the Drug Substance section.*

## 2.6. BLA Structure

***Question 6a:*** Does the Agency concur with the strategy for providing separate drug substance and drug product sections as described below to reflect differences for the two drug substance manufacturing sites?

***FDA Response to Question 6a:*** Yes. Please ensure that the differences between sections are clearly identified.

***Discussion:*** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

***Question 6b:*** Is it acceptable to include the following protocols as part of the BLA?

***FDA Response to Question 6b:*** Yes. The Agency notes that for qualification of additional working cell banks, material from one lot of DS will be placed on stability; additional testing of material manufactured from a new working cell bank will also be expected.

***Discussion:*** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

## 2.7. Samples for Analytical Method Validation

**Question 7:** Does the Agency concur that drug product and associated drug substance samples with their Certificates of Analysis, associated with the Section 3.2.R Regional Information to confirm analytical method validation for (b) (4) (FMC DS/Brinny DP) can be made available to the FDA no later than 31-March-2014? (Note: Corresponding (b) (4) DS/Brinny DP) will be available for inclusion in the original BLA)

**FDA Response to Question 7:** The Agency will not require the submission of samples as a part of the analytical method validation package for this BLA.

**Discussion:** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

## 2.8. Requesting to (b) (4) via the Pre-Launch Activities Importation Request

**Question 8:** Does the Agency concur to (b) (4) via the Pre-Launch Activities Importation Request (PLAIR) to ensure supply at the time of approval?

**FDA Response to Question 8:** A Pre-Launch Activities Importation Request should be submitted. Please refer to the Draft Guidance for Industry on PLAIR (July, 2013).  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM362177.pdf>

**Discussion:** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

## 2.9. Request for Early Feedback on Artwork

**Question 9:** Can the Agency provide early feedback on the vial label and carton packaging component artwork?

**FDA Response to Question 9:** Yes. Since Keytruda (MK-3475) is designated as breakthrough therapy, the Agency will provide early feedback on the proposed container label and carton labeling. We encourage you to submit the proposed label and labeling as soon as possible.

**Discussion:** *The sponsor accepted FDA's response (please see attached presentation); no discussion occurred.*

## 2.10. Manufacturing

**Question 10:** Consistent with activities to ensure compliant supply to fulfill expected launch, Merck intends to continue manufacturing across the MK-3475 supply chain during the BLA review. During this period the sites, Merck [REDACTED] (b) (4) [REDACTED] until approval is obtained. The rationale and plans are detailed below. Does the Agency agree with the sponsor's position?

**FDA Response to Question 10:** The information provided in the meeting package is not sufficient to allow the Agency to provide a response to this question. The intent of the question is not clear. This issue can be further discussed during the meeting, if necessary.

**Discussion:** *The sponsor provided a response to the Agency's comment (please see attached presentation). The Agency stated this appears to be acceptable, as long as the final release will mirror the approved commercial parameters and release specifications. The sponsor assured the Agency that nothing will be released until a final agreement with the Agency is made. The Agency inquired whether the [REDACTED] (b) (4) Agreement would be accessible during inspection; the sponsor responded "yes."*

### **Additional Meeting Discussion:**

- *An update regarding the [REDACTED] (b) (4) contamination at FMC was provided by the sponsor. No additional events have occurred to date.*
- *The Agency asked the sponsor to provide a Drug Substance production schedule in the BLA. The Agency specified that Drug Substance site inspections would need to occur during manufacturing of MK-3475 and that data from completed manufacturing runs should be available by the time of the inspection.*

## 3.0 ATTACHMENTS AND HANDOUTS

Sponsor's presentation is attached.

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/s/  
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RASHMI RAWAT  
11/05/2013

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125514/0

**LATE-CYCLE MEETING MINUTES**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Keytruda (Pembrolizumab).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 11, 2014.

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

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

Sincerely,

*{See appended electronic signature page}*

Marc Theoret, M.D.  
Lead Medical Officer, Melanoma/Sarcoma Team  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date:** August 11, 2014

**Application Number:** BLA 125514/0

**Product Name:** Keytruda (Pembrolizumab)

**Applicant Name:** Merck Sharp and Dohme Corp. (Merck)

**Meeting Chair:** Marc Theoret, M.D.

**Meeting Recorder:** Sharon Sickafuse, M.S.

**FDA ATTENDEES**

**Office of Hematology and Oncology Drug Products**

Richard Pazdur, M.D.

Paul Kluetz, M.D.

Division of Oncology Products 2

Jennie Chang, PharmD

Meredith Chuk, M.D.

Joseph Gootenberg, M.D.

Whitney Helms, Ph.D.

Sharon Sickafuse, M.S.

Marc Theoret, M.D.

Shawna Weis, Ph.D.

**Office of Biostatistics**

Division V

Emmanuel Sampene, Ph.D.

**Office of Clinical Pharmacology**

Liang Zhao

Division V

Stacy Shord, Ph.D.

**Office of Biotechnology Products**

Division of Monoclonal Antibodies

Mark Paciga, Ph.D.

Rashmi Rawat, Ph.D.

Deborah Schmiel, Ph.D.

**Office of Manufacturing and Product Quality**  
Division of Good Manufacturing Practice Assessment  
Biotech Manufacturing Assessment Branch  
Patricia Hughes, Ph.D.

**Office of Medical Policy Initiatives**  
Division of Medical Policy Programs  
Karen Dowdy

**MERCK ATTENDEES**

Cong Chen, Statistics  
Scot Ebbinghaus, Clinical Oncology  
Dennis Erb, Worldwide Global Regulatory  
Soonmo (Peter) Kang, Clinical Oncology  
Xiaoyun (Nicole) Li, Statistics  
Gargi Maheshwari, Manufacturing  
Tina Marks, Product Labeling  
Kimberly May, CMC Regulatory  
Nikhil Mehta, Biologics Regulatory  
Alise Reicin, Oncology Project Leadership  
Andrew Robertson, Regulatory Policy  
David Robinson, CMC Regulatory  
Eric Rubin, Clinical Oncology  
Melissa Tice, Biologics Regulatory  
Beth Hutchins, Biologics Operations  
Danuta Herzyk, Nonclinical Safety assessment  
Mary France Schubert, Clinical Safety

**1.0 BACKGROUND**

BLA 125514/0 was submitted on February 27, 2014, for Keytruda (pembrolizumab).

Proposed indication: treatment of unresectable or metastatic melanoma in patients whose disease has progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor

PDUFA goal date: October 28, 2014

FDA issued a Background Package in preparation for this meeting on July 30, 2014. Merck submitted a response on August 7, 2014.

## 2.0 DISCUSSION

### LCM AGENDA

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Outstanding Information Requests as of August 11, 2014

Request submitted on July 25, 2014, to update and resubmit the datasets that pertain to patient demographics, e.g., ADSL, DM, MH, CM, and other affected datasets to correctly reflect the information that has been submitted in response to FDA's information requests, specifically received on March 26, March 28, May 21, May 30, June 2, June 4, June 5, and June 12, 2014. On July 28, 2014, Merck proposed a database lock of July 25, 2014, with new datasets submitted by August 18, 2014. FDA agreed.

Discussion:

Merck is working on this and hope to submit earlier than August 18<sup>th</sup>.

FDA clarified that only the datasets pertaining to demographic information be submitted. Merck stated that the datasets will have a data cutoff date of December 31, 2013, which is the data cutoff date for the 120 day safety update report. FDA agreed.

3. REMS or Other Risk Management Actions

FDA requested that Merck submit a Medication Guide which is required as part of the approved labeling.

Discussion:

Merck submitted a proposed Medication Guide to the BLA on August 7, 2014. This is under review by FDA.

4. Postmarketing Requirements/Postmarketing Commitments

FDA is requesting the following PMRs/PMCs:

- **PMR:** 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. The final protocol(s) for the trial(s) were submitted on DATE. The trial(s) will be completed by DATE. The final study report and revised labeling will be submitted by DATE.

Merck's response of August 7, 2014:

Data from two ongoing studies will be used to fulfill this PMR. PN002, "Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma", was submitted to IND 110080 on September 7, 2012, and

subsequently amended on April 25, 2013, and October 2, 2013. PN006, “A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma”, was submitted to IND 100080 on May 29, 2013, and subsequently amended on February 25, 2014.

The final overall survival (OS) analysis for PN002 will occur on October 31, 2015, with submission of a clinical study report (CSR) and revised labeling on August 31, 2016. The final OS analysis for PN006 will occur on March 30, 2016, with submission of a CSR and revised labeling on January 31, 2017.

Discussion:

FDA clarified that results from either study may fulfill the PMR.

- **PMC:** Treatment with pembrolizumab may result in enhanced immune-mediated toxicity following vaccination and recall responses. To investigate this potential, perform a study to characterize the magnitude, kinetics, and resolution of the immune response following repeated vaccination (recall challenge) in anti-PD-1-treated versus control-treated animals. 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). Evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved. In half of the animals, continue dosing main study animals and reassess the magnitude of the recall response after a suitable period of continued dosing. In the other half, discontinue dosing and assess the magnitude of the response after the terminal phase. Monitor the magnitude of the recall response at least twice weekly in both subsets. Monitor clinical signs and body weight throughout the study. For animals that die on-study or are euthanized in extremis, histological examination of major organs is suggested to characterize potential vaccine-induced toxicities. The final study report will be submitted by October 31, 2015.

Merck’s response of August 7, 2014:

Merck agreed to submit a final study report by October 31, 2015

Discussion:

Merck submitted a study proposal on August 7, 2014. FDA stated that the study proposal was acceptable and requested that Merck submit the mouse study protocol to IND 110080 before initiating the study.

- **PMC:** 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 to be submitted by DATE.

Merck's response of August 7, 2014:

Merck agreed to submit a final study report by August 31, 2015.

Discussion:

FDA stated that the proposed date of submission of the final study report is acceptable.

- **PMC:** 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 to be submitted by DATE.

Merck's response of August 7, 2014:

Merck agreed to submit a final study report by October 31, 2015.

Discussion:

FDA stated that the proposed date of submission of the final study report is acceptable.

- **PMC:** 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 to be submitted by DATE.

Merck's response of August 7, 2014:

Merck agreed to submit a final study report by December 31, 2015.

Discussion:

FDA stated that the proposed date of submission of the final study report is acceptable.

- **PMC:** 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. The study protocol and report with data will be submitted by DATE.

Merck's response of August 7, 2014:

Merck agreed to submit a final study report by September 30, 2014.

Discussion:

FDA stated that the proposed date of submission for the final study report is acceptable.

5. Review Plans

Discussion:

FDA stated they will submit a revised proposed package insert to Merck tomorrow.

6. Wrap-up and Action Items

Discussion:

Merck stated that they have submitted their advertising materials to the Office of Professional Drug Promotion.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and, therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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MARC R THEORET  
08/26/2014



BLA 125514/0

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Merck Sharp & Dohme Corp.  
Attention: Melissa Tice, Ph.D.  
Executive Director, Global Regulatory Affairs  
125 East Lincoln Ave., RY33-200  
P.O. Box 2000  
Rahway, NJ 07065

Dear Dr. Tice:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Keytruda (pembrolizumab).

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 11, 2014. Attached is our background package, including our agenda, for this meeting.

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date:** August 11, 2014

**Application Number:** BLA 125514/0

**Product Name:** Keytruda (pembrolizumab)

**Indication:** Treatment of unresectable or metastatic melanoma in patients who progressed on or after treatment with ipilimumab and, if BRAF V600 mutation positive, received treatment with a BRAF (b) (4) inhibitor.

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

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

There are no substantive review issues.

### ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

## REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to the requirement for a risk evaluation and mitigation strategy (REMS) program have been identified to-date. Risk management will be managed via labeling and routine pharmacovigilance.

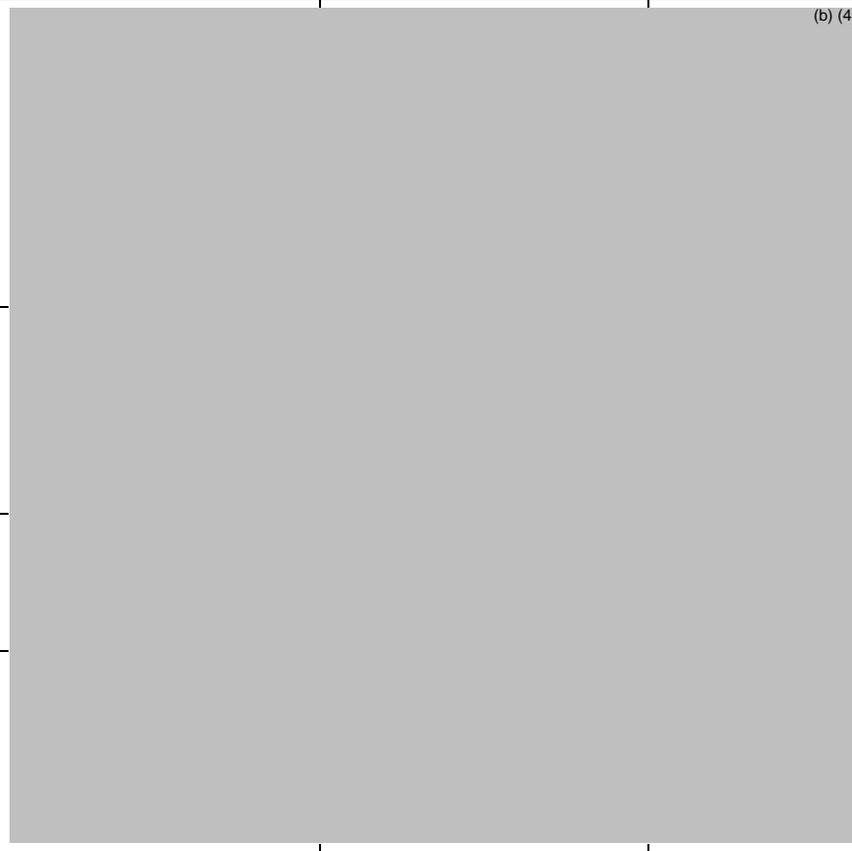
## LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)  
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Outstanding Information Requests – 20 minutes
  - a. Request submitted on July 25, 2014, to update and resubmit the datasets that pertain to patient demographics, e.g., ADSL, DM, MH, CM, and other affected datasets to correctly reflect the information that has been submitted in response to FDA's information requests, specifically received on March 26, March 28, May 21, May 30, June 2, June 4, June 5, and June 12, 2014. On July 28, 2014, Merck proposed a database lock of July 25, 2014, with new datasets submitted by August 18, 2014. FDA agreed.
  - b. Clinical information request submitted on July 29, 2014, for the following:
    - 1) Lab tables with a data cut-off of October 18 and December 31, 2013 with the addition of hemoglobin and neutrophils in SAS.xpt or excel files by July 30, 2014.
    - 2) Line listings of patients in Part B2 and the melanoma ISS (N=411) with AEOSI events including patient ID number, PT, event start and stop date by July 31, 2014.
    - 3) Vital sign tables with changes from baseline and analysis by July 31, 2014.
    - 4) Narratives for the following patients by July 31, 2014:
      - Patient 100042 with myasthenic syndrome
      - Patient 0063 with Grade 3 hemolytic anemia
      - Patient 0068 with Gr 3 rhabdomyolysis
      - Patient 0919 with Gr 5 diffuse alveolar damage
      - Patient 0106 with Gr 5 interstitial lung disease

c. CMC information request submitted on July 29, 2014, for the following to be submitted by July 30, 2014:

- 1) The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 for (b) (4) and FMC and 3.2.P.8.2 for (b) (4)) do not include information regarding the intention to submit data from the stability studies. Provide commitments to submit the data from all ongoing stability studies, including the leachable study, and the data from annual stability lots in the BLA annual reports.
  
- 2) The release data provided for the drug substance (DS) and drug product (DP) lots manufactured by the (b) (4) and FMC and (b) (4) manufacturing process and for the DS and DP lots used in the clinical studies do not support the proposed acceptance criteria for select release and stability specifications. We do not agree with the proposed acceptance criteria for the specifications indicated below and have the following recommendations. Submit revised DS and DP specifications and stability protocols for primary, process validation and post-approval DS and DP stability lots.

DS and DP Release Test	Release and Shelf life Acceptance Criteria for DS	Release and Shelf life Acceptance Criteria for DP
Clarity (Opalescence)	(b) (4)	(b) (4)
Appearance	Essentially free of visible particles	Essentially free of visible particles
Potency	(b) (4)	(b) (4)
(b) (4)		

		(b) (4)

- 3) The manufacturer information listed in sections 3.2.S.2.1 and 3.2.P.3.1 (Table 1) and Form 356h indicates that analytical methods for release and stability testing of the DS and DP are performed at more than one testing site. Data to demonstrate that appropriate method transfer studies were performed and that the methods perform equally and provide sufficiently similar data at both testing sites were not included in the BLA. Provide summary reports for analytical method transfer for the methods that are performed at more than one testing site.
- 4) The left hand sides of Tables 54 and 84 in Section 3.2.P.2.3 (p. 115 and 175) are cut off from the page. Revise this section to include complete tables, ensuring that the batch numbers are visible.

- d. Clinical information request submitted on July 30, 2014, for tables of treatment emergent laboratory abnormalities (chemistry and hematology) by toxicity grade of abnormality (Gr1, Gr2, Gr3, G4, all grades) that exclude patients who did not have an increase in grade from baseline for:
- Part B2 by dose
  - Melanoma ISS (n=411) by dose
  - Melanoma ISS all doses combined

Provide tables as SAS or excel files by August 5, 2014.

3. REMS or Other Risk Management Actions – 10 minutes

- Please submit a Medication Guide which is required as part of the approved labeling.

4. Postmarketing Requirements/Postmarketing Commitments – 20 minutes

FDA is requesting the following PMRs/PMCs:

- PMR: 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. The trial(s) will be completed by DATE. The final study report and revised labeling will be submitted by DATE.
- PMR: Treatment with pembrolizumab may result in enhanced immune-mediated toxicity following vaccination and recall responses. To investigate this potential, perform a study to characterize the magnitude, kinetics, and resolution of the immune response following repeated vaccination (recall challenge) in anti-PD-1-treated versus control-treated animals. 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). Evaluate the effect of PD-1 inhibition on the primary immune response once steady state plasma levels have been achieved. In half of the animals, continue dosing main study animals and reassess the magnitude of the recall response after a suitable period of continued dosing. In the other half, discontinue dosing and assess the magnitude of the response after the terminal phase. Monitor the magnitude of the recall response at least twice weekly in both subsets. Monitor clinical signs and body weight throughout the study. For animals that die on-study or are euthanized in extremis, histological examination of major organs is suggested to characterize potential vaccine-induced toxicities. The final study report will be submitted by October 31, 2015.
- PMC: 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 to be submitted by DATE.

- PMC: 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 to be submitted by DATE.
- PMC: 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 to be submitted by DATE.
- PMC: 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. The study protocol and report with data will be submitted by DATE.

5. Review Plans – 5 minutes

6. Wrap-up and Action Items – 10 minutes

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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  
07/30/2014