

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125377Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125377 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DBOP PDUFA Goal Date: 12/25/10 Stamp Date: 6/25/2010

Proprietary Name: NOT YET DESIGNATED

Established/Generic Name: Ipilimumab

Dosage Form: 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses.

Applicant/Sponsor: Bristol-Myers Squibb Company

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 advanced melanoma (unresectable Stage III and Stage IV melanoma) in patients who have received prior therapy.

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 [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<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 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

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

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}

Regulatory Project Manager

Erik Laughner 07/09/10

(Revised: 6/2008)

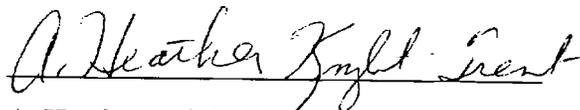
NOTE: If you have no other indications for this application, you may delete the attachments from this document.

BLA 125377/0/0

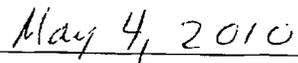
IPILIMUMAB (BMS-734016)

CERTIFICATION: DEBARRED PERSONS

Bristol-Myers Squibb hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(k)(1) of the Federal Food, Drug and Cosmetics Act in connection with this application.



A. Heather Knight-Trent, PharmD
Director - GRS Oncology
Bristol-Myers Squibb Company
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Certification Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 125377/0	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: YERVOY Established/Proper Name: IPILIMUMAB Dosage Form: Injection, for intravenous infusion		Applicant: BRISTOL-MYERS SQUIBB COMPANY Agent for Applicant (if applicable):
RPM: ERIK LAUGHNER		Division: DBOP
<p>NDA: 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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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"> • Proposed action • User Fee Goal Date is <u>March 26, 2010</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation </p> <p> <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p>Comments:</p>	
<p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p>	
❖ 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 checked="" type="checkbox"/> Yes, dates March 7, 2011 March 8, 2011
❖ 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
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO BURST

² 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.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ 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 03/25/11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	03/25/11 (same as approval)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	06/25/10
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

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"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	03/25/11 (same as approval)
<ul style="list-style-type: none"> Original applicant-proposed labeling 	06/25/10
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color 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"> Most-recent draft labeling 	03/11/11
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	09/28/10 LTR 03/18/11 09/27/10
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 07/08/10 <input checked="" type="checkbox"/> DMEPA 02/28/11 <input checked="" type="checkbox"/> DRISK 02/08/11 <input checked="" type="checkbox"/> DDMAC 02/08/11 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT 12/21/10 OBP 02/23/11
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	07/30/10 Mtg memo and RPM filing memo
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" 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 http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> Date reviewed by PeRC <u>ORPHAN STATUS</u> If PeRC review not necessary, explain: <u>Orphan Indication</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

Outgoing communications (*letters (except action letters), emails, faxes, telecons*)

03/25/11 IR
03/24/11 Tcon
03/24/11 IR
03/24/11 IR
03/23/11 IR
03/18/11 IR
03/17/11 IR
03/15/11 IR
03/15/11 IR
03/14/11 IR
03/14/11 IR
03/14/11 IR
03/14/11 IR
03/11/11 IR
03/11/11 IR
03/11/11 IR
03/10/11 IR
03/10/11 IR
03/08/11 IR
03/04/11 Tcon
03/04/11 IR
03/01/11 IR
02/25/11 Tcon
02/25/11 IR
02/23/11 IR
02/22/11 IR
02/22/11 IR
02/22/11 IR
02/22/11 IR
02/14/11 Tcon
02/14/11 IR
02/11/11 IR
02/09/11 IR
02/08/11 IR
02/07/11 IR
02/04/11 Tcon
02/04/11 IR #2
02/04/11 IR
02/03/11 IR
02/02/11 IR
01/28/11 IR
01/27/11 Tcon
01/25/11 IR
01/24/11 IR
01/21/11 IR
01/18/11 IR
01/14/11 IR
01/11/11 Tcon
01/11/11 IR
01/03/11 IR
12/15/10 IR
12/10/10 IR
12/08/10 IR
12/07/10 IR #2
12/07/10 IR
12/02/10 Tcon
11/30/10 IR

	<p>11/24/10 Tcon 11/24/10 IR 11/16/10 Tcon 11/04/10 IR 11/03/10 Tcon 11/02/10 IR 11/01/10 IR 10/29/10 IR 10/28/10 Review Ext LTR 10/19/10 Tcon 10/14/10 IR 10/13/10 Tcon 10/04/10 IR 10/01/10 IR 10/01/10 Tcon 09/21/10 IR 09/16/10 AI LTR 09/15/10 IR 09/14/10 IR 09/13/10 IR 09/09/10 IR 09/07/10 74-day LTR 08/16/10 Filing LTR 08/13/10 IR #2 08/13/10 IR 08/12/10 Tcon 08/09/10 IR 08/06/10 IR 08/05/10 Tcon 08/05/10 IR 08/02/10 IR 07/30/10 IR 07/27/10 Tcon 07/09/10 IR 07/08/10 Ack LTR</p>
<p>❖ Internal memoranda, telecons, etc.</p>	<p>03/17/11; REMS Mtg 03/15/11; REMS Mtg 03/04/11; Eleventh Lab Mtg 02/25/11; Tenth Lab Mtg 02/22/11; Ninth Lab Mtg 02/18/11; Team Wrap-up Mtg. 02/11/11; Eighth Lab Mtg 02/11/11; Monthly Team Mtg 02/02/11; Seventh Lab Mtg 01/20/11; Sixth Lab Mtg 01/18/11; Fifth Lab Mtg 01/14/11; Fourth Lab Mtg 01/07/11; Monthly Team Mtg 12/3/11; Monthly Team Mtg 11/16/10; Third Lab Mtg 11/05/10; Monthly Team Mtg 10/19/10 ODAC planning mtg 10/01/10; Second Lab Mtg. 10/01/10 Monthly Team Mtg 09/28/10; First Lab Mtg 09/14/10 ODAC planning mtg 09/24/10 Midcycle</p>

	09/02/10 Monthly Team Mtg 07/30/10 Review Designation 07/06/10; Planning Mtg
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 05/14/10 (no minutes in action pkg)
• 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>)	<input type="checkbox"/> No mtg 03/4/10
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	03/09/11 Special Meeting to discuss labeling issues 01/13/10
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 03/24/11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 03/24/11(addendum to 03/12/11 review) 03/12/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None DD is CDTL for this application
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 18
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	DD is CDTL for this application
• Clinical review(s) (<i>indicate date for each review</i>)	03/23/11 (addendum to 02/25/11 Review) 02/25/11
• 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>)	See Clinical Review 02/25/11 pg 16.
❖ 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"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	03/25/11 (same as approval) 03/23/11
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	08/30/10
• 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>)	<input type="checkbox"/> None 03/24/11 02/15/11 12/13/10

⁵ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 11/12/10, 11/8/10, 11/8/10, 11/05/10 LTRs 11/1/10 Review
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurrence given in TL review
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 02/25/11
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 02/25/11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurrence given in primary review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurrence given in primary review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 02/25/11 QT-IRT 11/09/10
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 03/04/11
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 03/02/11
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 02/24/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concurrence given in primary and TL review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 03/02/11
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 02/24/11
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 03/03/11 TL Review 03/02/11 DP Review 03/01/03 DS Review
❖ 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)(all original applications and all efficacy supplements that could increase the patient population)</i>	In product quality 02/24/11 review pg 5
<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) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: 03/08/11 <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)

⁶ 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.



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

Memorandum

Date: 03/25/11 ESL 03/25/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; correction to REMS website screenshot.

See Attached email.

Laughner, Erik

Subject: FW: STN 125377; FINAL BMS SUBMITTED REMS MATERIALS; WEBSITE CHANGED NEEDED

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]

Sent: Friday, March 25, 2011 8:22 AM

To: Knight Trent, Heather

Subject: STN 125377; FINAL BMS SUBMITTED REMS MATERIALS; WEBSITE CHANGED NEEDED

Good Morning Heather,

The Web site page has the following minor issue that needs corrected (see red boxes). For box 1, this should be, serious immune-mediated adverse reactions caused by YERVOY ^{(b) (4)}. Same goes for the second box. If you can make this change, and send me PDF by 10AM (also push thru as 03/25 amendment for today).

(b) (4)

Also on the Web Page

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



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

Memorandum

Date: 03/24/11 *SL 03/27/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; Requested FINAL Revisions to package insert and DHCP letter; agreement with Medguide

From: Laughner, Erik
Sent: Thursday, March 24, 2011 8:46 AM
To: 'Knight Trent, Heather'
Subject: STN 125377; FDA final revisions to Package Insert and Medguide; Final Draft DHCP letter
Importance: High

Heather,

Please see final package insert with medguide. There are only a few minor revisions (tracked) with a couple of comments. Unless BMS needs further discussion, please make the changes and prepare for formal submission as an amendment.



125377 PI and
Medguide FDA edi...

Please see final revisions to DHCP letter:



YERVOY_
S_DHCP_Letter_03..

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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

Memorandum

Date: 03/24/11 *SL 03/24/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
Public REMS document and REMS supportive document.

From: Laughner, Erik
Sent: Thursday, March 24, 2011 10:11 AM
To: 'Knight Trent, Heather'
Subject: STN 125377; REMS public document; changes needed to supportive document
Importance: High

Dear Heather,

Please see the following FDA cleared REMS public document. Please formally submit this to the BLA. Do not make any changes to this document:



Yervoy REMS doc
23-MAR-11 clea...

With regard to the REMS supportive document, here is the assessment language to be included in the REMS supporting document.

(b) (4)

Besides incorporating this paragraph, BMS needs to harmonize the REMS SD w/ the REMS public document.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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

Memorandum

Date: 03/24/11 *ESL 03/24/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information request;
Need month date for CMC PMCs which will be addressed by AR submission.

I contacted Heather Knight-Trent to note that for those agreed to CMC PMCs that have the final reports submitted to the Annual Report, FDA will need a month commitment in addition to a year for tracking purposes (this will also be reflected in the action letter). Heather acknowledged and agreed to provide a month for those PMCs via email.



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

Memorandum

Date: 03/23/11 rsl
3/23/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; Requested Revisions to REMS based on FDA edits

INTERNAL NOTE: PDF FILES ATTACHED IN EMAIL ARE IDENTICAL TO THOSE ALREADY PROVIDED BY BMS AS FORMAL AMENDMENT. FDA DID NOT MAKE EDITS TO THE FILES AND THEY ARE NOT PRINTED OUT AND ATTACHED TO THIS RECORD.

From: Laughner, Erik
Sent: Wednesday, March 23, 2011 4:44 PM
To: 'Knight Trent, Heather'
Subject: STN 125377; REMS Materials (Wallet card, Webpage, Housing Unit, Nursing checklist, Management Guide)

Heather,

FDA has reviewed the following most recent BMS revised REMS materials and has the following final comments (not embedded in documents) listed below:



YERVOY_REMS_Pati ent_Wallet_Car... 5_Web_Page_03.21.using_Unit_03.21... YERVOY_REMS_Ho sing_Checklist_... YERVOY_REMS_Nur YERVOY_REMS_Ma agement_Guide_0..

Nursing Immune-Mediated Checklist

Under Gastrointestinal, 5th line down, the statement (b) (4) does not avail itself to a yes or no response. Revise to "Are you doing anything to manage it, and if yes, describe those interventions" or "if yes, what" or a similar version.

Management Guide (from word document)

Page 9; Something appears different with the font used in the moderate and severe boxes under Determine Severity.

Page 15; move the grey and green text boxes closer to the blue boxes.

Page 2; Remove the following: (b) (4)

(We intended the language on page one to replace this.)

Page 11; (the page showing the management of skin events) Change the headings for management to "Moderate" and "Severe or Life-threatening" (this was on our previous mark-up; (b) (4))

Page 7; regarding Enterocolitis, in far right box under follow-up "Symptoms Ongoing >1Week, change to read: Continue steroids until improvement to mild severity or resolution; taper steroids as medically appropriate

Housing unit:

"These materials are part of an FDA-approved REMS" is on the pdf version, but not on the Word version. Please be sure this language is included.

THE FINAL PACKAGE INSERT, MEDGUIDE, AND DHCP FDA REVIEW/EDITS WILL BE PROVIDED THURSDAY MORNING (I EXPECT VERY MINOR EDITS)

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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301-796-1393
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<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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

Memorandum

Date: 03/18/11

SL 03/18/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA revisions to PI and Medguide



125377 PI and
Medguide FDA Edi...

Heather,

Please see FDA revisions to PI and Medguide. Please review and provide back to FDA by end of day Monday. FDA requests that BMS carefully QC final formatting for PLR requirements.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Memorandum

Date: March 17, 2011 ٤١٢ ٥٣/١٧/١١
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); REMS Meeting

FDA Attendees: Erik Laughner, Jeff Summers, Kaushik Shastri, Suzanne Robottom, Joyce Weaver, Kate Heinrich, Anahita Tavakoli

Discussion: This meeting was convened to discuss FDA's final revisions to the following REMS materials:

- Dear Healthcare Provider Letter
- Immune-Mediated Adverse Reaction Management Guide
- Patient Wallet Card
- [REDACTED] (b) (4) t
- Webpage Screen Shot
- REMS housing unit



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

Memorandum

Date: 03/17/11 *ERC 03/17/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
Requested Revisions to REMS based on FDA edits

From: Laughner, Erik
Sent: Thursday, March 17, 2011 1:08 PM
To: Knight Trent, Heather
Subject: STN 125377; REMS Materials; FDA advice

Heather,

Please see FDA revisions/comments to the following REMS materials:



3-17-11 YERVOY 3-17-11 YERVOY 3-17-11 YERVOY 3-17-11 YERVOY 3-17-11 YERVOY 3-17-11 YERVOY
EMS_Webpage_Sa.REMS_DHCP_Dea...REMS_Housing_Un...EMS_Management.REMS_Nurse_Chec...REMS_Wallet_Car...

FDA would like to note that the materials were edited for content, with a few comments on formatting, presentation, and readability. **BMS will need to carefully revise and reformat for readability and presentation**

Revisions should be provided by Monday March 21, 2011.

FDA has reviewed your planned launch timeline as provided yesterday and finds it acceptable. The timeline will be reflected in the public REMS document.

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 03/15/11 *ESL 03/15/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
Envelope for DHCP letter

From: Laughner, Erik
Sent: Tuesday, March 15, 2011 11:23 AM
To: 'Knight Trent, Heather'
Subject: STN 125377; FDA information request; envelope for DHCP letter

Heather,

FDA will need to review per 21 CFR 200.5, the envelope that will used for the DHCP letter. Can you please submit the mock-up ASAP?

Tx,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
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Memorandum

Date: 03/15/11 252 03/15/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; high-level edits to DHCP letter

From: Laughner, Erik
Sent: Tuesday, March 15, 2011 10:14 AM
To: 'Knight Trent, Heather'
Subject: STN 125377; DHCP Letter; need revisions by 12:30PM
Importance: High

Heather,

We have a REMS meeting today from 1-3PM. DBOP would like BMS to quickly revise this letter based on our preliminary edits and provide a revised draft back by 12:30PM today.

Please confirm receipt.

Sincerely,

Erik



YERVOY
REMS_DHCP_Dear _f

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



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

Memorandum

Date: March 15, 2011 ^{ERL 03/17/11}
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); REMS Meeting

FDA Attendees: Erik Laughner, Jeff Summers, Patricia Keegan, Kaushik Shastri, Suzanne Robottom, Joyce Weaver, Kate Heinrich

Discussion: This meeting was convened to discuss BMS's latest revisions to the following REMS materials:

- Immune-Mediated Adverse Reaction Management Guide
- Webpage Screen Shot



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

Memorandum

Date: 03/14/11 *ESL 03/14/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; REMS materials

From: Laughner, Erik
Sent: Monday, March 14, 2011 4:06 PM
To: 'Knight Trent, Heather'
Subject: RE: Ipilimumab 125377 Responses

Heather,

I have rec'd.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, March 14, 2011 3:51 PM
To: Laughner, Erik
Subject: RE: Ipilimumab 125377 Responses

Dear Erik,

As previously indicated the following are attached to this email and will be officially submitted to FDA tomorrow. Also the USPI, REMS public document/assessment document, and PMR/Cs were officially submitted today through egateway. Their cover letters are attached.

- Dear Healthcare Provider Letter
- Immune-Mediated Adverse Reaction Management Guide
- Patient Wallet Card
- (b) (4) t
- Webpage Screen Shot
- REMS housing unit

Sincerely,
Heather



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

Memorandum

Date: 03/14/11 03/24/11

From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; REMS materials

From: Laughner, Erik
Sent: Monday, March 14, 2011 2:46 PM
To: 'Knight Trent, Heather'
Subject: RE: STN 125377; FDA Information Request; draft REMS materials

Heather,

Regarding the REMS materials you provided via email Friday, I was asked to communicate to you that the language about availability of REMS materials will be modified to be sure the REMS is in place at the time of product launch. Instead of [REDACTED] (b) (4) the REMS will read, "At least [REDACTED] (b) (4) prior to first availability of YERVOY to healthcare providers"

Thus, # 1 was changed to the following:

At least [REDACTED] (b) (4) prior to first availability of YERVOY to healthcare providers, and every six months for three years thereafter, Bristol-Myers Squibb will send a communication via direct mail...

This change was made throughout.

Erik

From: Laughner, Erik
Sent: Monday, March 14, 2011 2:42 PM
To: 'Knight Trent, Heather'
Subject: RE: Ipilimumab 125377 Screen Shot of Website and REMS Supportive Document

Heather,

We would like to see the REMS supporting document no later than noon, this Thursday.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, March 14, 2011 1:59 PM
To: Laughner, Erik
Subject: FW: Ipilimumab 125377 Screen Shot of Website and REMS Supportive Document

Dear Erik,

The following will be emailed to you later today with submission to the BLA officially tomorrow. For clarification, when were you expecting to receive the REMS Supporting Document? the team was planning to provide it Friday.

- Dear Healthcare Provider Letter
- Immune-Mediated Adverse Reaction Management Guide
- Patient Wallet Card
- (b) (4)
- Webpage Screen Shot
- REMS housing unit

Sincerely,
Heather



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

Memorandum

Date: 03/14/11 *ESL 03/14/11*
From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; REMS materials

From: Laughner, Erik
Sent: Monday, March 14, 2011 2:42 PM
To: 'Knight Trent, Heather'
Subject: RE: Ipilimumab 125377 Screen Shot of Website and REMS Supportive Document

Heather,

We would like to see the REMS supporting document no later than noon, this Thursday.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, March 14, 2011 1:59 PM
To: Laughner, Erik
Subject: FW: Ipilimumab 125377 Screen Shot of Website and REMS Supportive Document

Dear Erik,

The following will be emailed to you later today with submission to the BLA officially tomorrow. For clarification, when were you expecting to receive the REMS Supporting Document? the team was planning to provide it Friday.

- Dear Healthcare Provider Letter
- Immune-Mediated Adverse Reaction Management Guide
- Patient Wallet Card
- [REDACTED] (b) (4)
- Webpage Screen Shot
- REMS housing unit

Sincerely,
Heather



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

Memorandum

Date: 03/14/11 *ER 03/14/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; REMS materials

From: Laughner, Erik
Sent: Monday, March 14, 2011 7:58 AM
To: 'Knight Trent, Heather'
Subject: RE: Ipilimumab 125377 Screen Shot of Website and REMS Supportive Document
Importance: High

Good Morning Heather,

FDA would like this information ASAP, but no later than Wednesday.

Will all the REMS materials should be submitted at the same time?

Dear Healthcare Provider Letter
Immune-Mediated Adverse Reaction Management Guide
Patient Wallet Card

(b) (4)

Can you advise of BMS target submission date?

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Friday, March 11, 2011 5:55 PM
To: Laughner, Erik
Subject: Ipilimumab 125377 Screen Shot of Website and REMS Supportive Document

Dear Erik,

Can you indicate when FDA would like to receive the revised Supporting Document and REMS webpage screen shot? The team wants to be prepared and not delay timelines.

Thanks,
Heather



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

Memorandum

Date: 03/11/11 *ESL 03/11/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
FDA proposed labeling to package insert and medguide

From: Laughner, Erik
Sent: Friday, March 11, 2011 3:42 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA PI and Medguide Revisions
Importance: High

Hello Heather,

Please see FDA proposed revisions to the PI and medguide. Please confirm receipt.



031111 PPI AND
MEDGUIDE FDA.d...

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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

Memorandum

Date: 03/11/11 *ESL 03/11/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; PMR/PMC final list

From: Laughner, Erik
Sent: Friday, March 11, 2011 2:06 PM
To: Knight Trent, Heather
Subject: STN 125377; LIST OF PMRs and PMCs

Hello Heather,

I have compiled the "list" of PMRs and PMCs as agreed for STN 125377. Based on the documents I have rec'd, I believe this covers all....

Can you please confirm with your team on the list and dates (note if BMS said 12/29 for example, we went ahead and moved to 12/31).

BMS can provide the final list thru the gateway as an amendment and we can reference that single date in the letter.

Please note that the final order in the letter may change and as the letter undergoes clearance there might be some minor wordsmithing of the PMR/PMCs, however, the dates should not change.



031111 memo
MC_PMR List.doc (..

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA

301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 03/11/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; List of PMCs and PMRs

PMRs

1. To submit the final report for study DN120020 (Intravenous Study of Pre- and Post-natal Developmental in Cynomolgus monkeys with a 6-Month Post-natal Evaluation).

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

Final Report Submission: December 31, 2011

2. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ipilimumab, including procedures for accurate detection of antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

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

Final Report Submission (Assay and Methodology): December 2, 2011

3. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ipilimumab, including procedures for accurate detection of neutralizing antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling. In the event such an assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided.

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

Final Report Submission (Assay and Methodology): February 20, 2012

4. To conduct an assessment of anti-drug antibody (ADA) response and neutralizing ADA responses to ipilimumab with a validated assay (required in PMR 2 and 3) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300

ipilimumab-treated patients enrolled in the required postmarketing study comparing 3 mg/kg versus 10 mg/kg of ipilimumab monotherapy. The final report will include information on the level of ipilimumab in each patient's test sample at each sampling time point.

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

Final Protocol Submission:	September 30, 2011
Patient Accrual Completed	December 31, 2014
Trial Completion Date:	August 31, 2017
Final Report Submission:	December 29, 2017

5. During the conduct of the required postmarketing study comparing 3mg/kg vs. 10mg/kg ipilimumab monotherapy, you will obtain comprehensive baseline DNA sample acquisition (\geq 95% of ITT) and conduct pharmacogenomic association analyses to assess the potential clinical utility of CD86 gene polymorphisms as genetic determinants of immune related adverse events. You will provide a protocol that addresses SNP selection, data analyses approaches, and other methodological issues. You will provide a Final Report including electronic datasets.

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

Draft Protocol Submission;	November 30, 2011
Final Protocol Submission:	May 30, 2012
Final Report Submission:	December 29, 2016

6. Following the assessment of data from Trial CA184024, the applicant will design and conduct a trial to compare the efficacy, with the primary endpoint of overall survival, and the safety of ipilimumab at doses of 3mg/kg versus 10mg/kg given as monotherapy every three weeks for four doses in patients with unresectable stage III or Stage IV melanoma.

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

Preliminary CA184024 Data Submission:	June 30, 2011
Draft Protocol Synopsis Submission:	June 30, 2011
Final Protocol Submission:	September 30, 2011
First Patient Accrued to Trial:	March 30, 2012
Last Patient Accrued to Trial:	December 31, 2014
Trial Completion:	August, 31, 2017
Final Report Submission:	December 31, 2017

PMCs

7. To identify further genetic determinants of immune-related adverse events caused by ipilimumab. DNA samples from the required postmarketing study comparing 3 mg/kg vs. 10 mg/kg ipilimumab monotherapy will be used to conduct genome-wide association analyses. The design of these analyses will be reviewed by FDA and a final report with electronic datasets will be provided.

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

Draft Protocol Submission:	December 29, 2016
Final Protocol Submission:	July 31, 2017
Final Report Submission:	December 31, 2017

8. To develop and validate a semi-quantitative assay to evaluate visible particulates in drug product. The assay will be incorporated into the drug product release and stability testing programs. The final validation report with the specifications and method validation will be submitted as a CBE-30 by May 30, 2011.

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

Final Report Submission as a CBE 30: May 30, 2011

9. To replace the IEF assay with the CEX assay for the release of drug product after sufficient data has been acquired to support establishment of CEX acceptance criteria. The final study report will be submitted as a CBE-30 by June 30, 2011.

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

Final Report Submission as a CBE 30: June 30, 2011

10. To discontinue the IEF method as a specification for charge in the drug substance and drug product stability programs after three years of market life data are collected for the CEX assay on three batches of drug substance and three batches of either presentation of drug product. The final results and proposed CEX specification will be submitted as a CBE-30 by March 31, 2014.

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

Final Report Submission as a CBE 30: March 31, 2014

11. To perform studies to confirm that clearance [REDACTED] (b) (4) is well controlled by the manufacturing process and provide a risk assessment for [REDACTED] (b) (4) that may be present in the drug product. The final study report will be submitted as a CBE-0 by July 29, 2011.

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

Final Report Submission as a CBE-0: July 29, 2011

12. To develop and validate a process-specific host cell protein (HCP) ELISA. This assay will replace the current Cygnus Kit ELISA being used in the drug substance release program. The final study and validation reports will be submitted as a CBE-30 by November 30, 2011.

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

Final Report Submission as a CBE 30: November 30, 2011

13. To reassess release and stability specifications for ipilimumab drug substance and drug product through April 30, 2013. The assessment will be submitted in the 2013 Annual Report.

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

Final Report Submission (Annual Report): 2013

14. To submit the final study reports for studies performed to confirm product stability over the course of the in-process hold times of [REDACTED] (b) (4). Final study results will be submitted in the 2012 Annual Report.

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

Final Report Submission (Annual Report): 2012

15. To submit the final concurrent column life-time study reports for the Poros 50HS, Q-Sepharose and CHT Type II columns. The final report will be submitted in the 2013 Annual Report.

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

Final Report Submission (Annual Report): 2013

16. To submit the final study reports for the drug substance storage container leachate studies to assess the volatile organic compounds (VOC), semi-VOC, non-VOC and trace metals in drug substance and formulation buffer samples held at 2 to 8°C for up to 3 years and under accelerated aging conditions of 40°C to simulate 3 years at 2 to 8°C. Final study reports will be submitted in the 2013 Annual Report.

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

Final Report Submission (Annual Report): 2013

17. To re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4) sample volume and submit the summary report in a CBE-O supplement by March 31, 2013.

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

Final Report Submission as a CBE -0: March 31, 2013

18. To develop and implement a container closure integrity test to replace the sterility test in the stability program. The ability of a container closure system to maintain the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf-life should be demonstrated. Submit the summary report and data in a CBE-O supplement by December 2011.

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

Final Report Submission as a CBE -0: December 31, 2011



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

Memorandum

Date: 03/11/11 *ESL 03/11/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
PMR/PMC

From: Laughner, Erik
Sent: Friday, March 11, 2011 9:01 AM
To: 'Knight Trent, Heather'
Subject: STN 125377; FDA information request; pharmacogenomic PMR/PMC

Hello Heather,

FDA proposes the following language in response to your email yesterday:

PMR ##

During the conduct of the required postmarketing study comparing 3mg/kg vs. 10mg/kg ipilimumab monotherapy, you will obtain comprehensive baseline DNA sample acquisition ($\geq 95\%$ of ITT) and conduct pharmacogenomic association analyses to assess the potential clinical utility of CD86 gene polymorphisms as genetic determinants of immune related adverse events. You will provide a protocol that addresses SNP selection, data analyses approaches, and other methodological issues. You will provide a Final Report including electronic datasets.

- Final Protocol Submission: (b) (4)
- Final Report Submission: on or before December 29, 2016

PMC ##

To identify further genetic determinants of immune-related adverse events caused by ipilimumab. DNA samples from the required post-marketing study comparing 3 mg/kg vs. 10 mg/kg ipilimumab monotherapy will be used to conduct genome-wide association analyses. The design of these analyses will be reviewed by FDA and a Final Report with electronic datasets will be provided.

- Draft Protocol Submission: December 29, 2016
- Final Protocol Submission: July 31, 2017
- Final Report Submission: on or before December 31, 2018

Please confirm that this is acceptable.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 03/10/11 3:30 PM

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request; Revisions to REMS materials

From: Laughner, Erik
Sent: Thursday, March 10, 2011 9:56 AM
To: 'Knight Trent, Heather'
Subject: STN 125377; FDA Information Request; draft REMS materials

Heather,

As discussed yesterday, please see FDA's proposed drafts for REMS. Our expectation is that we will receive BMS's reply (mark-up on draft documents) today or tomorrow. We are hoping to start the REMS clearance process in the next few days.



3-9-11 Ipi draft 3-9-11 Required for
REMS.doc (75 ... REMS asses...

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
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Memorandum

Date: 03/10/11 *SL 03/09/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
Final Carton/Container draft labeling

From: Laughner, Erik
Sent: Thursday, March 10, 2011 10:07 AM
To: 'Knight Trent, Heather'
Subject: RE: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card

Heather,

The carton/container labels appear to address all remaining FDA edits. Have these been formally submitted as the final drafts to the BLA?

Tx,

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, March 07, 2011 3:39 PM
To: Laughner, Erik
Subject: RE: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card

Dear Erik,

The response document and revised carton/containers are attached.

Sincerely,

Heather



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: 03/09/11

ESL 03/09/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Face-to-Face Meeting with BMS at White Oak to resolve package insert labeling and align corresponding REMS materials.

FDA Attendees: Erik Laughner, Jeff Summers, Patricia Keegan, Yuan Li-Shen, Kaushik Shastri, Joyce Weaver, Grace Carmouze

BMS Attendees:

- Michael Giordano
- Brian Daniels
- Margo Heath-Chiozzi
- Renzo Canetta
- April Heather Knight-Trent
- David Berman
- Tai-Tsang Chen
- Todd Rider
- Gita Motupally
- Ramy Ibrahim
- Anne Cross
- Allison Hunt
- Seon won Han

Background: On March 4, 2011, BMS was notified that a working face-to-face meeting was required with FDA to resolve outstanding issues with the proposed YERVOY package insert regarding safety descriptions and the analyses used to generate the data. FDA had requested that BMS arrange to bring representation from statisticians, clinical team, and their REMS working group to White Oak on Wednesday March 9th from 9AM to 3PM. On March 8, 2011, FDA provided BMS via email, a partial list of information requests regarding the label to be addressed during the meeting. As this was not a formal PDUFA meeting, no formal minutes were taken.

Summary Discussion: FDA and BMS spent the day working through the proposed package insert for YERVOY. BMS provided needed clarifications on the safety characterization across the development program and within the primary efficacy study. FDA and BMS resolved many outstanding items regarding patient numbers and wording in the label. During the day, several BMS and FDA attendees held a “break-out” session to discuss the REMS program and reached agreement on the information needed to complete the materials needed.



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Memorandum

Date: 03/08/11 *FSL 03/08/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request;
Clinical

From: Laughner, Erik
Sent: Tuesday, March 08, 2011 4:21 PM
To: 'Knight Trent, Heather'
Subject: STN 125377; Information Requests in advance of 03/08/11 tcon

Heather,

At this time, we have a partial list of information requests to provide in advance of tomorrow's discussion.

I should be in the office around 8AM tomorrow.

Please confirm receipt.

Sincerely,

Erik



030811 IR
Memo.doc (38 KB)

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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FDA 030811 Questions for BMS:

Note: this is only a partial list.

2.2 Recommended Dose Modifications

- Protocol specified that if patients had treatment withheld for grade 2 toxicity, treatment may not be restarted while the patient is being treated with systemic corticosteroids. How often did this occur?

5.1 Immune-mediated Enterocolitis

- Table 1 “Frequency of Immune-Mediated Adverse Reactions within each Category” of your response document lists only 35 patients with Grade 3-5 enterocolitis; however, 36 patients were in the dataset; please clarify this discrepancy.
- Of the 5 patients who are listed as not having received systemic corticosteroid are having received low dose steroid, at least 4 appear to have received high dose steroid according to patient narratives. Why did you elect to not consider the information provided in the patient narratives.
- Per IB, patients should undergo colonoscopy first prior to systemic corticosteroid therapy. How often did this happen in study 1?
- In your response to 1/25/11 comment #14, you stated that “for subjects with severe enterocolitis, the median time on high-dose corticosteroid was 2.4 weeks and the median time on ANY corticosteroids, including taper, was 4.4 weeks”. Please indicate the location of this information regarding duration of any corticosteroids.

5.2 Immune-mediated Hepatitis

- An additional 2.7% of patients experienced moderate hepatotoxicity in YERVOY treated patients. Why is there is no information provided for these patients?
- Among patients with evidence of severe hepatotoxicity, 25% were treated with high-dose corticosteroids (100 mg/day of prednisone or equivalent), 38% received low-dose corticosteroids, and the remainder received no therapy. Please confirm.
- The instructions are to withhold YERVOY dosing in patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal. Did this happen for the 14 patients with moderate hepatic toxicity? How were these patients managed?



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Memorandum

Date: 03/04/11 *ESC 03/04/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (Carton/Container Revisions; advice on "business card")

From: Laughner, Erik
Sent: Friday, March 04, 2011 1:28 PM
To: Knight Trent, Heather
Subject: RE: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card

Heather,

We have reviewed the carton/container labels as revised and have the final following comments:

Container Label and Carton Labeling

Increase the font size of the route of administration, *For Intravenous Infusion Only*, so that it is more prominent than the *Single-use vial; Discard unused portion* statement.

Carton Labeling

Revise the statement, [REDACTED]

(b) (4)

to read:

Administer diluted solution through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

Note addition of the words *diluted solution*.

Please confirm receipt.

Sincerely,

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Wednesday, March 02, 2011 12:33 PM
To: Laughner, Erik
Subject: RE: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card

Dear Erik,

The response document and proposed artwork for the carton and containers are attached. As per your request these will not be submitted officially at this time to the BLA until we have a response from FDA.

Sincerely,
Heather



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Drug Evaluation and Research

Memorandum

Date: 03/04/11

SL 03/04/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA request for Face-to-Face Meeting.

FDA Attendees: Erik Laughner, Jeff Summers, Patricia Keegan, Yuan Li-Shen, Kaushik Shastri

BMS Attendees: Heather Knight-Trent

Discussion: Heather was notified that a working face-to-face meeting was required between BMS and FDA to resolve outstanding issues with the proposed YERVOY package insert (and safety analyses used to generate the data). FDA requested that BMS arrange to bring their statisticians, clinical team, and REMS working group to White Oak on Wednesday March 7th from 9AM to 3PM. FDA requested that a likely attendee list be provided by COB today so that any foreign visitors can be cleared in time given this short notice. Heather acknowledged and agreed to provide a list. A teleconference line would also be available if needed.

FDA noted that the characterization of safety continued to be an issue and stated that any future applications submitted like STN 125377 would receive an RTF.



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Memorandum

Date: March 4, 2011 EEL 03/04/11
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Eleventh Labeling Meeting

FDA Attendees: Erik Laughner, Jeff Summers, Patricia Keegan, Yuan Li-Shen, Kaushik Shastri

Discussion: This labeling meeting was convened to discuss safety analysis and revisions of the most recent USPI as submitted by BMS.



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Memorandum

Date: 03/01/11 *ESC 03/01/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (advice on "business card")

From: Laughner, Erik
Sent: Tuesday, March 01, 2011 1:32 PM
To: Knight Trent, Heather
Subject: FW: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card

Hello Heather,

As this will not be an accelerated approval, BMS's only obligation will be to submit the promotional materials along with the completed transmittal form FDA-2253 to DDMAC at the time of dissemination.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, February 28, 2011 2:27 PM
To: Laughner, Erik
Subject: RE: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card

Dear Erik,

The team requires clarification on FDA's comment #4 regarding the business card prior to submitting the response. Does the FDA have concern with inclusion of the business card in the carton? We will provide the business card for appropriate review.

Thanks,
Heather



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Center for Drug Evaluation and Research

Memorandum

Date: 02/25/11

SL 02/25/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request
(Carton/Container Revisions; advice on "business card")

From: Laughner, Erik
Sent: Friday, February 25, 2011 4:24 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA proposed edits to Carton/Containers; comment regarding business card
Importance: High

Hello Heather,

Please see FDA's proposed revisions for the YERVOY carton/container labels. You may submit revisions via email first and if approved, I can have BMS provide the formal amendment of final DRAFT labeling.



022511 IR Memo
Carton_Containe...

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 02/25/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA Proposed Edits to 01/20/11 submitted Carton/Container Labeling (50mg and 200mg presentations) and notification regarding "business card"

1. **CONTAINER:**

- a. If space permits, please add the statement, "See package insert for dosage and administration."

[Redacted] (b) (4)

- c. The following information is not required for a full container label and can be removed or modified to permit more room: (b) (4)

[Redacted]

- d. Per 1c., if space now permits, add the Medication Guide statement as per carton. See 21 CFR 610.60.

2. **CARTON:**

- a. Per 21 CFR 610.61(r), please add the statement, "No U.S. Standard of Potency."
- b. Per 21 CFR 610.61 and 21 CFR 201.7, please add the lot number and expiration date to the carton labels.
- c. Per 21 CFR 201.15, please remove [Redacted] (b) (4)

[Redacted] (b) (4)

- d. The following information is not required and can be removed or modified to permit the addition of required statements: (b) (4)

[REDACTED]

3. **CONTAINER AND CARTON:**

- a. Please move the “Single-Use Vial” statement and remove (b) (4) statement located below the NDC presentation to prevent crowding and provide increased visibility of the NDC number. See recommended format per 3b below.
- b. Please consider revising the presentation of the tradename, proper name, dosage form, strength, and route of administration to the following recommended format (note need for at least ½ prominence of proper name and dosage form to tradename):

YERVOY™
(ipilimumab)
Injection

XX mg/ mL
(X mg/ mL)

For Intravenous Infusion Only
Single-use vial; Discard unused portion

- c. Decrease the prominence of the “Rx only” statement by removing the surrounding box.

4. **REGARDING THE PROPOSED “BUSINESS CARD LABEL” THAT IS INCLUDED WITH EVERY VIAL OF YERVOY:**

DDMAC considers the business card promotional labeling. The final version of the business card along with a copy of the approved professional labeling should be submitted to DDMAC on Form FDA-2253 at the time of initial dissemination. Alternatively, BMS may pre-submit a voluntary request to DDMAC on advisory comments on the business card.



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Memorandum

Date: 02/25/11 ESC 02/25/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding Applicant address for BLA; labeling

I spoke with Heather Knight-Trent at BMS to note that the 356h forms submitted with all the BLA amendments listed the primary applicant in Connecticut; however, all the proposed labeling has the applicant in Princeton, New Jersey. Heather agreed that the main headquarters for Bristol-Myers Squibb Company was in Princeton, New Jersey and that should be the applicant address as currently indicated for the ORENCIA BLA. Heather understood the issue and agreed to list Princeton, NJ on all future amendments 356h forms (front page) and provide a cover-letter formally clarifying that the main applicant address would be in Princeton, New Jersey.

I also indicated the FDA would provide edits to the Medication Guide today for review and that carton/container labeling edits would follow either today or early next week.



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Memorandum

Date: 02/25/11 *ESL 02/25/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request
(Medication Guide Revisions)

From: Laughner, Erik
Sent: Friday, February 25, 2011 1:04 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA proposed Medication Guide Revisions 02/25/11

Hello Heather,

FDA provides the following proposed Medication Guide for YERVOY. I have decided to provide as a clean version to make BMS's review and any counter-revisions more efficient.



FDA 022511
ledguide Edits Clea.

Please review and provide a response back by early next week.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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301-796-1393
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<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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



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Memorandum

Date: February 25, 2011 *ESL 02/25/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Tenth Labeling Meeting

FDA Attendees: Erik Laughner, Kimberly Rains, Karen Jones, Jibril Abdus-Samad

Discussion: This labeling meeting was convened to discuss revisions of the proposed carton/containers for Yervoy.



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Memorandum

Date: 02/23/11 *ESC 02/23/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (PMRs 1-5)

From: Laughner, Erik
Sent: Wednesday, February 23, 2011 4:22 PM
To: 'Knight Trent, Heather'
Subject: RE: STN 125377; FDA proposed PMRs; please review and provide feedback

Heather,

There is a slight revision under PMR 5.

See attached.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Wednesday, February 23, 2011 4:11 PM
To: Laughner, Erik
Subject: RE: STN 125377; FDA proposed PMRs; please review and provide feedback

Dear Erik,
I confirm receipt and will work with the team on a response.
Sincerely,
Heather

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Wednesday, February 23, 2011 3:52 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA proposed PMRs; please review and provide feedback
Importance: High

Heather,

FDA has now proposed a total of 5 PMRs for STN 125377 which can be reviewed in the attached memo for consideration and agreement. Please fill-in dates where needed.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 02/23/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA Proposed PMRs 1-5

PROPOSED POSTMARKETING REQUIREMENTS 1-5 UNDER 505(o) FOR STN 125377

1. Regarding your 01/18/11 submission for the nonclinical repro-toxicology study, FDA proposes that the Final Report Submission date will be 12/31/11.

To submit the Final Report for study DN10020 on the enhanced pre- and post-natal developmental (ePPND) toxicity of ipilimumab in cynomolgus monkeys.

Final Report Submission: 12/31/11 (changed from [REDACTED] (b)(4) to actual day which is needed)

2. Regarding the proposed 3 vs. 10mg clinical study, FDA proposes the following in response to your 01/18/11 submission:

Following the assessment of data from Trial CA184024, the applicant will design and conduct a trial to compare the efficacy, with the primary endpoint of overall survival, and the safety of ipilimumab at doses of 3mg/kg versus 10mg/kg given as monotherapy every three weeks for four doses in patients with unresectable stage III or Stage IV melanoma.

- **Preliminary CA184024 Data Submission:** June 30, 2011 (needed month/day)
- **Draft Protocol Synopsis Submission:** June 30, 2011
- **Final Protocol Submission:** September 30, 2011
- **First Patient Accrued to Trial:** March (b)(4), 2012
- **Last Patient Accrued to Trial:** by Month, Day, Year
- **Trial Completion:** by Month, Day, Year
- **Final Report Submission:** December 31, (b)(4)

FDA proposes the following new immuno specific PMRs:

3. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ipilimumab, including procedures for accurate detection of antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

Final Report Submission (Assay and Methodology): by Month, Day, Year

4. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ipilimumab, including procedures for accurate detection of neutralizing antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling. In the event such an assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided.

Final Report Submission (Assay and Methodology): by Month, Day, Year

5. To conduct an assessment of anti-drug antibody (ADA) response and neutralizing ADA responses to ipilimumab with a validated assay (required in PMR 3 and 4) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 ipilimumab-treated patients enrolled in the required postmarketing study comparing 3 mg/kg versus 10 mg/kg of ipilimumab monotherapy. The final report will include information on the level of ipilimumab in each patient's test sample at each sampling time point.

Final Protocol Submission:	by Month, Day, Year
Patient Accrual Completed	by Month, Day, Year
Trial Completion Date:	by Month, Day, Year
Final Report Submission:	by Month, Day, Year



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Memorandum

Date: 02/22/11 *ESC 02/22/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (Pharmacogenomics PMCs)

From: Laughner, Erik
Sent: Tuesday, February 22, 2011 6:31 PM
To: Laughner, Erik; Knight Trent, Heather
Subject: Correction; STN 125377; Proposed Pharmacogenomic PMCs

Heather,

In my previous email, I used the wrong header.

These were PMCs for pharmacogenomic PMCs. I will be sending the proposed immuno PMRs under separate cover in the next day or two.

Erik

From: Laughner, Erik
Sent: Tuesday, February 22, 2011 6:24 PM
To: 'Knight Trent, Heather'
Subject: STN 125377; Proposed Immuno PMRs

Heather,

Please see the following proposed PMRs. Please review and provide milestone dates.

PMC ##

To identify genetic determinants of immune related adverse reactions caused by Ipilimumab, you will obtain $\geq 95\%$ complete DNA sample acquisition from the required postmarketing study comparing 3 mg/kg vs 10 mg/kg Ipilimumab monotherapy and then conduct genome-wide association analyses and specific candidate gene (CD86, HLA family) analyses on these samples. You will provide a Final Report specific for this PMC including electronic data sets that address the identification and association of genetic determinants with adjudicated cases of immune related adverse reactions.

PMC ##

To perform pharmacogenomic reanalysis of your dataset from Study MDX010-20 using the adjudicated cases based on the FDA agreed upon case definitions of immune-related adverse reactions.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 02/22/11

ESL 02/22/11

From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (CMC)

From: Laughner, Erik
Sent: Tuesday, February 22, 2011 5:39 PM
To: Knight Trent, Heather
Cc: Peck, David
Subject: STN 125377; FDA information request CMC and PMC

Hello Heather,

Please see the following information requests and proposed additional PMCs from the facility group. A timely response for 1-3 is appreciated.

INFORMATION REQUESTS:

1.

[Redacted] (b) (4)

2. Please provide summary and information data on the current maximum valid dilution (MVD) and inhibition/enhancement results for 3 lots of drug product. Please indicate which dilution will be used in release testing the drug product.

3. Please provide additional information and data for validation of the microbial ingress test for container closure integrity. Indicate the [Redacted] (b) (4) used on the vials and the [Redacted] (b) (4) conditions used in the performance of the test. Describe the sensitivity of the test (minimum detectable leak size) and the positive controls used. Confirm that the media used in the test was tested for growth promotion.

PROPOSED PMCs:

1. Please commit to complete the shipping validation studies on drug product vials using worst case shipping conditions (time and temperature). Describe the time and temperature shipping acceptance criteria and the study completion. Summary data should be submitted as a PMC in a CBE-0 supplement by December 2011.

2. The ability of a container closure system to maintain the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf-life should be demonstrated per 1994 FDA Guidance (Submission documentation for sterilization Process validation)

and 2008 Guidance (Container and Closure System Integrity Testing in lieu of Sterility Testing). It is recommended that a container closure integrity test be developed and be implemented to replace the sterility test on samples on stability. Please develop and implement a container closure integrity test to replace the sterility test in the stability program in a CBE-0 as a PMC by December 2011.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA

301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: February 18, 2011 *EL 2/18/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Team Wrap-up Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Kun He, Anne Pilaro, Christian Grimstein, Barbara Rellahan, Carla Lankford, Grace Carmouze, Jeff Summers, Andrew McDougal, Joyce Weaver, Kalavati Suvarna, Patricia Hughes, Sue Kang, Donald Obenhuber, Sue Kang, Kim Rains, Andrew McDougal, Yuan-Li Shen, Kun He, Aakanksha Khandelwal, Robert Pratt, Donald Obenhuber, Steve Morin, Tamy Kim, Karen Jones, Issam Zineh, Subramanian Muthukumar, Deanne Varney

Participants were present from major disciplines. Per 21st Century review, this meeting was held with the following objectives:

- Develop a comprehensive understanding of the safety, efficacy and quality of the proposed product through presentations of key findings of all reviews, consults and inspections.
- Identify any issues that could preclude an approval action.
- Come to agreement on a preliminary decision on the regulatory action.
- have discussions regarding potential post-marketing commitments and labeling.



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Memorandum

Date: 02/14/11 ^{ESL}
02/14/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding
CMC/PMCs

FDA Attendees:

Erik Laughner- DBOP
Subramanian Muthukkumar- DMA
Barbara Rellahan- DMA

BMS Attendees:

Dave Peck, Associate Director, Global Regulatory Sciences - CMC
Mark Rosolowsky, Vice President, Global Regulatory Sciences - CMC
David Smolin, Vice President, Biologics Process and Product Development
Michael Grace, Executive Director, Biologics Process and Product Development – Analytical
Development
Jonathan Basch, Senior Research Scientist, Biologics Process and Product Development -
Analytical Development
Ralph Abraham, Associate Director, Biologics Process and Product Development – Analytical
Development
Susan Abu-Absi, Senior Research Scientist, Biologics Process and Product Development –
Manufacturing Sciences
Rajesh Gandhi, Director, Biopharmaceutics
Madhav Kamat, Research Fellow, Biopharmaceutics

Background: FDA requested a tcon with BMS. Prior to the actual tcon, FDA provided BMS
comments and proposed CMC PMCs on February 8, 2011.

DISCUSSION/ACTION ITEM AGREEMENTS:

BMS agreed to update ref. std. qualification spec to (b) (4)

BMS agreed to update DS acceptance criteria for basic region to (b) (4) and main peak to (b) (4)

BMS agreed to replace CEX with IEF test for DP release including acceptance criteria, spec
justification, method summary and validation summary.

BMS will provide commitment to submit CEX as a DP release test by June 30, 2011 (CBE-30)

BMS agreed to provide semiquantitative assessment of HCP impurity coverage as soon as possible

Regarding the FDA proposed PMCs, BMS agreed and provided the following dates:

- (b) (4) Clearance – final study report – July 29, 2011 (CBE-0)
- Replace IEF with CEX for DS and DP stability programs by March 31, 2014 (CBE-30)
- Reassess release and stability specifications for DS and DP and submit in 2013 AR
- Submit column life-time final study reports for the 3 chromatography resins in the 2013 AR
- Provide final study reports confirming product stability during the in-process holds in the 2012 AR
- Submit final study reports on DS container leachate studies in the 2013 AR



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Memorandum

SE
02/14/11
Date: 02/14/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (CMC)

From: Laughner, Erik
Sent: Monday, February 14, 2011 9:03 AM
To: Peck, David
Cc: Knight Trent, Heather
Subject: RE: BLA STN 125377 (ipilimumab) -CMC Follow-up
Importance: High

Hi Dave,

Please see FDA clarification:

Your response to the August 2, 2010 request is inadequate. Valid hold times for (b) (4) should be established based on commercial manufacturing data (b) (4). It should be established as the shortest of the 3 longest hold times. The data you have provided for the manufacturing scale runs do not support microbial control at the end of the hold times you have established. You can either use the data you have available to establish a revised hold time or commit to conducting a study to support the established hold times for all (b) (4). If you decide to revise the hold times, please provide an updated Table with the revised hold times for each (b) (4) along with the supporting data (3 longest hold times observed during commercial manufacturing scale runs).

Please confirm receipt.

Sincerely,

Erik Laughner, RPM

From: Peck, David [mailto:david.peck@bms.com]
Sent: Friday, February 11, 2011 4:55 PM
To: Laughner, Erik
Subject: RE: BLA STN 125377 (ipilimumab) - Conference Call 11 am - BMS Attendees

Hi again – the response from the Feb 2 IR will be submitted with the Feb IR (mentioned below).
Dave

From: Peck, David
Sent: Friday, February 11, 2011 4:49 PM
To: 'Laughner, Erik'
Subject: RE: BLA STN 125377 (ipilimumab) - Conference Call 11 am - BMS Attendees

Hi Erik –

a) All BMS attendees listed were on line.

b) Action Items:

- Provide updates to relevant sections of the BLA by Feb 22, desk copy provided earlier for IRs dated Feb 2 and Feb 8
 - Update ref. std. qualification spec to (b) (4) %
 - Update DS acceptance criteria for basic region to (b) (4) % and main peak to (b) (4) %
 - Replace CEX with IEF test for DP release including acceptance criteria, spec justification, method summary and validation summary. BMS will provide commitment to submit CEX as a DP release test by June 30, 2011 (CBE-30)
 - Provide semiquantitative assessment of HCP impurity coverage as soon as possible
- PMCs – submit “available dates” to BLA
 - (b) (4) Clearance – final study report – July 29, 2011 (CBE-0)
 - Replace IEF with CEX for DS and DP stability programs by March 31, 2014 (CBE-30)
 - Reassess release and stability specifications for DS and DP and submit in 2013 AR
 - Submit column life-time final study reports for the 3 chromatography resins in the 2013 AR
 - Provide final study reports confirming product stability during the in-process holds in the 2012 AR
 - Submit final study reports on DS container leachate studies in the 2013 AR

c) We would like to ask a clarification question regarding FDA's requested for information dated Feb 2, 2011.

1. *The submitted data does not support the established hold time for (b) (4). Please provide data to support microbial control at the end of established hold conditions from 3 lots of each (b) (4) or revise the established hold time based on data collected during actual manufacturing for each of the (b) (4).*

A similar request was made by FDA in the Aug 2, 2010 request for information (Facilities), which was item #6 as indicated below

6. *Please provide data from 3 commercial lots to demonstrate microbial control of (b) (4) and drug substance for the established hold times.*

BMS provided a response on Aug 30, 2010 (serial 0012) with supporting data. This response summarized the approach taken to validate hold times for (b) (4) that included microbial control, and the actual (b) (4) validation reports. Validations studies were completed at (b) (4) to validate hold times at manufacturing scale. Growth promotion studies were completed to indicate these solutions were capable of supporting growth. In response to the FDA question, BMS committed to a supplementary validation protocol in which three commercial lots of ipilimumab would be held at a single defined "worst case" hold point from an equipment design / microbiological perspective, that would further validated the (b) (4) hold times. BMS believes that these two studies already completed, as well as the supplementary protocol mentioned above, are sufficient evidence to validate microbial control for the in (b) (4) hold times.

During the PAI inspection at (b) (4) in October, BMS recollection is that FDA reviewed the (b) (4) studies and found them to be acceptable. Per FDA request, BMS sent to FDA after the inspection the actual maximum hold times from the history of ipilimumab manufacturing at (b) (4).

BMS understanding was that the information provided to question #6 on August 30, 2010 was acceptable to FDA, and that the studies/data reviewed ruing the PAI were acceptable for microbial control of (b) (4) and hold time validation.

Given the new request from Feb. 2, it would be helpful for BMS to understand what the FDA comments and concerns are with the (b) (4) studies and the supplementary full scale validation protocol to confirm the validation using 3 lots of ipilimumab. Understanding where the FDA concerns are will help BMS to ensure they provide a response that meets the needs of FDA.

If you could get a quick response, it would help us meet the submission targets.
Thank you,
Dave

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Friday, February 11, 2011 11:23 AM
To: Peck, David
Subject: RE: BLA STN 125377 (ipilimumab) - Conference Call 11 am - BMS Attendees

Hi Dave,

Can you confirm all from BMS were present as noted in your pre-meeting email?

FDA was:

Erik Laughner- DBOP
Subramanian Muthukkumar- DMA
Barbara Rellahan.- DMA

Can you please send me a quick action item summary of today's tcon?

Tx,

Erik

From: Peck, David [mailto:david.peck@bms.com]
Sent: Friday, February 11, 2011 7:59 AM
To: Laughner, Erik
Subject: BLA STN 125377 (ipilimumab) - Conference Call 11 am - BMS Attendees

Hi Erik – Here are the attendees on our side:

Dave Peck, Associate Director, Global Regulatory Sciences - CMC
Mark Rosolowsky, Vice President, Global Regulatory Sciences - CMC
David Smolin, Vice President, Biologics Process and Product Development
Michael Grace, Executive Director, Biologics Process and Product Development – Analytical Development
Jonathan Basch, Senior Research Scientist, Biologics Process and Product Development - Analytical Development
Ralph Abraham, Associate Director, Biologics Process and Product Development – Analytical Development
Susan Abu-Absi, Senior Research Scientist, Biologics Process and Product Development – Manufacturing Sciences
Rajesh Gandhi, Director, Biopharmaceutics
Madhav Kamat, Research Fellow, Biopharamceutics

To simplify the role call I'll just let you know if there are any differences at the beginning of the meeting.

Conference Call Information (unchanged from what Heather provided):

Dial-in Number: 866-217-3840

Code: 0331122723

Regards,
Dave

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

Memorandum

Date: 02/11/11 *Σ 5 02/11/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Draft Partial FDA Labeling

From: Laughner, Erik
Sent: Friday, February 11, 2011 4:45 PM
To: Knight Trent, Heather
Subject: FW: STN 125377; FDA section specific proposed labeling 021111

Heather,

I just rec'd a late request to add the following to the label that we provided (for your review):

Add % age >=65 in the geriatric session (141/511=28%).

Erik

From: Laughner, Erik
Sent: Friday, February 11, 2011 4:29 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA section specific proposed labeling 021111
Importance: High

Hello Heather,

Attached you will find a word file of section specific FDA proposed labeling to your 01/06/11 label. Rather than provide an entire label back to you, I have only retained those sections (non-safety) that we worked on today.

We ask that BMS review and integrate any counter-revisions into your complete label that it targeted to FDA on 02/18.

We anticipated that upon review of the 02/18 label and supporting document we will have in internal "REMS regrouping meeting" to layout a strategy for focusing our efforts on reviewing the REMS components.

Please confirm receipt of this message.

Sincerely,

Erik

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



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Memorandum

Date: February 11, 2011 *ESL 02/11/2011*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Eighth Labeling Meeting

FDA Attendees: Kaushik Shastri, Erik Laughner, Carol Broadnax, Yuan-Li Shen, Joyce Weaver, Kim Rains, Aakanksha Khandelwal, Hong Zhao, Grace Carmouze, Barabara Rellahan, Kun He, Christian Grimstein, Jibril Abdus-Samad

Discussion: This labeling meeting was convened to discuss revisions to the complete package insert minus those outstanding revisions still needed by BMS regarding safety presentation.



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Memorandum

Date: February 11, 2011 Esc 02/11/11
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Standing Monthly Team Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Kun He, Anne Pilaro, Christian Grimstein, Barbara Rellahan Carla Lankford, Grace Carmouze, Jeff Summers, Andrew McDougal, Jibril Abdus-Samad, Joyce Weaver, Kalavati Suvarna, Patricia Hughes. Sue Kang, Donald Obenhuber, Sue Kang, Kim Rains, Andrew McDougal, Yuan-Li Shen, Kun He

Participants were present from major disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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Memorandum

Date: 02/22/11 Esc 02/22/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (CMC)

From: Laughner, Erik
Sent: Tuesday, February 22, 2011 12:17 PM
To: Knight Trent, Heather
Cc: Peck, David
Subject: STN 125377; Information request; PMC (CMC)
Importance: High

Heather,

In the response Dave provided via email to FDA last week, we have the following information request:

Please send proposed wording for the post-marketing commitment discussed in response to request #2 (STN 125377 CMC Desk Copy Response to Information Request Date Feb 2, 2011) along with the schedule milestone dates or review the wording in the next sentence and provide edits. The commitment is "To re-assess the bioburden action limits for the (b) (4) based on the manufacturing scale data from (b) (4) sample volume and submit the final summary report in a CBE-0 supplement by March 31, 2013".

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 02/22/11 *SSL 02/22/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (CMC)

From: Laughner, Erik
Sent: Tuesday, February 22, 2011 12:12 PM
To: Knight Trent, Heather
Cc: Peck, David
Subject: STN 125377 ; Information Request; CMC
Importance: High

Heather,

Please see the following advice/information requests:

1. Provide data to justify the (b) (4) overfill volume used for the 40 mL vial presentation. This data should demonstrate that (b) (4) is a minimum volume required to permit withdrawal and administration of the labeled volume. If this data is not available provide a PMC to assess the overfill volume required for the 40 mL vial and include information that this PMC will be submitted as a CBE-30 by a specified date.
2. Based on the data submitted in the BLA the approved shelf-life for the DS and DP will be 36 months. However, because both are stored at 2-8C, the total combined end-to-end shelf-life for the DP will be limited to (b) (4) from the time of DS manufacture. So the approved shelf-life of the DP will read:

The dating period for ipilimumab drug product shall be 36 months from the date of manufacture when stored at 2-8°C, but should not exceed (b) (4) from the date of drug substance manufacture.

A response to item 1 is requested by COB tomorrow.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
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Memorandum

Date: February 22, 2011 *ESL 2/22/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Ninth Labeling Meeting

FDA Attendees: Kaushik Shastri, Erik Laughner, Kate Heinrich, Joyce Weaver, Patricia Keegan, Barbara Fuller, Steve Morin, Jeff Summers, Sue Kang, Kendra Jones

Discussion: This labeling meeting was convened to discuss revisions of the proposed Medguide.



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Memorandum

Date: 02/09/11 ^{ESL} 02/09/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(Clinical)

From: Laughner, Erik
Sent: Wednesday, February 09, 2011 1:57 PM
To: Knight Trent, Heather
Subject: FDA advice/information request; STN 125377

Hello Heather,

Please see the following response document.



FDA response
07-Feb-2011 - Fin...

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 02/08/11

ESL
02/08/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (CMC)

From: Laughner, Erik
Sent: Tuesday, February 08, 2011 1:19 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA Information Request (CMC)
Importance: High

Heather,

For Friday's CMC tcon, please see the following information request.



STN 125377
0811 CMC IR memo

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 02/08/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA CMC information request

1. The acceptance criterion for the reference standard qualification specification for potency needs to be narrowed (e.g., (b)(4)%) to prevent process drift.
2. The drug substance acceptance criteria for the CEX assay for the basic and main peaks are too broad and are not justified by the data. Narrow the acceptance criteria to more closely align with clinical experience.
3. The data provided to justify the CEX acceptance criteria for drug product (DP) release is not adequate. You will need to provide data from DP batches or remove the CEX assay from DP release. If the CEX assay is removed, the IEF assay will need to be included as an assay to control for product charge. In addition you would need to provide a commitment to establish a DP CEX specification based on data collected from DP lots at release and after storage. The commitment should indicate that the final results and proposed CEX specification will be submitted as a CBE-30 by a specified date (month, day and year).
4. For the HCP assay, provide an estimate of the percentage of HCP impurities that are recognized by the anti-HCP antiserum. Include an explanation of how the value was calculated.

Provide a post-marketing commitment for the following. Please include a specified date as indicated.

1. To perform studies to confirm that clearance of (b)(4) is well controlled by the manufacturing process and provide a risk assessment for (b)(4) that may be present in the drug product. The final study report will be submitted as a CBE-0 by Month, Day, and Year.
2. To replace the IEF method with an CEX method as the specification for charge in the drug substance and drug product stability programs after three years of market life data are collected for the CEX assay on three batches of drug substance and three batches of either presentation of drug product. The final results and proposed CEX specification will be submitted as a CBE-30 by Month, Day, Year.

3. To reassess release and stability specifications for ipilimumab drug substance and drug product through April 30, 2013. The assessment will be submitted in the 2013 Annual Report.
4. To submit the final concurrent column life-time study reports for the Poros 50HS, Q-Sepharose and CHT Type II columns. The final report will be submitted in the 20XX Annual Report.
5. To submit the final study reports for studies performed to confirm product stability over the course of the in-process hold times of [REDACTED] ^{(b) (4)}. Final study results will be submitted in the 20XX Annual Report.
6. To submit the final study reports for the drug substance storage container leachate studies to assess the volatile organic compounds (VOC), semi-VOC, non-VOC and trace metals in drug substance and formulation buffer samples held at 2 to 8°C for up to 3 years and under accelerated aging conditions of 40°C to simulate 3 years at 2 to 8°C. Final study reports will be submitted in the 20XX Annual Report.



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Memorandum

Date: 02/07/11 ^{ES} 02/09/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Monday, February 07, 2011 2:45 PM
To: Knight Trent, Heather
Subject: RE: Business card label; STN 125377

Heather,

Thanks for the response. However, we still need some clarification.

Does the business card circulate with the shipping box of the carton/container?

We are just unclear how this is shared with a Health Care Provider as it was in the same folder as the carton/container labeling.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, February 07, 2011 2:33 PM
To: Laughner, Erik
Subject: RE: Business card label; STN 125377

Dear Erik,

I have attached the response to this email. It will be submitted officially after processing. The team is finalizing the wording for the label with links to the mock tables to be emailed to you today. Do you have a tentative time for the teleconference to discuss?

Sincerely,
Heather

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Monday, February 07, 2011 2:03 PM
To: Knight Trent, Heather
Subject: RE: Business card label; STN 125377

Hello Heather,

Can you advise on this?

Tx,

Erik

From: Laughner, Erik

Sent: Wednesday, February 02, 2011 4:38 PM

To: Knight Trent, Heather

Subject: Business card label; STN 125377

Heather,

In your 01/20 carton/container revision, you provided a business card label. Can you clarify what this is and the purpose? I've attached as well.

Tx,

Erik



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

ZSL
02/04/11

Date: 02/04/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding clinical safety analysis

FDA Attendees:

Erik Laughner- RPM
 Yuan Li-Shen- Statistics
 Kaushik Shastri- Clinical
 Patricia Keegan, Director
 Jeff Summers, Deputy Director Safety

BMS Attendees:

BMS Participants	Title
Anne Cross, Ph.D.	Executive Director, Global Biometric Sciences Oncology
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory Science & Pharmacovigilance
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science Virology and Oncology
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Rachel Humphrey, M.D.	Vice President, Ipilimumab Development
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences Oncology
Todd Rider	Senior Manager, GBS Programming
Heather Knight-Trent, Pharm.D.	Director, Global Regulatory Science-Oncology
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
David Berman, M.D.	Group Director, Oncology, Global Clinical Development
Ramy Ibrahim, M.D.	Group Director, Oncology, Global Clinical Development
Michael Giordano, M.D.	Head of Clinical

Background: FDA requested a tcon with BMS to discuss their 02/02/11 document provided via email in response to FDA's 01/28/11 comments regarding safety analysis/characterization.

DISCUSSION:

FDA noted that for steroid management, important information should include: # of patients who did not receive or did receive. If received, define the duration, dose amount given per pay, FDA requested that the steroids used in the datasets be normalized to some standard equivalent. BMS acknowledged and agreed to provide.

BMS clarified to FDA that the composite terms are really composites of composite terms.

BMS clarified that AST and ALT did include labs and investigator reports.

(b) (4)

FDA noted that terms such as stomatitis or esophagitis were not mapped to the composite term of enterocolitis and BMS noted that these events were deemed clinically different from ipilimumab induced colitis.

(b) (4) BMS

agreed to review and provide a response.

FDA asked that the censoring rule for the time to resolution analysis be provided. BMS acknowledged.

(b) (4)

BMS agreed to provide by 02/07 proposed draft wording for the package insert [section 5] with placeholders for actual numbers and hyperlinks to mock tables. FDA acknowledged and agreed to review in a timely fashion to move this forward.

FDA noted that other sections of the label would be reviewed and feedback provided to BMS to keep the process moving in regard to the PDUFA date.



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Memorandum

Date: 02/04/11

ESL
02/04/11

From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Friday, February 04, 2011 4:45 PM
To: Knight Trent, Heather
Subject: STN 125377; FDA Information Request

Heather,

Per discussion today, please see attached for moving forward.



020411

Characterization (sumr

We will presume that you will provide us the "mock" paragraphs with annotations to source tables etc as discussed.

We will review and can then arrange a tcon.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

Feb 4, 2011; FDA Information Request STN 125377

Note: This is just an example of the type of characterization that FDA is looking for. The dose-delay and discontinuation due to all adverse events in general, and due to specific autoimmune categories is also useful information, although not identified in the example below.

(b) (4)



Feb 4, 2011; FDA Information Request STN 125377

Note: This is just an example of the type of characterization that FDA is looking for. The dose-delay and discontinuation due to all adverse events in general, and due to specific autoimmune categories is also useful information, although not identified in the example below.

(b) (4)





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Memorandum

Date: 02/04/11 ^{ESC} 02/04/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (CMC)

From: Laughner, Erik
Sent: Friday, February 04, 2011 4:12 PM
To: Knight Trent, Heather
Subject: Request for CMC tcon 02/11 (Friday)

Hello Heather,

The CMC team would like to have a tcon with the BMS CMC group next Friday. I am targeting 11AM ET.

Please let me know early next week if this will work for BMS (David Peck et al).

FDA will provide something in writing in advance of the call.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
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Memorandum

Date: 02/03/11

ESC
02/03/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Advice (Clinical)

From: Laughner, Erik
Sent: Thursday, February 03, 2011 1:22 PM
To: Knight Trent, Heather
Subject: RE: updates STN 125377

Hello Heather,

It is my expectation that the discussion tomorrow will focus on the document you provided yesterday. I don't anticipate having anything to provide in writing prior to the con.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Wednesday, February 02, 2011 1:34 PM
To: Laughner, Erik
Subject: RE: updates STN 125377



bms-734016-respons
e-us-fda-rfi-2011-01-

Dear Erik,

BMS is providing our proposed plans to respond to the January 28 request. The revisions to the label are dependent on agreement on how to address the comments. The spreadsheet of the previous submissions to FDA will be provided in advance of the teleconference on Friday. The following is a summary of what is provided prior to the teleconference and clarifying questions:

- The responses to the FDA requests on January 28 are attached including example mocked up tables for discussion and agreement
 - BMS has consulted with 3 outside melanoma experts while preparing this response
- Revisions to the label are dependent on the new analyses and the answers to the following clarifying questions:
 - BMS has identified a term "immune-mediated" to address FDA's concern with the word autoimmune. Is this acceptable?
 - BMS requests clarification on which parts of the highlights FDA's considered in their comment were not useful for patient management. It is not clear in the version provided which section was referenced.

- BMS is proposing to provide safety data from the entire study duration instead of just the induction period. Does FDA agree?

Sincerely,
Heather

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Wednesday, February 02, 2011 12:34 PM
To: Knight Trent, Heather
Subject: updates STN 125377

Hi Heather,

Is BMS planning to send any information back to us prior to the Friday tcon?
Also, do you still intend to provide the spreadsheet of all submissions for the BLA?

Tx,

Erik



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 02/02/11
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (CMC)

From: Laughner, Erik
Sent: Wednesday, February 02, 2011 12:02 PM
To: Knight Trent, Heather
Subject: FDA information Request; STN 125377 (CMC)

Hello Heather,

Please see the following CMC information requests:

1. The submitted data does not support the established hold time for (b) (4). Please provide data to support microbial control at the end of established hold conditions from 3 lots of each (b) (4) or revise the established hold time based on data collected during actual manufacturing for each of the (b) (4).
2. The bioburden test is performed using a (b) (4). A (b) (4) sample volume should be tested to improve the sensitivity of the method. Re-assess the bioburden action limits based on manufacturing scale data from (b) (4) using the increased sample volume. This information can be submitted as a post-marketing commitment.
3. Please submit data supporting microbial control (b) (4) s over its lifetime.

We would like a proposed timeframe in responding to these.

Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: February 2, 2011 ESC 02/02/11
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Seventh Labeling Meeting

FDA Attendees: Kaushik Shastri, Erik Laughner, Jeff Summers, Kendra Jones, Jibril Abdus-Samad

Discussion: This labeling meeting was convened to discuss the proposed MedGuide.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 01/28/11

01/28/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Advice (clinical)

From: Laughner, Erik
Sent: Friday, January 28, 2011 11:44 AM
To: 'Knight Trent, Heather'
Subject: FDA Advice Post 01/27/11 Tcon; STN 125377

Heather,

We hope that the following post-meeting clarifying comments will assist BMS with the issues discussed in the label and at yesterday's tcon:

In order to characterize the ipilimumab induced enterocolitis, use a 'group' case definition that incorporates all patients adjudicated as having AE with 'composite' terms of diarrhea, colitis and intestinal perforation. Use the first occurrence of any grade event with any of these 'composite' terms, and the last date of resolution of any of these 'composite' terms to describe the duration of the event, and time to event measures. Effect of immunosuppressants should also be assessed with this enterocolitis group definition.

In order to characterize the ipilimumab induced dermatitis, use a 'group' case definition that incorporates all patients adjudicated as having AE with 'composite' terms of rash, and pruritus. Use the first occurrence of any grade event with any of these 'composite' terms, and the last date of resolution of any of these 'composite' terms to describe the duration of the event, and time to event measures.

Table 3 showing endocrinopathies must reflect that primary hypopituitarism was the primary disorder in patients with secondary hypo function of other glands. This is important information.

FDA Additional Comment:

In Table 3, under elevated transaminases of \geq Gr 3, confirm that the % numbers reflect all the abnormal laboratory values which were not due to disease progression in the liver and not just preferred terms.

Please confirm receipt of this email.

Sincerely,

Erik



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 01/27/11 ^{CS} 01/27/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding safety analysis, proposed package insert label. FDA information request

FDA Attendees:

Erik Laughner, RPM OODP/DBOP
Kaushik Shastri, Clinical Reviewer OODP/DBOP
Patricia Keegan, Director, OODP/DBOP
Yuan Li-Shen, Statistical Reviewer, OODP/DBOP

BMS Attendees:

BMS Participants	Title
Anne Cross, Ph.D.	Executive Director, Global Biometric Sciences Oncology
Mathias Hukkelhoven	Senior Vice President, Global Regulatory Science & Pharmacovigilance
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science Virology and Oncology
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Rachel Humphrey, M.D.	Vice President, Ipilimumab Development
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences Oncology
Todd Rider	Senior Manager, GBS Programming
Marianne Messina, M.S.	Associate Director, Global Biometric Sciences Oncology
Heather Knight-Trent, Pharm.D.	Director, Global Regulatory Science-Oncology
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
David Berman, M.D.	Group Director, Oncology, Global Clinical Development
Ramy Ibrahim, M.D.	Group Director, Oncology, Global Clinical Development
Seong won Han, M.D.	Executive Director Immunology and Oncology Medical Safety Assessment

Background: FDA provided BMS a revised label (with embedded comments) on Tuesday, January 25, 2011. FDA requested a tcon with BMS to discuss unresolved concerns with the presentation of safety data in the label.

DISCUSSION: FDA noted that the Dosage and Administration section of the label was problematic as the proposed labeling did not represent how this was carried out in the primary

clinical study (-020). BMS acknowledged and noted that the ipilimumab program had evolved over time and this was reflected in various Investigator Brochure revisions. BMS noted that the proposed guidelines in the label reflected the best judgment of the experts as to how to dose ipilimumab; i.e. whether to delay the dose or skip a dose in the event of toxicity. FDA stated that unless BMS had objective data from clinical studies to show that one method of dose adjustment was better than other, FDA's standard practice for writing a label is to follow what happened in the primary clinical protocol, since the efficacy and safety data for the indication are obtained from that study. FDA advised BMS to characterize and provide justification as to what happened to those patients that allowed for dose delay. BMS agreed to go back and review the patient data but noted that the CRFs were not set up to capture specific AEs as to cause of delaying/stopping rules for dosing. BMS also noted that median time to complete resolution was provided in the label.

FDA noted that they continued to struggle with how BMS characterized ipilimumab induced enterocolitis, as it related to diarrhea, colitis and intestinal perforation. FDA stated it was also unclear that immunosuppressants were beneficial for those patients when an AE was identified early. FDA advised that BMS should create a 'group' case definition that incorporates all patients adjudicated as having AE with 'composite' terms. BMS inquired whether FDA was implying that the original revised case definitions were now "off the table" as it appeared FDA had agreed they were acceptable. FDA clarified that upon review all cases of diarrhea, who had an endoscopy done had colitis. Hence distinguishing colitis as separate from diarrhea did not make sense, especially stating that diarrhea and colitis had different resolution times in the same patient.

FDA noted that difficulties in finishing the safety review prevented the ability to move forward on the REMS. BMS acknowledged and inquired whether it would be helpful if a team came to White Oak to work with the FDA review team on trying to resolve the safety issues. FDA noted that they would like to see BMS's response to the labeling (and labeling comments) as well as the discussion today before that possibility.

BMS expressed concern that the proposed FDA label had changed the term (b) (4) to autoimmune. (b) (4)

(b) (4) FDA stated they were uncomfortable with the term (b) (4) and BMS should try to then propose an alternate term.

(b) (4)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 01/25/11 ^{ESL}
_{01/25/11}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Draft Partial FDA labeling

From: Laughner, Erik
Sent: Tuesday, January 25, 2011 10:53 AM
To: Knight Trent, Heather
Subject: STN 125377; FDA Labeling Revision
Importance: High

Good Morning Heather,

FDA provides the following ipilimumab label. FDA edits are red-lined off BMS's 01/06/11 clean revised label.

There are a number of issues to resolve as noted in the labeling comments. FDA anticipates that BMS can provide a revision back within 1 week.

We also will discuss at the tcon Thursday.



012511 FDA
roposed Draft Labe.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
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Memorandum

Date: 01/24/11 ^{ESL}
_{01/24/11}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(Clinical)

From: Laughner, Erik
Sent: Monday, January 24, 2011 11:24 AM
To: 'Knight Trent, Heather'
Subject: FDA information request; STN 125377
Importance: High

Hello Heather,

We have the following information request:

FDA can not confirm Table 5.3.3 for Prior Antineoplastic therapy related to study medication. Please submit related SAS programs as stated for creating this table, i.e. tpshx1.sas, tprhx1.sas and sfty_lmed.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM



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Memorandum

Date: 01/21/11 *ssc 01/23/11*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical pharmacology/CMC)

From: Laughner, Erik
Sent: Friday, January 21, 2011 12:53 PM
To: 'Knight Trent, Heather'
Subject: FDA Information Request; STN 125377

Hello Heather,

We have the following information requests:

1. Data from study CA184022 indicates that at least 6.9% of the subjects who received a 0.3 mg/kg dose of ipilimumab developed anti-drug antibodies (ADA). Because both the serum and plasma ADA assays have relatively high sensitivity to product interference and a 0.3 mg/kg dose would be expected to have the lowest level of product interference of the three dose cohorts, we consider the incidence of ADA in the low dose group to be the most reliable data on which to base the probably of an ADA response and propose to use this incidence (6.9%) in the label. Provide comment and any additional data that would suggest ADA incidence in the 0.3 mg/kg is not a reliable predictor of product immunogenicity at the 3 mg/kg dose.
2. Provide information of the levels of drug product that were present in patient samples at the time the samples are collected for ADA analysis for studies MDX010-20 and CA184022. Provide this information as the percent of patients that would have had $\leq 5\text{ug/mL}$, between 5-10 ug/mL and those that had $> 10\text{ug/mL}$ drug product in their samples for each trial.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
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Memorandum

Date: January 20, 2011 ^{EL} 01/20/11
From: Erik Laughner, M.S., DBOP/ODDP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Sixth Labeling Meeting

FDA Attendees: Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Erik Laughner

Discussion: This labeling meeting was convened to discuss the
“CONTRAINDICATIONS, OVERDOSAGE, WARNINGS AND PRECAUTIONS,
and ADVERSE REACTIONS” sections of the proposed package insert label.



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Memorandum

Date: January 18, 2011 ECL 01/18/11
From: Erik Laughner, M.S., DBOP/ODDP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Fifth Labeling Meeting

FDA Attendees: Kaushik Shastri, Patricia Keegan, Barbara Rellahan, Andrew McDougal, Jeff Summers, Erik Laughner

Discussion: This labeling meeting was convened to discuss the “CONTRAINDICATIONS; OVERDOSAGE, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS” sections of the proposed package insert label.



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Memorandum

Date: 01/18/11 ²⁵²
_{01/18/11}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Tuesday, January 18, 2011 11:29 AM
To: Knight Trent, Heather
Subject: FDA Information Request; STN 125377 (ipilimumb)
Importance: High

Good Morning Heather,

We have the following information requests which we need a response in within 24hrs:

- (1) Provide the program used to generate the adverse events data (n=1498) submitted in the Yervoy labeling support document on 1/6/11
- (2) Confirm that study MDX010-03 (listed in the frequency of study drug related adverse events table on page 1 of 27 submitted on 1/6/11) was included in the ISS datasets submitted with the original application.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
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Memorandum

Date: January 14, 2011 Σ<L 01/14/11
From: Erik Laughner, M.S., DBOP/ODDP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Fourth Labeling Meeting

FDA Attendees: Yuan Li-Shen, Kaushik Shastri, Patricia Keegan, Carol Broadnax, Joyce Weaver, Barbara Rellahan, Subramnian Muthukkumar, Erik Laughner

Discussion: This labeling meeting was convened to discuss the "CONTRAINDICATIONS, OVERDOSAGE, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS" sections of the proposed package insert label.



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Memorandum

Date: 01/14/11 *See 01/14/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Friday, January 14, 2011 9:18 AM
To: Knight Trent, Heather
Subject: STN 125377; FDA information Request
Importance: High

Hello Heather,

Please see the following information request:

Although you provided dataset and analyses programs for time to resolution of ipilimumab related inflammatory adverse events in your submission dated 1/6/11, we could not find the summary report of the results of actual analyses of the resolution times of these events. Please provide this report as soon as possible.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM



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Memorandum

Date: 01/11/11 *ESL 1/11/11*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON: regarding safety analysis

FDA Attendees:

Erik Laughner, RPM OODP/DBOP
Kaushik Shastri, Clinical Reviewer OODP/DBOP
Yuan Li-Shen, Stastical Reviewer OODP/DBOP

BMS Attendees:

BMS Participants	Title
Anne Cross, Ph.D.	Executive Director, Global Biometric Sciences Oncology
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science Virology and Oncology
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences Oncology
Todd Rider	Senior Manager, GBS Programming
Marianne Messina, M.S.	Associate Director, Global Biometric Sciences Oncology
Veerle De Pril	Principal Statistician, Global Biometric Sciences
Heather Knight-Trent, Pharm.D.	Director, Global Regulatory Science-Oncology
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
David Berman, M.D.	Group Director, Oncology, Global Clinical Development
Ramy Ibrahim, M.D.	Group Director, Oncology, Global Clinical Development

Background: BMS requested a teleconference to with FDA to discuss the following FDA information request provided to BMS on December 7, 2010:

3. Please create a flags in the newly created dataset for (1) adverse events for special interest for those events occurring during induction phase, and (2) cycle number. In the description and summary of the adjudicated inflammatory events, please also provide a separate description for events only occurring in the induction period.

In the coverletter to the December 23, 2010, BLA amendment, BMS noted the following:

The request for cycle number flags has not been addressed in the AEEOSI dataset (AEEOSI.XPT) due to a lack of understanding the specifics of the FDA request. We would like to request a teleconference to clarify this request in the context of the terminology in the protocol, the treatment schedule and the data collection. In the context of this protocol, four cycles were considered. Cycle 1, 2, 3, and 4 represent induction cycle (i.e., induction phase), first re-induction cycle, second re-induction cycle, and third re-induction cycle respectively. Within each protocol defined cycle, a maximum of 4 doses every three weeks was administered. BMS is unclear as to whether the request refers to the protocol description of cycles or whether it refers to dose number within a cycle, or dose number from start of treatment.

DISCUSSION: FDA requested that BMS provided clarification on the observation difference between the AEEOSI datasets submitted for the Grade 3 and higher analysis and the Grade 2 and higher analysis. BMS noted that the CTC grade 2 AST and ALT labs were added to the most recent AEEOSI dataset. FDA noted that supportive documentation was not submitted for the Grade 2 and higher inflammatory events. BMS acknowledged and stated that this was because very little supportive documentation was available. FDA indicated that the algorithm for Grade 2 events was not as definitive as for Grade 3.

BMS also advised FDA that the proposed PMRs for the clinical study and nonclinical study would be provided next week rather than the end of January as originally targeted. FDA acknowledged.



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Memorandum

Date: 01/11/11

ESL
01/11/11

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(statistical)

From: Laughner, Erik
Sent: Tuesday, January 11, 2011 3:41 PM
To: Knight Trent, Heather
Subject: FDA Information Request; BLA STN 125377
Importance: High

Hello Heather,

I have the following information request from stats:

There is a LABRES dataset used in SAS program m-fda-aeoosi-outcome-v02, but it was not included in the submission. Please clarify how to create LABRES using LABRE01 and LABRE02.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
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Memorandum

Date: January 7, 2011 *SS- 01/07/11*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Standing Monthly Team Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Kun He, Anne Pilaro, Christian Grimstein, Barbara Rellahan Carla Lankford, Grace Carmouze, Jeff Summers, Andrew McDougal, Jibril Abdus-Samad, Joyce Weaver, Kalavati Suvarna, Patricia Hughes. Sue Kang

Participants were present from major disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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Memorandum

Date: 12/15/10 ^{Σ 56}
12/15/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Requests (CMC)

From: Laughner, Erik
Sent: Wednesday, December 15, 2010 4:05 PM
To: 'Knight Trent, Heather'
Subject: STN 125377; FDA information Request CMC
Importance: High

Hello Heather,



121510 IR
Memo.doc (77 KB)

Please see the attached information requests regarding CMC for STN 125377.

FDA would like to have a response back on this information by January 12, 2011.

The CMC team informed me that they can then have a tcon with BMS if needed to hear BMS's proposals with regard to setting final specifications as outlined in the information request.

Please confirm receipt of this email.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
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Memorandum

Date: December 15, 2010
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125377 (Ipilimumab)

Product

1. Data submitted is not sufficient to support lack of release testing for the product's basic and main peak charge isoforms. Revise the drug substance (DS) and drug product (DP) release acceptance criteria for the CEX chromatography assay to include numerical specifications for all the major charge isoforms (i.e., percent main, acidic and basic). Provide a justification for the proposed acceptance criteria.
2. The data submitted do not support use of the CEX assay in the post-approval stability protocol. Revise the DS and DP post-approval stability protocol to include the IEF assay with acceptance criteria for control of product charge. Update the BLA with revised DS and DP stability specifications. The CEX assay can be implemented when sufficient real-time stability data is submitted to support its use.
3. Revise the DP release and stability specification for sub-visible particulate matter to reflect clinical and manufacturing experience. Provide a justification for the proposed specification.
4. (b) (4)
[REDACTED]
The proposed glycosylation acceptance criteria are all significantly wider than the calculated 95% tolerance intervals and values seen with product lots used clinically. Revise the acceptance criteria to more accurately reflect clinical experience or provide a strong justification for the proposed limits.
5. Narrow the DS release specification for host cell protein to more accurately reflect clinical experience.
6. The DS and DP acceptance criterion for appearance is not acceptable since it does not provide control over the level of visible particles. Since particles are present, a semi-quantitative assay will need to be developed and implemented (See comment 37 below). Until that assay has been developed and implemented, the visible particulate specification should include some type of limit description such as 'few' to limit the number allowed. Provide a revised acceptance criterion for visible particles.
7. Update the appropriate sections of the BLA with the revised DS and DP release specifications per comments 1, 3, and 4-6.
8. Polysorbate 80 can exhibit (b) (4)
[REDACTED]
Provide information that describes how polysorbate

- 80 quality is controlled during raw material acceptance and storage. In addition, provide information on polysorbate 80 storage conditions and whether opened containers can be reused.
9. Unlike indicated in section "Control of Process Related Impurities" CHOP and DNA are not identified as process parameters for the CEX chromatography (Table 3.2.S.2.4.2.2.T02). Please clarify and update the BLA if required.
 10. The submission indicates that samples are collected for drug substance release testing (b) (4). This does not represent the point in drug substance manufacture that would be expected to be most at risk for product quality issues, particularly for estimation of bioburden load. It is recommended that samples be collected (b) (4). Provide comment and a justification that the current sampling procedure provides an accurate assessment of product quality.
 11. Provide the Certificate of Analyses for (b) (4).
 12. Provide a list of the viruses tested for in the in assays for (b) (4) virus tests performed for cell bank testing.
 13. Figure 3.2.S.2.3.5.3.F09-Northern blot analysis for the cell banks, demonstrates (b) (4). Provide an explanation for this difference and justify that this does not represent (b) (4).
 14. Provide the description (vendor, model, name, etc) of the (b) (4) system described as "equivalent" to the (b) (4) in section 3.2.P.3.3. Provide the results supporting the classification of this alternative (b) (4) as equivalent, the raw material acceptance criteria for the (b) (4) and leachable/extractable information.
 15. Update section 3.2.P.3.5, extractable study for (b) (4), to include information on the solvent used and study conditions. Include a patient impact risk assessment on the identified extractables.
 16. Confirm that drug product lots will be produced from a single drug substance lot. If multiple drug substance lots are used to produce a drug product lot, validation data will need to be provided to support this procedure. In addition information on how the drug product shelf-life will be calculated should be provided.
 17. Provide detailed information on the composition and configuration for all DP shipping containers.
 18. Provide data to support stability of the drug product during shipment from the manufacturing site to the BMS distribution center and from the distribution center to the end user. Analysis of product quality should include, but not be limited to, an assessment of shipping induced aggregation and particulate formation.
 19. Update section 3.2.P.3.5, to include the ISTA 1A shock and vibration study report performed as part of the shipping evaluation.
 20. The BLA indicates that BMS (East Syracuse, NY) is an alternative site for the ELISA binding, SDS-PAGE and residual DNA assay. The BLA, however, does not appear to contain information to support BMS as an alternative site for these assays. Provide the method transfer protocol and report for these assays (or other relevant information/data) to support BMS as an alternative testing site, indicate where this

information is located in the BLA or remove BMS as an alternative site for these assays.

21. Provide the final study report cited in section 3.2.S.3.1.5 that compared the ability of AUC and SE-HPLC to detect HMW species. It was noted that during validation of the SE-HPLC assay, when samples were spiked with HMW species, the value for percent monomer did not decrease by approximately the percent of contaminating HMW species that were added to the samples. (b) (4)

Taken together these data raise concerns as to whether the SEC-HPLC assay has the capability to sensitivity detect product aggregates. Provide the requested information/data and any additional data you have to support the ability of the assay to detect aggregates derived from the assay that is being run at the (b) (4).

22. In regard to validation of the N-linked oligosaccharide assay:

- a. The validation report is from (b) (4) yet the assay is apparently being run at BMS. Provide the method transfer protocol and results to support use of this assay by BMS.

(b) (4)

- c. During validation, the oligosaccharide assay appears to have repeatedly failed system suitability requirements raising questions as to whether the assay is robust enough to be suitable for routine lot release. Provide comment and a summary of any additional available data that supports the reliability of this assay. In addition provide the assay's SOP including the system suitability criteria and procedures that will be followed if these criteria are not met.
- d. Table 3-*Accuracy Results* does not include results from the (b) (4) analysis. Provide a complete table that includes these results.

(b) (4)

25. Provide the final study reports for the small scale life time limit studies performed to support life time limits for the AEX, HA and CEX columns.
26. Data provided to support biochemical stability during the in-process hold times was not sufficient to support the proposed times. In particular, the way in which the data was provided for charge by IEF and purity by SDS-PAGE did not allow us to assess

whether there was a change in these attributes during storage. Provide additional information on the results of these studies that indicates whether there were alterations seen during storage. For example, did you record whether there was any change in the charge and purity profile observed compared to the reference standard (i.e., were the results comparable to reference standard at the end of the hold periods)? Alternatively more quantitative data could be provided such as a specific numerical value for product purity (i.e., percent purity) and for the percent main peak for charge.

27. Update section 3.2.S.5 to include a table that lists all the complete list of specifications with acceptance criteria that will be used to qualify new reference standard lots (please note comment 29 below and incorporate this change into the specifications).
28. Update the table in section 3.2.S.5.4 to include specific acceptance criteria that will be used to re-qualify new reference standard lots. Acceptance criteria of (b) (4); (b) (4) ' is not acceptable (please note comments 29-31 below).
29. It is noted that DS lots typically are released with (b) (4) SDS-PAGE purity values of (b) (4). Reference standard lots should be derived from DS lots with a high level of purity. Revise the (b) (4) SDS-PAGE specification for reference standard qualification and re-qualification to more closely reflect that typically observed at DS release (e.g., (b) (4)).
30. (b) (4) SDS-PAGE assay should be performed for reference standard re-qualification. Provide confirmation that both are included in the re-qualification protocol.
31. The protocol indicates that if the reference standard meets the indicated criteria it will be used for an additional year. Basing reference standard re-qualification solely on conformance with this specification does not address instances where there may be a consistent stability trend that indicates the reference standard may be undergoing degradation. We recommend that a trend analysis linked with an extrapolation of the rate of change predicted to occur over the following 12 months also be performed for assays with numerical acceptance criteria to provide greater assurance of continued reference standard stability. Provide comment and an update to the reference standard re-qualification section if appropriate.
32. Provide detailed information on the conditions of the scaled down models used during viral removal validation compared to those used for commercial manufacturing. The information provided should demonstrate that performance of the scale-down model was representative of the full scale process.
33. 48 out of 511 patients were reported to be anti-drug antibody (ADA) positive using the Plasma ECL ADA assay. However, based on their post-dose to per-dose titer ratios these samples were categorized as ADA negative. It is unclear why a post-dose to pre-dose ratio was used to make a final determination as to whether a patient sample would be gauged ADA positive or not. Provide information, supported by data that demonstrates this is an acceptable approach for evaluation of ADA responses. Include an explanation on why other, more standard, approaches such as

use of a competition assay were not used to confirm true ADA responses. Include data on the ratios that were calculated for these 48 patients or indicate where this information can be found in the submission.

34. For the 48 patient samples that were initially ADA positive, provide information on the level of ipilimumab that would be expected to be present at the time the sample was collected. Provide an evaluation of whether the level of ipilimumab in the sample would be expected to interfere with detection of ADA responses by the Plasma ECL ADA assay.
35. It is unclear why the Human Plasma ECL ADA assay was used to monitor ADA responses in the pivotal trial when the Human Serum ECL ADA assay used in the phase 2 studies appears to be a more sensitive assay with a higher drug tolerance limit. Provide an explanation on why the Human Plasma ECL assay was selected for use in the pivotal trial. This should include information/data to support selection and use of the Human Plasma ECL assay over the Human Serum ECL assay for detection of anti-ipilimumab antibody responses.
36. Provide a protocol for and commit to perform concurrent chromatography resin lifetime studies at commercial-scale in subsequent production campaigns to confirm the scale-down resin life-time study results.
37. Provide a commitment to develop and implement an assay for visible particulates for DP release and stability testing. The final validation report should be submitted as a CBE30. Provide a date by which the CBE30 will be submitted.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 12/10/10

ESC
12/10/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Draft Partial FDA labeling

From: Laughner, Erik
Sent: Friday, December 10, 2010 12:15 PM
To: Knight Trent, Heather
Subject: FDA Partial Draft 121010 Label; STN 125377
Importance: High

Hello Heather,

We provide the following label as currently reviewed by FDA. The adverse event/safety information has not been reviewed and it is expected that BMS will substantially revise all those pertinent sections based on the revised safety analysis.

FDA will likely provide some high-level guidance on how to present those sections after we have had a chance to review the revised safety data

BMS should target to provide a revised label which addresses the provided edits and revised safety the week of January 3, 2011.

Please confirm receipt of this email.

Sincerely,

Erik



121010 FDA
Proposed Partial D..

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 12/08/10 ^{ESC}
_{12/08/10}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Wednesday, December 08, 2010 3:00 PM
To: Knight Trent, Heather
Subject: RE: STN 125377; FDA information request/comments

Heather,

Dr. Shastri acknowledges the plan as outlined, but requires a target submission date from BMS for the grade 1/2 events of interest.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Wednesday, December 08, 2010 2:21 PM
To: Laughner, Erik
Subject: RE: STN 125377; FDA information request/comments

Dear Erik,

The team met to discuss the comments provided in your email below. The following was communicated to you via phone and you indicated that you would inform the appropriate reviewers.

- The team is targeting submission of the grade 3 and higher safety response early next week. This is the bulk of the data for the FDA to review. We would like to send this to the reviewers as soon as possible, so they can start the review. Please note that the Grade 1 and 2 safety data will be included in the datasets, but will not have had the clinical review.
- BMS will be sending clarifying questions to FDA regarding the comments provided yesterday.

Thank you for your continuing assistance with this review.

Sincerely,
Heather

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, December 07, 2010 9:39 AM

To: Knight Trent, Heather
Subject: STN 125377; FDA information request/comments

Heather,

We have the following comments/information requests regarding the safety characterization:

1. The adjudication for attribution as an inflammatory event should be conducted for all grade events and not only for \geq grade 3 events.
2. It is not clear why [REDACTED] ^{(b) (4)} is included among immunosuppressants, since it is unlikely to be used as a treatment for an ipilimumab induced inflammatory event. Please also clarify that the term 'tumor necrosis factor' is included in the search term to search for tumor necrosis factor inhibitors.
3. Please create a flags in the newly created dataset for (1) adverse events for special interest for those events occurring during induction phase, and (2) cycle number. In the description and summary of the adjudicated inflammatory events, please also provide a separate description for events only occurring in the induction period.
4. As previously communicated during the teleconference on 12/2/10, please also include in the characterization of inflammatory events, those occurring in the gp100 alone treatment arm.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 12/07/10 *See 12/07/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (nonclinical)

From: Laughner, Erik
Sent: Tuesday, December 07, 2010 9:23 AM
To: Knight Trent, Heather
Subject: STN 125377; FDA information request; update on monkey gestation data
Importance: High

Hello Heather,

The nonclinical reviewer has requested an update as to the final gestation data for the following study: "IPILIMUMAB (BMS-734016): INTRAVENOUS STUDY OF PRE- AND POSTNATAL DEVELOPMENT IN CYNOMOLGUS MONKEYS WITH A 6-MONTH POSTNATAL EVALUATION."

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 12/07/10 *Σ sc 12/07/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (clinical)

From: Laughner, Erik
Sent: Tuesday, December 07, 2010 9:39 AM
To: Knight Trent, Heather
Subject: STN 125377; FDA information request/comments

Heather,

We have the following comments/information requests regarding the safety characterization:

1. The adjudication for attribution as an inflammatory event should be conducted for all grade events and not only for \geq grade 3 events.
2. It is not clear why (b) (4) is included among immunosuppressants, since it is unlikely to be used as a treatment for an ipilimumab induced inflammatory event. Please also clarify that the term 'tumor necrosis factor' is included in the search term to search for tumor necrosis factor inhibitors.
3. Please create a flags in the newly created dataset for (1) adverse events for special interest for those events occurring during induction phase, and (2) cycle number. In the description and summary of the adjudicated inflammatory events, please also provide a separate description for events only occurring in the induction period.
4. As previously communicated during the teleconference on 12/2/10, please also include in the characterization of inflammatory events, those occurring in the gp100 alone treatment arm.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Memorandum

Date: December 3, 2010 ESL 12/3/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Standing Monthly Team Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Anne Pilaro, Aakanskha Khandelwal, Christian Grimstein, Barbara Rellahan, Grace Carmouze, Jeff Summers, Andrew McDougal, Jibril Abdus-Samad, Carol Broadnax, Donald Obenhuber, Joyce Weaver

Participants were present from major disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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Memorandum

Date: 12/2/10 ^{ESL}
12/2/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding ODAC; review of BLA

FDA Attendees:

Erik Laughner, RPM OODP/DBOP
Kaushik Shastri, Clinical Reviewer, OODP/DBOP
Patricia Keegan, Director, OODP/DBOP

BMS Attendees:

Dr. Mathias Hukkelhoven- SVP, Global Regulatory Science and Global Pharmacovigilance
Dr. Margo Heath-Chiozzi- VP, Global Regulatory Science Oncology and Virology
Dr. Renzo Canetta- VP, Global Clinical Research Oncology
Dr. Heather Knight-Trent- Director, Global Regulatory Science Oncology

Background: FDA requested a teleconference to discuss the proposed February ODAC.

Discussion: FDA informed BMS that after some internal discussion with the team it was decided that an ODAC would not be needed. BMS should instead devote their full attention at the characterization of the safety components of the BLA. BMS acknowledged and agreed that is was a better use of resources and the remaining time to address FDA's issues concerning the safety presentation. BMS noted that it was their intent to provide the full data to FDA next week and inquired if FDA had any comments on the "mini-SAP" that was provided via email on 12/1. FDA noted this was still under review but would work on providing any concerns soon. FDA commented that BMS should perform the safety analysis on the gp100 arm as well as the ipilimumab containing arms as an "internal control" for the revised case definitions. This information may not necessarily be included in the label. BMS acknowledged and noted that they had already considered this and would provide. FDA stated that after the analysis, BMS should revise the proposed labeling to reflect the new case definitions. BMS inquired whether FDA was prepared to send any portions of labeling to move the process along. FDA acknowledged that the non-safety portions of the label had been worked on and that they would discuss with the team at an internal meeting today, the possibility of sending those sections to BMS next week. BMS acknowledged and appreciated FDA's willingness to do so. BMS inquired on the REMS review and FDA noted that the safety analysis and label would have to be put together first. FDA also reminded BMS that they should be working on providing a proposal with timelines for the PMR regarding the 3mg vs. 10mg dose. This study would also

have to be a component of the eventual FDA review of the pending -024 study data. BMS noted that the -024 study was in a different line of melanoma, but FDA commented that “lines” were irrelevant with respect to advanced melanoma as there was no effective therapy. BMS acknowledged.



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Memorandum

Date: 11/30/10 ^{Σ 44}
11/30/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Advice/Information Request; Quality Assessment Form

From: Laughner, Erik
Sent: Tuesday, November 30, 2010 3:37 PM
To: Knight Trent, Heather
Subject: Quality Assessment Form BLA STN 125377

Hello Heather,

Hope you had a nice holiday weekend!

Please see a quality assessment review form to complete.



QA BLA STN
25377.doc (163 KB)

FDA will also complete this form by the end of the review cycle and it can be used during the post-action feedback meeting (should BMS request one).

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
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<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 11/24/10 ^{E.S.L.}
11/24/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON: regarding safety analysis

FDA Attendees:

Erik Laughner, RPM OODP/DBOP
Kaushik Shastri, Clinical Reviewer OODP/DBOP
Yuan Li Shen, Statistical Reviewer DV5/OB
Jeff Summers, DDS OODP/DBOP

BMS Attendees:

Renzo Canetta, MD, VP Global Clinical Research
Axel Hoos, MD, Global Medical Lead for ipi
David Berman, MD- Global Clinical Research
Rachel Humphrey, MD, Global Development Lead for ipi
Michael Giordano, MD- VP, Oncology Development
Tai-Tsang Chen, PhD- Statistics
Anne Cross, PhD- Statistics
Marianne Federici- Global Dossier Management
Helen Liu, MD- Global Pharmacovigilance
Margo Heath-Chiozzi, MD- VP, Global Regulatory Science

Background: As a result of the 11/16/10 tcon with FDA, on 11/19/10, BMS provided via email, a draft proposal for inflammatory event “case definitions”. BMS requested feedback from FDA. FDA agreed and prior to the teleconference, FDA provided the following written comments on 11/24/10.

1. The definitions should be more explicit. For example, the definition should be any 1 item in column A or B in the absence of any item in C. The label should reflect the definition.
2. Efficacy of steroids/immunosuppressants will have to be interpreted with caution, since the definition includes response to steroids. The lack of efficacy of steroids/immunosuppressants will only be available for items that exclude that definition from B.
3. There appears to an error in first item in column C in Table 4. Table 4 should be revised to include hypothyroidism and adrenal hypo function.

4. Please clarify item 1 in Table 2 column C , so that if the known incidence of hepatitis for a suspect chemotherapy is very low then it is considered likely that ipilimumab caused the hepatitis.
5. Please describe how you plan to collect these data and how they will be presented (hyperlink or at least a page number of the CRF where this information is located and flags in the AE dataset for items in each column for each category and an overall flag for the final adjudication for the AE)

DISCUSSION:

BMS acknowledged FDA's written comments and agreed to address 1,3,4.

Regarding FDA comment 2:

BMS acknowledged and noted that the plan was to provide the requested information at the "event" level using different components of the proposed case definitions. This would be "transparent" to FDA. The cases themselves would be few and readily identifiable. FDA acknowledged that the proposed case definitions were agreeable with the caveat that for Table 1 of the proposal, improvement was needed in column B to make it clear that "AE improves or resolves" should not capture those of a temporary nature. BMS noted that to resolve meant to grade 0. To improve meant to decrease at least 1 grade.

Regarding FDA comment 5:

BMS acknowledged and noted that the plan was to start with grade 3 or greater AE and then look at the clinical data in the narratives. This information would be provided in a excel spreadsheet per "A", "B", "C" as defined in the case definition to characterize safety and provide final adjudication of the adverse events. The excel file would link to the dataset and contain autoflags. The dataset would be new and hyper-link to narratives. BMS intended to send FDA a "mini-SAP" for comment that will outline the "how/where" the data was derived from. FDA cautioned that BMS should direct to 1-2 pages of the narrative. BMS should also provide pertinent and critical supporting document not otherwise captured in the CRF (i.e. from pharmacovigilance and other data sources which contributed to the narratives), BMS acknowledged and stated that they are in internal discussions as to how best to provide these.

At the end of the teleconference, BMS agreed to:

1. Send analysis plan/"mini-SAP" to FDA early next week
2. To review above adverse events according to the revised case definitions and identify source of critical data supporting the clinical assessment
3. Provide analyses and programs to characterize the inflammatory adverse events in the clinical database.

QUESTION 1

Please provide a proposal for FDA agreement for case definitions for inflammatory adverse events.

RESPONSE

Consistent with its mechanism of action, ipilimumab induces a significant increase in the mean percent of circulating activated lymphocytes.¹ In subjects administered ipilimumab who develop diarrhea, rash or hepatitis and who have had biopsies of the respective organ, histologic examination has demonstrated inflammation.^{2,3} Therefore, the definitive method for proving that an adverse events (AE) is inflammatory should be through biopsy of the involved organ with exclusion of alternative etiologies. However, biopsy is not always feasible since some organ sites are not easily accessible (e.g. hypophysitis), invasive procedures may be clinically inadvisable (e.g. hepatitis), or appropriate clinical management of the event dictates immediate treatment with corticosteroids to prevent progression of symptoms. Where biopsies are not available, supportive clinical, radiologic and laboratory data may provide insight into whether an AE is at least likely attributable to ipilimumab-associated inflammation.

As a tool to identify and characterize ipilimumab-associated inflammatory AEs cases, a proposal for a case definition has been developed. (b) (4)

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Memorandum

Date: 11/24/10 ^{ESC}
_{11/24/10}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Wednesday, November 24, 2010 9:59 AM
To: Heath-Chiozzi, Margo
Cc: Knight Trent, Heather
Subject: FDA Comments re: BMS draft proposal for Case Definitions STN 125377
Importance: High

Hello Margo,

In preparation of this afternoon's 1PM tcon, we convey the following comments regarding BMS's 11/19 proposal for case definitions:

1. The definitions should be more explicit. For example, the definition should be any 1 item in column A or B in the absence of any item in C. The label should reflect the definition.
2. Efficacy of steroids/immunosuppressants will have to be interpreted with caution, since the definition includes response to steroids. The lack of efficacy of steroids/immunosuppressants will only be available for items that exclude that definition from B.
3. There appears to an error in first item in column C in Table 4. Table 4 should be revised to include hypothyroidism and adrenal hypo function.
4. Please clarify item 1 in Table 2 column C , so that if the known incidence of hepatitis for a suspect chemotherapy is very low then it is considered likely that ipilimumab caused the hepatitis.
5. Please describe how you plan to collect these data and how they will be presented (hyperlink or at least a page number of the CRF where this information is located and flags in the AE dataset for items in each column for each category and an overall flag for the final adjudication for the AE)

Please confirm receipt and provide a call-in number.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA

301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Friday, November 19, 2010 3:25 PM
To: Laughner, Erik
Subject: RE: Ipilimumab: Follow-up on 16 Nov 2010 TC

Dear Erik,

I have attached a draft proposal on the case definitions for the review team. The BMS team would be available on Monday to discuss the proposal at a convenient time for FDA and ensure we are on the same page. On Tuesday afternoon, I'll be traveling to WV. Monday would be the optimal time especially so we can provide the final response next week.

Thanks for your help,
Heather

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Memorandum

Date: November 16, 2010 2<< 11/16/10
From: Erik Laughner, M.S., DBOP/ODDP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Third Labeling Meeting

FDA Attendees: Christine Garnett, Erik Laughner, Patricia Keegan, Anshu Marathe, Christian Grimstein, Kaushik Shatri, Hong Zhao, Andrew McDougal, Barbara Rellahan, Leyla Sahin

Discussion: This labeling meeting was convened to discuss the "CLINICAL PHARMACOLOGY, NONCLINICAL TOXICOLOGY, DRUG INTERACTIONS, and USE IN SPECIFIC POPULATIONS" sections of the proposed package insert label.



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 11/16/10 ^{ESS} 11/14/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding FDA regarding safety analysis

FDA Attendees:

Erik Laughner, RPM OODP/DBOP
 Kaushik Shastri, Clinical Reviewer OODP/DBOP
 Patricia Keegan, Director OODP/DBOP
 Yuan Li Shen, Statistical Reviewer DBV/OB
 Jeff Summers, DDS OODP/DBOP

BMS Attendees:

BMS Participants	Title
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science- Oncology & Virology
Michael Giordano, M.D.	Vice President Development Teams- Global Development and Medical Affairs
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Allan Safferman, M.D.	Executive Director, GPV&E Medical Safety Assessment
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
Heather Knight-Trent, Pharm.D	Director, Global Regulatory Science- Oncology
Ramy Ibrahim, M.D.	Director, Oncology, Global Clinical Development
Anne Cross, Ph.D.	Executive Director, Oncology, Global Biometric Sciences
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences

Background: FDA requested a brief tcon with BMS to discuss their October 18, 19, and 22 formal responses to FDA's comments 1,5,7,13 from the October 4, information request.

DISCUSSION:

Regarding BMS's response to comment 5:

FDA clarified that full electronic copies of all versions of the investigator's brochures (IB) should be provided to the BLA for review. BMS acknowledged and agreed to

provide.

Regarding BMS's response to comment 1:

FDA acknowledged BMS's response and clarified that BMS should work to develop new case definitions (CD) for inflammatory events, i.e., those events caused by breaking of immune tolerance, with an end result to provide a package insert label with more accurate incident rates as well as for the development of the REMS. The current proposal was not acceptable because the terms were too broad and therefore misleading in trying to determine an accurate incident rate. For example, it was not appropriate to (b) (4). FDA noted that BMS should first create a list of those events of interest (GI, dermatologic, hepatic, and rarer events like myocardial, uveitis etc), regardless of causality, and compare against known inflammatory MeDRA terms. Then, using defined recognition criteria, the various CDs could be developed. FDA would review the proposed CDs and if acceptable, instruct BMS to perform a re-analysis of the AEs to allow for the revised labeling. FDA noted that when BMS addresses comment 1, FDA would like to see all the pertinent information readily available for verification (preferably hyperlinked or at least with a page number to the CRF or any other source document)

Regarding BMS's response to comment 7:

FDA noted that hyperlinking to the specific page of the CRF was more useful than to an entire ~500 pg document. FDA inquired on the process on how the narratives were created and BMS indicated that the narratives were created based on information in the CRFs and in BMS's pharmacovigilance database. BMS indicated that the monitors compared the CRFs to the source data at the site and that the narratives contained the most information for each respective case. FDA stated that BMS should provide the pertinent source information in the BLA, if the CRFs do not have such information.

Regarding BMS's response to comment 13:

FDA acknowledged BMS's limited data from the expanded access program and noted that the previously discussed likely PMR study comparing the 3mg vs. 10mg dose would also have to contain comprehensive pre-specified safety data collection.

At the end of the teleconference, BMS agreed to provide FDA a revised list of AEs of special interest as well as proposed CDs within a week.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: November 5, 2010 ^{ESL} 11/5/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Standing Monthly Team Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Andrew McDougal, Anne Pilaro, Aakanskha Khandelwal, Christian Grimstein, Hong Zhao, Barbara Rellahan, Grace Carmouze, Sue Kang, Annette Ragosta (CBER), Lauren Iacono-Connor, Jibril Abdus-Samad, Carol Broadnax, Kalavati Suvarna, Donald Obenhuber, Anshu Marathe, Leyla Sahin, Carla Lankford, Subramania Muthukkumar

Participants were present from major disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 11/4/10 ^{ESC}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Advice/Information Request

From: Laughner, Erik
Sent: Thursday, November 04, 2010 12:50 PM
To: 'Knight Trent, Heather'
Subject: FDA information Request STN 125377 (Ipilimumab): Monkey repro DN10020 FDA telecon 11-3-10

Hello Heather,

As a follow-up to yesterday's discussion, we have the following additional comments:

Regarding the ongoing enhanced pre- and post-natal development study in monkeys (study # DN10020), FDA strongly recommends that placenta histopathology for the all three treatment groups be evaluated to the extent feasible. FDA is aware that placenta tissue samples may not have been collected for all previously-completed pregnancies (as per the protocol).

During the teleconference, BMS indicated the intent to follow protocol by returning mothers whose infants survive to colony, rather than performing necropsy on all animals. FDA has no objection to this plan. If and to the extent feasible, please provide relevant historical control data for each endpoint potentially affected by ipilimumab (e.g. 3rd trimester losses and infant deaths in future ESRs, gross and histopathology in the draft report).

During the 11/03/2010 teleconference, BMS indicated that infant birth weights had been included in the 10/15/2010 report. The FDA reviewer requests assistance in locating the infant birth weight data (i.e. only the adult weights are found). If these infant birth weight (and subsequent weight) data are available but not yet submitted, please submit them.

Please confirm receipt.

Sincerely,

Erik Laughner, RPM



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: 11/3/10 ^{ESL}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding nonclinical data

FDA Attendees:

Erik Laughner, RPM
Patricia Keegan, Director
Anne Pilaro (joined late), Supervisory Toxicologist
Andrew McDougal, Nonclinical Reviewer
Jeff Summers, Deputy Director Safety
John Leighton, Supervisory Pharmacologist

BMS Attendees:

BMS Participants	Title
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science- Oncology & Virology
Allan Safferman, M.D.	Executive Director, GPV&E Medical Safety Assessment
Heather Knight-Trent, Pharm.D	Director, Global Regulatory Science- Oncology
Helen Liu, M.D.	Medical Director, GPV&E Medical Safety Assessment
Todd Bunch, Ph.D.	Director of Toxicology
Karen Price, M.S.	Group Leader, Immunotoxicology
Maryellen Mcnerney, Ph.D.	Director, Reproductive Toxicology

Background: FDA requested a brief tcon with BMS to discuss the recent nonclinical update regarding "IPILIMUMAB (BMS-734016): INTRAVENOUS STUDY OF PRE- AND POSTNATAL DEVELOPMENT IN CYNOMOLGUS MONKEYS WITH A 6-MONTH POSTNATAL EVALUATION" in the 10/19/10 BLA amendment. Specifically, FDA requested an update on the expedited safety reporting (ESR), to discuss BMS's plan to communicate the updated nonclinical information to investigators and whether there were any plans to update the proposed labeling in the current BLA submission. Prior to the telecon, BMS provided a short slide deck (attached to these minutes).

Discussion: FDA acknowledged receipt and review of the slide deck and BMS reviewed slide 4 which was an overall summary of BMS's actions to date regarding the recent nonclinical findings in the EPPD study. BMS acknowledged that the ESR was inadvertently delayed which was

traced back to human error. BMS committed to perform an internal review to review procedures/practices to prevent this delay in the future. FDA acknowledged. BMS noted that follow-up reporting to investigators was communicated today. BMS agreed to check with their clinical operations group and confirm that all investigators, including those from cross-referenced INDs were informed. BMS noted that they did not intend to modify the current BLA proposed label until more gestation data was available at the end of November. BMS clarified that not all primate mothers would be necropsied, just the ones who lost pregnancy or delivered infant who then died. BMS noted that gross pathology did not indicate any signals for the observed third trimester losses. FDA commented on the capture of infant birth weight data, and BMS indicated that this information was included in the 10/15/2010 report.

4 Page(s) has been Withheld in Full as B4 (CCI/TS)
immediately following this page



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

Memorandum

Date: 11/2/10 ^{ESC}
From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(nonclinical)

From: Laughner, Erik
Sent: Tuesday, November 02, 2010 12:45 PM
To: 'Knight Trent, Heather'
Subject: BLA STN 125377; FDA request for tcon; discuss recent nonclinical repro findings in monkey
Importance: High

Hello Heather,

FDA would like a brief tcon with BMS to discuss the recent nonclinical update regarding "**IPILIMUMAB (BMS-734016): INTRAVENOUS STUDY OF PRE- AND POSTNATAL DEVELOPMENT IN CYNOMOLGUS MONKEYS WITH A 6-MONTH POSTNATAL EVALUATION**" in the 10/19/10 BLA amendment.

Can you provide a update on the ESR as indicated in the submission?

FDA would like to discuss BMS's plan to communicate this information to investigators and BMS's plans to update the proposed labeling in the BLA.

Can you accommodate tomorrow afternoon at 3PM?

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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Memorandum

Date: 11/1/10 ^{ESL} _{ef/cho}
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Advice

From: Laughner, Erik
Sent: Monday, November 01, 2010 6:59 AM
To: 'Knight Trent, Heather'
Subject: RE: Ipilimumab: Communications Regarding PDUFA Date Change

Hello Heather,

It is not common practice for FDA to make any announcements regarding PDUFA clock extensions as the status of a file under review is confidential.

The Major Amendment letter is provided to the Sponsor and the Sponsor then decides what information will go in the form of a press release to notify the public of FDA's need to extend the review clock.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Friday, October 29, 2010 2:48 PM
To: Laughner, Erik
Subject: Ipilimumab: Communications Regarding PDUFA Date Change

Dear Erik,

I tried to reach you by phone, but missed you. I have been in discussions with our public communications group. We have the following questions that would be very helpful to us:

- Will the extension of the PDUFA date be communicated to the public? Based on our previous discussions, I thought that only the information regarding the ODAC meeting would be made public.
- If it is communicated to the public, will it be in 1 announcement with the ODAC meeting or a separate announcement?
- If the change in the PDUFA date will be communicated to the public, can I also be notified 24 hours in advance as FDA has promised for the ODAC meeting communication?
- If you notify me, can the wording be provided, so we can align our public announcements with it?

Thank you for your continued help with the review of ipilimumab.

Have a nice weekend,
Heather



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Memorandum

Date: 10/29/10 ^{Σ>L}
10/29/10

From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(Statistical)

From: Laughner, Erik
Sent: Friday, October 29, 2010 1:42 PM
To: 'Knight Trent, Heather'
Subject: FDA information Request STN 125377 (Ipilimumab)

Hello Heather,

Please see the following information request regarding the data files:

Please clarify the three datasets, odac20.eoispsdb odac4.eoispsdb and odac22.eoispsdb, used in programs s18-ttr-eoi-min-max.sas and s19-ttr-eoi-min-max.sas. FDA was not able to locate these three datasets.

Please confirm receipt.

Sincerely,

Erik



Our STN: BL 125377/0

**REVIEW EXTENSION
EFFICACY SUPPLEMENT**

October 28, 2010

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, Pharm D.
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

Please refer to your biologics license application (BLA), dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act for ipilimumab. Also refer to our filing letter dated August 16, 2010.

We received your October 22, 2010, amendment to this application and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to March 26, 2011, to provide time for a full review of the amendment.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 26, 2011.

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

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



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

Memorandum

Date: 10/19/10 ^{ESL} 10/17/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding ODAC and clinical data

FDA Attendees:

Kaushik Shastri, Clinical, DBOP
Patricia Keegan Director, DBOP
Richard Pazdur, Director, OODP
Yuan Li Shen, Statistics, DV5
Kun He, Stastical Team Leader
Rajeshwari Sridhara, Acting Division Director, DB5
Aakanksha Khandelwal, Clin Pharm, DCP5
Anshu Marathe, Pharmacometrics, PS
Hong Zhao, Pharmacology Team Leader, DCP5
Jeff Summers, Deputy Director Safety, DBOP

BMS Attendees:

BMS Participants	Title
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science- Oncology & Virology
Michael Giordano, M.D.	Vice President Development Teams- Global Development and Medical Affairs
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Allan Safferman, M.D.	Executive Director, GPV&E Medical Safety Assessment
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
Heather Knight-Trent, Pharm.D	Director, Global Regulatory Science- Oncology
Ramy Ibrahim, M.D.	Director, Oncology, Global Clinical Development
Anne Cross, Ph.D.	Executive Director, Oncology, Global Biometric Sciences
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences

Background: FDA requested a brief tcon with BMS to discuss the review status of the BLA and ODAC preparation.

DISCUSSION: FDA informed BMS that the focus of an ODAC would be specific to safety and not efficacy. BMS inquired on the status of the October 4, 2010 information request with regard to FDA comments 1,6,and 7. BMS noted that they were currently finishing the hyper-linking of narratives to the Grade 3/4/5 AE events as well as the linking from text to narrative and CRFs. BMS anticipated that this information would be provided by October 22. FDA noted as they would not have enough time to review and prepare this information prior to submission of the ODAC briefing document and the December 2, 2010, ODAC, the ODAC would be postponed. FDA informed BMS that the submission of this information would also be classified as a Major Amendment. The PDUFA clock will be extended for 3 months from the original goal date. FDA will notify BMS at a later date as to the possible scheduling in late January/early February of another ODAC date.

FDA also noted that based on their review of the confidential high-level K-M survival results of ipilimumab use in a HLA-unrestricted melanoma population from the -024 study (BMS is censored to this data), this Office will no longer require HLA restriction for the indication in the current BLA. Therefore, neither a treatment-IDE nor PMA for the HLA assay needs to be pursued. FDA would consider an indication for treatment of metastatic melanoma. FDA stated that they would be asking the DSMC for the raw data to replicate the K-M data provided. BMS confirmed that Mathias Hukkelhoven at BMS was the only point of contact to communicate this request to as all others were embargoed. FDA acknowledged.

FDA inquired how BMS will reconcile the dosing issue of 3mg vs. 10mg in the two studies. BMS noted that the 3mg was for the second-line setting while the 10mg dose was for first-line. FDA noted that it seemed illogical to give a different dose for this disease between the first and second line setting. FDA noted that based on the -020 study, it was unclear if BMS had done enough to demonstrate what was the best dose in terms of balancing efficacy/safety. BMS noted the BLA under review at this moment is for 3mg dosing and that the -024 data was not available for BMS review to comment on or to consider. FDA indicated if the current BLA is approved, a likely PMR will be for BMS to perform a new head-to-head superiority study of 3mg vs. 10mg as single agent therapy to determine the ideal dose. FDA stressed that BMS should also take this time to review their other development programs to date (b) (4)

(b) (4)

FDA clarified that the unexpected -020 study data has created a reason to re-think that. BMS acknowledged that the AE profiles between the doses were different and agreed that it was in their best interest to find the least toxic efficacious dose.

BMS indicated that they would summarize the discussion and provide to the BLA as an amendment.



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Memorandum

Date: October 19, 2010 ^{ESC 10/19/10}
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Meeting

FDA Attendees (may not be all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Kun He, Dianne Spillman, Hong Zhao, Rajeshwari Sridhara, Grace Carmouze, Aakanksha Khandelwal, Richard Pazdur, Anshu Marathe, Andrew McDougal, Joyce Weaver, Jeff Summers

Meeting held for discussing need of ODAC.



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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 10/14/10 ^{ZSL} 10/14/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (QT-IRT)

From: Laughner, Erik
Sent: Thursday, October 14, 2010 1:19 PM
To: 'Knight Trent, Heather'
Subject: RE: FDA information Request STN 125377 (Ipilimumab)

Hello Heather,

The QT review team has requested that BMS fill out the following ClinPharm table and submit back to us as soon as possible.



HighlightsofClinicalPharmacology.doc

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm091745.htm>

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STN 125377 (BMS); Ipilimumab

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and

		meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	



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Memorandum

Date: 10/13/10 ^{ESC}
10/13/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding safety analysis

FDA Attendees: Erik Laughner, Patricia Keegan, Yuan-Li Shen, Jeff Summers

BMS Attendees:

BMS Participants	Title
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science- Oncology & Virology
Michael Giordano, M.D.	Vice President Development Teams- Global Development and Medical Affairs
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Jeffrey Humphrey, M.D.	Vice President, Oncology Medical Strategy
Allan Safferman, M.D.	Executive Director, GPV&E Medical Safety Assessment
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
Helen Liu, M.D.	Medical Director, GPV&E Medical Safety Assessment
Heather Knight-Trent, Pharm.D	Director, Global Regulatory Science- Oncology
Mariana Bielefield	Director, Senior Operations Lead
Ramy Ibrahim, M.D.	Director, Oncology, Global Clinical Development
Anne Cross, Ph.D.	Executive Director, Oncology, Global Biometric Sciences
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences

Background: BMS requested a brief tcon with FDA to discuss comment 1 of the October 4, 2010 information request. Prior to the call, BMS provided a written response/proposal regarding characterization of immune related adverse events.

DISCUSSION: BMS acknowledged FDA's position regarding concerns on how the immune related AEs were presented in the BLA. As noted in the provided written response, BMS acknowledged that capture of safety information for Study MDX10-020 originally required investigators assessment of the nature of an immune adverse event on a case-by-case basis and manually document these on the CRFs. However, through a later amendment (Amendment 3; dated October, 2006) the supplemental CRF page for individual investigator assessments of irAEs was no longer used. BMS believed that ~300 patients were enrolled in study -20 prior to this amendment change with ~60 supplemental data forms available. BMS agreed to review and provide any additional information to FDA.

BMS reviewed their written revised proposal to lists all AEs without investigator attribution and noted that Grade 3/4/5/ AE's could be more "narrowly" coded to a set of preferred MEDRA terms. FDA acknowledged, but also noted that Grade 1/2 AE's should also be reviewed as for example, prolonged Grade 2 diarrhea could be an irAE. FDA noted that BMS could have taken the CRF data and created a new algorithm to better tease out the non-immune related AE's. FDA noted that the table as provide in the written response was "on the right track" however FDA would have to review the CRFs and narratives. BMS noted that under the current time constraints, the Grade 3/4/5 AE's would be re-analyzed first. FDA stated that the ultimate goal was to provide a new summary table showing revised rates that could be used for labeling.

BMS noted that FDA's comment 1 from the 10/4/10 information request was also related to comments 6 and 7. FDA's request for hyperlinking to supportive documents would likely be too time consuming considering the review clock. FDA acknowledged, but noted that BMS should have a way to "flag" or identify the documents as this was also a problem for FDA review. BMS agreed to review and provide at least an alternative.

BMS stated that all the responses to the 10/4/10 information request would be submitted by 10/18/10 with the exception of FDA comments 1, 6, and 7.



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Memorandum

Date: 10/04/10 *ESC 10/04/10*

From: Erik Laughner, RPM DBOP/ODDP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Monday, October 04, 2010 2:14 PM
To: 'Knight Trent, Heather'
Subject: FDA Information Request STN 125377 (Ipilimumab); CMC
Importance: High

Hello Heather,

As follow-up to the teleconference Friday, see the following information requests for BLA STN 125377.

Please confirm receipt.



100410 IR
Memo.pdf (25 KB)

Sincerely,

Erik

Erik Laughner, RPM
DBOP/ODDP/CDER/FDA



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: October 4, 2010
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125377 (Ipilimumab)

General comments: Please note that all the data analyses in response to the following requests should be accompanied by corresponding SAS programs and all the supplemental files/programs that are necessary for FDA to run the programs and reproduce the results.

We have the following items that require a response within 2 weeks or earlier:

1. We do not agree with your characterization of immune related adverse events. Please develop case definitions for immune related adverse events that will identify only those events that are truly likely to be immune related. Include all available information (e.g., endoscopic evaluation, histology/cytology, intervention with immunosuppressants). The criteria should be specific enough to exclude events that are clearly infectious in nature or result from other interventions (surgery) or co-morbid conditions. Please use the criteria specified in the protocols for establishing irAR's rather than the criteria for screening to identify potential irARs, as you have provided in the submission. Provide analyses and tabular summaries with the corresponding datasets and SAS programs for established immune related adverse events. The analyses should include treatment arm, category of irAR, time to onset in relation to study drug, outcome and time to outcome, and type of intervention or treatment given. Provide case narratives with hyperlink to all supportive information for selected biopsy, procedures or laboratory tests that establish the irAR.
2. The original submission coded adverse events in MedDRA ver 12.1. All adverse events must be coded in this version of MedDRA for the entirety of the review.
3. Please provide a summary table and a listing of all patients who initiated immunosuppressant drugs at any time post-treatment (e.g., during treatment phase and during follow-up) in each treatment arm. Please create a flag in the con med dataset for immunosuppressants drugs. Also provide a flag in the adverse event data set for those adverse events that prompted initiation of immunosuppressant therapy.
4. Please indicate which variable flag in the dataset differentiates between patients with a recurrence following prior therapy (i.e., CR or PR then progressed), resistance to prior therapy (no response) or intolerant to prior therapy. Provide an analysis of comparing these characteristics across treatment arms.

5. Provide the versions of the investigator's brochure for gp100 and ipilimumab that were distributed to the investigators participating in the MDX010-20 trial.
6. Provide descriptive analyses in a tabular summary along with corresponding SAS programs used to generate the analysis and all derived variables, and identify (or if not present, insert a flag) for each patient where one or more adverse events were identified the clinical investigator as autoimmune breakthrough events (ABE) on the adverse event case report form.
7. Please submit all the supplemental case report forms (CRF) for each ABE that was identified by the investigator on the adverse event CRF. Please incorporate the data from the supplemental CRFs into the dataset, provide narrative summaries with hyperlinks to the supportive documents that contain the description and report of the procedures described in this form, summary of hospitalization, surgical, radiologic, and pathologic reports. Provide a descriptive summary for all ABE events using the data from the supplemental form.
8. Provide analyses of study drug related adverse events based on the specific drug attribution indicated by the investigator on the CRF; for example, these analyses should identify those events attributed by the investigator to only one of the two study drugs, e.g. if the investigator indicated that event was attributed to "gp100" and did not relate the event to "ipilimumab". Provide corresponding SAS programs that are used to generate these analyses.
9. Please provide an explanation regarding the study drug related deaths in the MDX010-20 CSR for subject M20-378-0723. This death is considered as related to study drug gp100, although the case narratives and CRF describe as unrelated to study drug.
10. Provide the following supportive documents for the specified death events:
 - M20-001-0230: surgical pathology report at the time of surgery for bowel perforation.
 - M20-424-0118: Please include English translations of all supportive documents such as hospital discharge summaries, reports of procedures and diagnostic tests for this 35 year old who died of cardiac failure.
11. Please provide the datasets used in the SAS programs that were used to derive the safety results included in the labeling. For example, IRAE and MED_VER were not included in the submitted data for running d-safety-irae-tto-resol-v01. Please also include files needed to run the SAS programs. For example, MAC-184 and file FT20F001 as shown on d-safety-irae-tto-resol-v01.txt should be included if it is necessary for the SAS program to run successfully.

12. Please confirm that all analysis datasets contain the derived variables that were included for every safety result included in proposed product labeling were provided.
13. Provide a dataset containing the adverse events captured in the expanded access program since March 2010 using the 3 mg/kg dose. Provide a summary analysis comparing all adverse events (Grades 1-5) and Grade 3-5 adverse events in the expanded access and the MDX010-20 ipilimumab-monootherapy treated patients.



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Memorandum

Date: 10/01/10 *ESC 10/01/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Requests (CMC)

From: Laughner, Erik
Sent: Friday, October 01, 2010 1:45 PM
To: 'Knight Trent, Heather'
Subject: FDA Information Request STN 125377 (Ipilimumab); CMC
Importance: High

Hello Heather,

We have the following CMC information requests for BLA STN 125377. FDA would like a 2-3 week turn around.



100110 IR
Memo.pdf (81 KB)

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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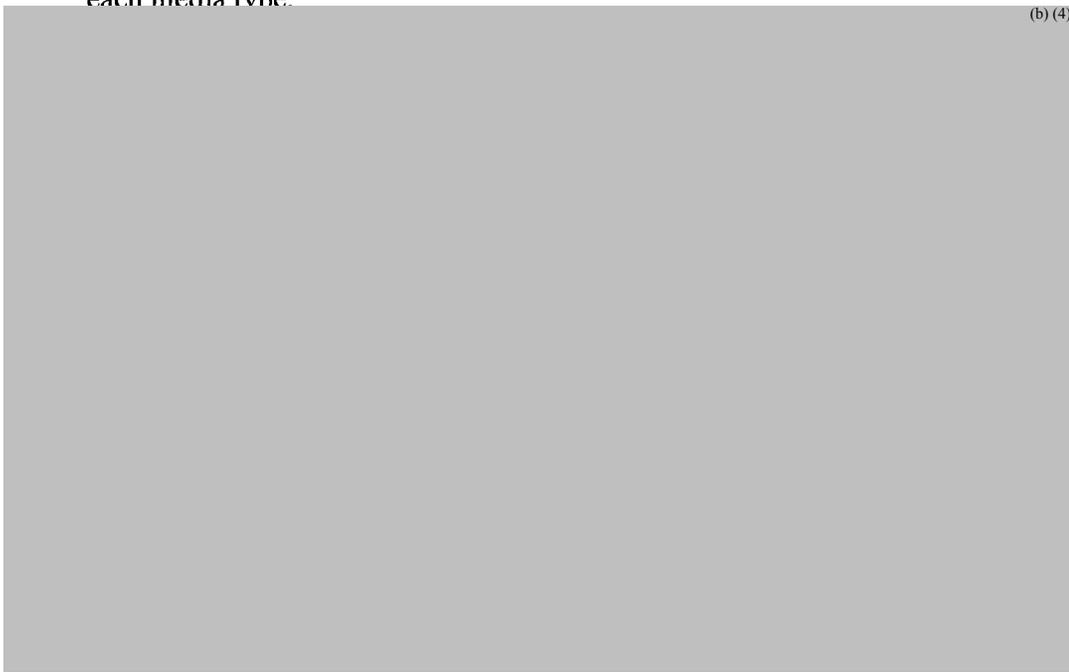
Memorandum

Date: October 1, 2010
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125377 (Ipilimumab)

CMC

1. In-process control for [REDACTED] (b) (4), should include acceptance criteria for the [REDACTED] (b) (4) bioburden. Provide comment and update controls section if appropriate.
2. Please describe actions that will be taken if bioburden action limits are exceeded during the [REDACTED] (b) (4). This should include an evaluation of product impact.
3. Provide all raw material acceptance criteria for compendial and non-compendial raw materials. The acceptance criteria should indicate whether the test is performed by BMS, or the raw material supplier as a component of the material's certificate of analysis. Include a detailed description of the raw material sampling, testing and acceptance process.
4. The submission indicates that multiple types of media are used for growth and expansion of the cell substrate. Provide a list of all media used in the manufacturing process, their source and a list of the individual components of each media type.

(b) (4)



11. Provide a protocol, with specifications and acceptance criteria, for generation of new working cell banks.
12. Submit a protocol for monitoring MCB and WCB stability with information/data that is supportive of the testing scheme and intervals. It is recommended that a comprehensive protocol be developed that incorporates, but is not limited to, adequate trend analysis of WCB performance parameters (i.e. viability at thaw and in vitro growth characteristics), criteria that will be used to determine when to establish a new WCB, and a more in-depth analysis of master cell bank performance after thaw.
13. Provide a list of the specifications, with acceptance criteria, that will be used to qualify a new reference standard.
14. Provide a list of specifications, with acceptance criteria, that will be used to monitor the stability of reference standard lots. This should include a description of the method (s) that will be used to monitor product potency.
15. Please submit information that demonstrates the (b) (4) (b) (4) is comparable and equivalent to the (b) (4) (21 CFR 610.9).
16. Visible particulates are present in the DS. Provide a description of the composition of the visible particulates and the procedures in place that control visible particulate levels in the DS. Provide available information on the ability of DP manufacturing steps to remove visible particles that are present in the DS.
17. Provide the validation reports for the mycoplasma, isoelectric focusing (IEF), DNA, human recombinant (b) (4), (b) (4) and HCP assays.
18. Provide a summary description for each compendial method used in the release and stability assessment of drug substance and drug product batches.
19. Provide the performance verification report for all compendial methods (e.g., particulate matter, container weight, extractable volume, appearance, pH, osmolality, and sub-visible particulate matter used for drug substance and drug product release.
20. While USP <788> is a compendial method, biotechnology products do require product specific method SOP to control aspects of product handling such as (b) (4). Provide the SOP for the DP particulate matter assay.
21. Provide information/data from studies that evaluated leachate levels in the DS and DP.
22. Provide extractable study reports for relevant DP container/closure systems and filters. Provide a risk assessment based on these findings for the leachate studies reported in the BLA.

23. Provide the final study reports for the DS container/closure leachate studies. Include the final risk assessment report on the absolute amount of each leachable detected in the test solutions and values used to support the levels present in the final product do not pose a safety risk for patients.
24. Provide validation reports to support all DS and DP process intermediate hold times and temperatures.
25. Because data is not provided to support classification of process parameters as critical versus non-critical, acceptance criteria for controlled operating and performance parameters listed in the submission for each manufacturing step need to be provided in sections 3.2.P.3.3 and 3.2.P.3.4. Update the BLA with a detailed tabular summary of controlled process parameters (operating and performance) with in-process acceptance criteria for all steps in the drug product manufacturing process.
26. Update section 3.2.P.3.5 to support the revised controlled operating and performance parameters if applicable.
27. Update sections 3.2.S.7.2 and 3.2.P.8.2 with a list of the assays, with acceptance criteria and assay SOP number that will be used to monitor DS and DP stability respectively.



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

Memorandum

Date: 10/01/10 *ESL 10/01/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding FDA safety analysis

FDA Attendees: Erik Laughner, Patricia Keegan, Yuan-Li Shen, Kaushik Shastri

BMS Attendees:

BMS Participants	Title
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory Sciences, Pharmacovigilance & Epidemiology (GPV&E)
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science- Oncology & Virology
Michael Giordano, M.D.	Vice President Development Teams- Global Development and Medical Affairs
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Allan Safferman, M.D.	Executive Director, GPV&E Medical Safety Assessment
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
Helen Liu, M.D.	Medical Director, GPV&E Medical Safety Assessment
Heather Knight-Trent, Pharm.D	Director, Global Regulatory Science- Oncology
Ramy Ibrahim, M.D.	Director, Oncology, Global Clinical Development
Marianne Messina, M.S.	Associate Director, Global Biometric Sciences

DISCUSSION:

PRIOR TO THE DISCUSSION, BMS PROVIDED A BRIEF SLIDE DECK ON HOW IMMUNE RELATED ADVERSE EVENTS WERE CAPTURED. FDA REVIEWED BUT DECLINED A FORMAL PRESENTATION OF THE SLIDES FOR THE TELECON

REGARDING PRESENTATION OF SAFETY ANALYSIS

FDA notified BMS that the characterization of immune related adverse events based on broad composite terms was not appropriate. BMS would need to develop better case definitions for immune related adverse events that will identify only those events that are truly likely to be immune related. Include all available information (e.g., endoscopic evaluation, histology/cytology, intervention with immunosuppressants). The criteria should be specific enough to exclude events that are clearly infectious in nature or result from other interventions (surgery) or co-morbid conditions. Please use the criteria specified in the protocols for establishing irAR's rather than the criteria for screening to identify potential irARs, as you have provided in the submission. Provide analyses and tabular summaries with the corresponding datasets and SAS programs for established immune related adverse events. The analyses should include treatment arm, category of irAR, time to onset in relation to study drug, outcome and time to outcome, and type of intervention or treatment given. Provide case narratives with hyperlink to all supportive information for selected biopsy, procedures or laboratory tests that establish the irAR.

FDA requested that BMS either create indicate which variable flag in the dataset differentiates between patients with a recurrence following prior therapy (i.e., CR or PR then progressed), resistance to prior therapy (no response) or intolerant to prior therapy.

FDA noted that as the original submission coded adverse events in MedDRA ver 12.1, all adverse events must be coded in this version of MedDRA for the entirety of the review.

REGARDING PROPOSED "REMS" IN BLA

FDA requested that BMS provide a summary analysis comparing adverse events between the expanded access program and MDX010-20 ipilimumab-monotheapy treated patients. This information was needed to get a sense of the safety experience outside the formal clinical trial setting. BMS noted that as of March, the 3mg/kg dose was used in the expanded access program.

(b) (4)

REGARDING SAS PROGRAMS

FDA noted that there were issues with the SAS programs used to derive the safety results. Some of the programs could not run. For example, IRAE and MED_VER were not included in the submitted data for running d-safety-irae-tto-resol-v01. FDA requested that BMS evaluate and include all files needed to run the SAS programs. BMS acknowledged and agreed to review and fix.

REGARDING THE ODAC

BMS noted that the top-line survival curve from the -024 study should arrive next week (directly to Dr. Keegan from the DSMB). BMS expressed a desire to work with FDA on "concepts" to be presented at the ODAC. FDA noted that broad concepts could be discussed; however, the information discussed above regarding the safety would be very important. FDA would have to review this information before any specific discussions regarding the ODAC could begin. BMS inquired whether BMS and FDA could interact during the week of October 18 to discuss. FDA

acknowledged the possibility.

4 Page(s) has been Withheld in Full as B4 (CCI/TS)
immediately following this page



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

Memorandum

Date: October 1, 2010 ^{ELC} 10/1/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Second Labeling Meeting

FDA Attendees: Sue Kang, Jibril Abdus-Samad, Patricia Keegan, Kaushik Shastri, Erik Laughner, Barbara Rellahan, Subramanian Muthukkumar

Discussion: This labeling meeting was convened to discuss the "DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, "HOW SUPPLIED/STORAGE AND HANDLING" and DESCRIPTION" sections of the proposed package insert label.



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

Memorandum

Date: October 1, 2010 ^{εεε} 10/1/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Standing Monthly Team Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Andrew McDougal, Anne Pilaro, Aakanskha Khandelwal, Christian Grimstein, Hong Zhao, Barbara Rellahan, Grace Carmouze, Sue Kang, Annette Ragosta (CBER), Lauren Iacono-Connor

Participants were present from major disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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

Memorandum

Date: September 2, 2010 *εε 07/02/10*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Standing Monthly Team Meeting

FDA Attendees (not all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Andrew McDougal, Anne Pilaro, Aakanskha Khandelwal, Christian Grimstein, Hong Zhao, Barbara Rellahan, Kalavati Suvarna, Donald Obenhuber, Jeff Summers, Grace Carmouze, Jibril Abdus-Samad, Donna Rosceo, Sue Kang, Annette Ragosta (CBER), Sheryl Kochman (CBER)

Participants were present from all disciplines. This monthly standing meeting provided reviewers/teams opportunity to discuss review status of BLA.



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

Memorandum

Date: September 28, 2010 2010/09/28
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); First Labeling Meeting

FDA Attendees: Patricia Keegan, Kaushik Shastri, Erik Laughner, Yuan Li-Shen, Kun He

Discussion: This labeling meeting was convened to discuss the "INDICATIONS AND USAGE and CLINICAL STUDIES" sections of the proposed package insert label.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125377

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492-7660

SEP 28 2010

ATTENTION: A. Heather Knight-Trent, PharmD
Director, Global Regulatory Science

Dear Dr. Knight-Trent:

Please refer to your Biologics License Application (BLA) dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act, for Ipilimumab Injection, 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL).

We also refer to your June 30, 2010, correspondence, received June 30, 2010, requesting review of your proposed proprietary name, Yervoy. We have completed our review of the proposed proprietary name, Yervoy, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your June 25, 2010 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 Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Erik Laughner at (301) 796-1393.

Sincerely,

Carol Holquist 9/28/10
Carol Holquist, RPh
Director

Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research



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

Memorandum

Date: September 24, 2010 ECL 09/24/10
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Mid-Cycle Meeting

A mid-cycle meeting was held. Participants were present from all disciplines. The following disciplines gave slide presentations to OODP:

- Erik Laughner, RPM
- Subramanian Muthukkumar, CMC
- Andrew McDougal, Nonclinical
- Kaushik Shastri and Yuan-Li Shen, Clinical/Stats
- Jun Yang, Clinical Pharmacology
- Joyce Weaver, OSE (DRISK)



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

Memorandum

Date: 09/21/10 ^{ESC 07/14/10}

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(nonclinical)

From: Laughner, Erik
Sent: Tuesday, September 21, 2010 3:38 PM
To: 'Knight Trent, Heather'
Subject: FDA Response; Information Request STN 125377 (Ipilimumab) Regarding DART PMR

Hello Heather,

In response to your email of August 6, 2010, in which you requested clarification on the DART study, we provide the following comments:

FDA requested that BMS propose a postmarketing requirement (PMR), and not a postmarketing commitment, to conduct a nonclinical developmental and reproductive toxicity (DART) study of ipilimumab in pregnant cynomolgus monkeys. Conduct of this nonclinical study as a PMR conforms to current FDA policy, i.e. it is general policy to obtain adequate nonclinical DART testing results for anti-cancer therapeutics that may be used to treat women who are, may be, or may become pregnant. This policy arises, in part, from implementation of FDAAA section 901, recent guidance (ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, published March 2010) and the Patient Protection and Affordable Care Act (signed March 23, 2010).

The nonclinical study conducted as a PMR is intended to obtain data to assess or identify potential DART safety issues for women who are pregnant or become pregnant while receiving ipilimumab for the labeled indication (i.e. for the treatment of advanced melanoma after receiving prior therapy). The resulting data from fulfillment of the PMR is intended for use in product labeling, to inform patients and their physicians regarding the potential benefits and the potential risks to the fetus of ipilimumab use. [The nonclinical data obtained that fulfill the PMR is not intended to support investigational use, potential off-label use, the license application, or accelerated approval.]

The specific safety concern which the nonclinical study conducted as a PMR is intended to address is increased by the ongoing review of BLA 125377, which notes:

- That treatment with ipilimumab may be associated with longer life expectancy in patients with metastatic melanoma
- A clearer understanding of the intended patient population

- That the labeled use of ipilimumab may not be limited to combination therapy with chemotherapy or IL-2 [REDACTED] (b) (4)

FDA notes that the pre/postnatal developmental toxicity study (ePPND) in monkeys (study # DN10020 and/or # MA00439) is ongoing, and realizes that initiation of treatment of substantial numbers of animals with ipilimumab may not be planned prior to mid-October 2010. FDA is not requesting an adjustment to the design or timelines of the DART study. To reiterate the August 05, 2010 email, FDA is requesting data, if available, from the DART study by approximately October 15, 2010, prior to labeling negotiations. FDA is requesting timely safety reporting for the DART study, and that the applicant propose a timeline for reporting of the DART study results, prior to PMR negotiations.

Please confirm receipt of this email.

Sincerely,

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Friday, August 06, 2010 10:46 AM
To: Laughner, Erik
Subject: RE: FDA Information Request STN 125377 (Ipilimumab)

Dear Erik,
BMS has been working on the reprotox study in question [REDACTED] (b) (4) We were not required to perform it for advanced melanoma. Can you clarify with the tox reviewers that this applies to advanced melanoma and if there has been a change in FDA's thinking? We are conducting the study regardless, but I'm concerned about it being a potential post marketing commitment for advanced melanoma.
Thanks,
Heather

From: Laughner, Erik [Erik.Laughner@fda.hhs.gov]
Sent: Thursday, August 05, 2010 2:00 PM
To: Knight Trent, Heather
Subject: FDA Information Request STN 125377 (Ipilimumab)

Hello Heather,
We have the following information requests for BLA STN 125377. Please review with your team and let me know your estimates for providing a timely response.
Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager

Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/cder/Offices/ODDP/about.htm>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125377/0

September 16, 2010

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, Pharm D.
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

This letter is in regard to your August 16, 2010, amendment to your biologics license application (BLA) STN 125377 dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act for ipilimumab.

This amendment provides a revised plan for submission of the high-level survival data from study CA184024 to the BLA. We agree with the proposal as outlined. We acknowledge that your submission also requested FDA feedback regarding your following concerns with respect to preserving the integrity of study CA184024:

- A limited number of people within FDA will have access to the overall survival data.
- The SPA for protocol CA184024 should remain intact.
- Data will not be provided to, or discussed with, other health authorities.
- Data will not be provided to, or discussed with, the ODAC members or consultants.

We confirm that the SPA for protocol CA184024 will remain in place. Regarding your other concerns noted above, FDA will follow standard confidentiality measures regarding submission of proprietary information.

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Patricia Keegan/

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: 09/15/10 *ESL 09/15/10*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(Clinical/Stats)

From: Laughner, Erik
Sent: Wednesday, September 15, 2010 12:36 PM
To: 'Knight Trent, Heather'
Subject: FDA Information Request; STN 125377 (Ipilimumab)

Hello Heather,

FDA would like BMS to submit as a formal amendment to the BLA, the final protocol and SAP that was agreed to by FDA at the time of the SPA approval for study MDX010-20.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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Memorandum

Date: 09/14/10 ^{Esc} 09/14/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (clinical)

From: Laughner, Erik
Sent: Tuesday, September 14, 2010 2:13 PM
To: 'Knight Trent, Heather'
Subject: RE: FDA Information Request; STN 125377 (Ipilimumab)

Hi Heather,

Can you also provide the SAP that was part of the approved SPA?

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Tuesday, September 14, 2010 12:54 PM
To: Laughner, Erik
Subject: FW: FDA Information Request; STN 125377 (Ipilimumab)

Dear Erik,
It is a little complicated, so I have sent more than one document to help you. Please let me know if this is not what was needed.

Sincerely,
Heather

From: Laughner, Erik [mailto:Erik.Laughner@fda.hhs.gov]
Sent: Tuesday, September 14, 2010 11:27 AM
To: Knight Trent, Heather
Subject: FDA Information Request; STN 125377 (Ipilimumab)

Heather,

FDA would like a copy of the original protocol for study MDX010-20 (prior to any amendments) as soon as possible.

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products

Office of Oncology Drug Products

CDER/FDA

301-796-1393

erik.laughner@fda.hhs.gov

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

Memorandum

Date: September 14, 2010 ^{ESC 09/14/10}
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Meeting

FDA Attendees (may not be all inclusive): Erik Laughner, Kaushik Shastri, Patricia Keegan, Yuan-Li Shen, Kun He, Dianne Spillman, Hong Zhao, Rajeshwari Sridhara, Grace Carmouze, Aakanksha Khandelwal, Richard Pazdur

Meeting held for planning possible presentation of this application at ODAC.



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

Memorandum

Date: 09/13/10 *ESL 09/13/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request
(clinical)

From: Laughner, Erik
Sent: Monday, September 13, 2010 10:10 AM
To: 'Knight Trent, Heather'
Subject: FW: Ipilimumab: BLA 125377

Heather,

Dr. Shastri has confirmed per your instructions the XML files can be converted to PDF.

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Thursday, August 12, 2010 3:24 PM
To: Laughner, Erik
Subject: Ipilimumab: BLA 125377

Dear Erik,

The submissions group has encountered some issues with providing the define.pdf version of the define.xml for each of the studies. It is causing problems with the hyperlinking. Can you ask the reviewers if the attached document indicating how to print the define.xml files is sufficient instead of providing the define.pdf files? At the navigation meeting on July 16, 2010, the reviewers indicated that the purpose of the define.pdf files was to print. Please let us know as soon as you can so we can find another solution.

Have you received an answer regarding the nonclinical reprotox post-marketing commitment question?

(b) (4) Is a monthly email sufficient or do you also want the number of events submitted officially to the BLA?

Thanks for your continued help,
Heather



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

Memorandum

Date: 09/09/10 *ESL 09/09/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; Information Request (QT-IRT)

From: Laughner, Erik
Sent: Thursday, September 09, 2010 7:50 AM
To: 'Knight Trent, Heather'
Subject: RE: FDA information Request STN 125377 (Ipilimumab)

Hello Heather,

I rec'd this info request from the QT review team regarding the recent submission to the ECG warehouse:

With this reload all ECGs have consistent Q,S and T annotations which we find acceptable for QT and QRS measurements but no P annotations,. However the sponsor reports PR interval data in the study report- Also if the ECGs have been re-annotated now, this would mean they have been re-read and and re-analyzed which implies that the new data/ECG report would have to be re-submitted. Can you kindly request the sponsor to provide an explanation?

Can you advise?
Thanks,

Erik

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Tuesday, August 24, 2010 4:51 PM
To: Chaudhry, Danyal
Cc: Laughner, Erik
Subject: FW: FDA information Request STN 125377 (Ipilimumab)

Dear Danyal,

I wanted you to be aware that we are working with the ECG warehouse on the request from Erik on August 6, 2010. The current status is below.

- The files were loaded to the ECG warehouse yesterday.
- An Import report indicated an issue with the way the files were handled by the system (representative beat vs global median beat). As a result the files need to be reprocessed.
- The files will be reprocessed and then submitted to the warehouse.

Sincerely,
Heather



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125377/0

FILING ISSUES

September 7, 2010

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, Pharm D.
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

Please refer to your biologics license application (BLA), dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act for ipilimumab. Also refer to our filing letter dated August 16, 2010. While conducting our filing review we identified the following potential review issues:

1. You have stated that the sample size for MDX010-20 was calculated “on the basis of a simulation using the collected blinded survival data from this study and historical literature data” in amendment 6 of the protocol. Please provide the references for the “historical literature data.”
2. Summarize the number of patients who received anti-cancer treatment after disease progression and if possible, the timing of receiving such treatment. This summary could be based on the data from concomitant medication page from the case report form (CRF) or from telephone follow-up data.
3. Provide an additional analysis of progression free survival (PFS) by censoring patients:
 - a. at time of the last assessment before patients discontinued treatment for toxicity or other reason prior to progression;
 - b. at the time of the last assessment before patients receive anti-cancer treatment prior to progression; and,
 - c. at the time of the last assessment before patients died or progressed after more than one missed assessment visit.

In a dataset, provide indicator variables and the date of the last assessment prior to the occurrence of the events stated above.

4. As previously communicated to you in an electronic mail (email) correspondence on July 30, 2010, please revise the Adverse Reactions section of the proposed package insert so that the adverse reactions derived from the MDX-020 study reflect the experience from the entire study duration and is not limited to adverse reactions occurring only during the induction period. Please also revise the adverse reactions tables accordingly.
5. We remind you that the purpose of the safety update is to provide only critical new safety information that has emerged since the application was submitted. The purpose of the safety update is not to provide new clinical study reports or to reanalyze and retabulate adverse reactions tables in the package insert using new data. Please refer to our March 30, 2010, meeting minutes of the March 4, 2010 pre-BLA meeting regarding the agreed upon contents of the safety update.
6. We requested in our email correspondence on July 30, 2010, that you revise the indication statement of the proposed package insert to reflect the population studied, i.e., patients that are HLA-A*0201-Positive. We acknowledge your August 6, 2010, response requesting that this discussion be deferred until after high level data from trial CA184024 has been reviewed, however, we refer to our March 30, 2010, pre-BLA meeting minutes and our April 21, 2010, follow-up advice letter in which we advised that any expansion of the labeling through removal of the restriction for HLA-A*0201 typing, would require final study report and datasets from CA184024 (which will not be reviewed for this original BLA). In addition to a revised indication statement, you should also provide information to the BLA which specifies the companion diagnostic that will be used for purposes of labeling.

We acknowledge your August 6, 2010, response that the following information requested on July 30, 2010, will be communicated by September 10, 2010:

7. Please identify and correct any dataset variables across the datasets that have the same variable name but indicate different things.
8. Please identify and correct across the datasets if different names are used to indicate the same treatment.
9. In the demographic dataset for CSS and CSE, please include an indicator variable for treatment arms. For examples of these treatment arms please see the treatment category in Tables 4.4.1B for CSE (page 36) and Table 5.3 for CSS (page 47) in Module 2.5 Clinical Overview.

We also have the following product information requests:

10. Please provide information on the epitope specificity of ipilimumab or provide a statement that such information is not available.

11. Please clarify whether or not verification of amino acid sequence analysis by LC-S/MS confirms 100% of the predicted amino acid composition of ipilimumab. If not, align the sequences and identify the degree of variability between actual and predicted sequences.
12. (b) (4)

(b) (4) Please clarify how (b) (4) duration is recorded and how the over all *in vitro* cell age of each lot is monitored, documented and controlled to ensure all lots are maintained within the validated time period. Provide information on (b) (4).
13. In process hold time acceptance criteria for process intermediates appear to be of significantly longer duration than the duration supported by the process validation data submitted. Provide data from small scale studies and/or process validation runs to support process intermediate storage times at controlled room temperature and 2-8°C.
14. For Section 3.2.S.2.4, provide clarification on the actual temperature range that will be maintained for all instances where 'room temperature' is used to describe the temperature.
15. Batch genealogy shown in the Tables 3.2.P.5.4.1.T01 and 3.2.S.4.4.1.T01 should identify the cell bank vial used. Provide updated Tables containing this information.
16. Tables 2.3.S.4.T02 and 2.3.P.5.T02 could not be found. Clarify where they are located in the submission or update the BLA to include them.
17. Drug substance lots 43628 and 43964 are listed in Table 3.2.S.4.4.1.T01 as being used for process validation but they are not included in Table 3.2.S.2.5.T01-*Summary of lots used for process validation study*, nor are they described in the validation section. Provide an explanation on why these lots were not included in the process validation summary.

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 complete 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. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional 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.

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Patricia Keegan/

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125377/0

FILING COMMUNICATION
August 16, 2010

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, Pharm D.
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

This letter is in regard to your biologics license application (BLA), dated June 25, 2010, received June 25, 2010, submitted under section 351 of the Public Health Service Act for ipilimumab.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The review classification for this application is Priority. Therefore, the user fee goal date is December 25, 2010. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before September 7, 2010.

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 commitment requests by November 25, 2010.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Joseph E. Gootenberg/

Joseph E. Gootenberg, M.D., on behalf of Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



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

Memorandum

Date: 08/13/10 (email #2) ^{ESC} 08/13/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (clinical)

From: Laughner, Erik
Sent: Friday, August 13, 2010 11:43 AM
To: 'Knight Trent, Heather'
Subject: FDA Information Request STN 125377 (Ipilimumab); Safety Update

Heather,

FDA would like to clarify that the safety update should use the same MedDRA version (12.1) as the original application and not a newer version 13.

Please confirm receipt.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Memorandum

Date: 08/13/10 *ESC 08/13/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (pharmacogenomics)

From: Laughner, Erik
Sent: Friday, August 13, 2010 9:51 AM
To: 'Knight Trent, Heather'
Subject: STN 125377 (info request)

Hi Heather,

In your response for info request 12, can you clarify a turn around time?

Tx,

Erik

QUESTION 12

Please submit individual genotype data for subjects who provided a DNA sample in CA184004, CA184007, CA184008, and CA184022. SAS data sets would be fine, a formal report is not needed.

RESPONSE

For each of the 4 phase 2 studies, BMS will submit two SAS datasets, one containing deidentified single-nucleotide polymorphism (SNP), safety, and efficacy data and one containing assay-level information. BMS also will submit an additional 2 such datasets integrating data across studies CA184-007, CA184-008, and CA184-022. Corresponding define.doc files will be provided. SNP data and selected efficacy and safety data were de-identified in order to comply with patient confidentiality agreements regarding submission of DNA samples for analysis, as outlined in the informed consent for studies CA184-004, CA184-007, CA184-008, and CA184-022.

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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301-796-1393
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<http://www.fda.gov/cder/Offices/OODP/about.htm>

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Memorandum

Date: 08/12/10

ESL
08/12/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; TCON; regarding -024

I called Heather Knight-Trent at BMS to clarify that FDA requested the top-line -024 OS K-M curve also include the hazard ratios and the confidence intervals. P-values would be optional. FDA would not impose a statistical penalty on this DSMB censored analysis. Heather acknowledged the request and agreed to discuss with team and provide a response back.



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

Memorandum

Date: 08/09/10 *ΣΣΣ 08/09/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information request (QT-IRT)

From: Laughner, Erik
Sent: Monday, August 09, 2010 11:04 AM
To: 'Knight Trent, Heather'
Subject: RE: FDA information Request STN 125377 (Ipilimumab)

Hi Heather,

I have only been told that a lot of them are not acceptable. The following PDF are a few examples of the issues.

Erik



BLA125377ECG.pdf

From: Knight Trent, Heather [mailto:heather.knighttrent@bms.com]
Sent: Monday, August 09, 2010 10:33 AM
To: Laughner, Erik
Subject: RE: FDA information Request STN 125377 (Ipilimumab)

Dear Erik,

There seems to be a lot of ECGs for this study. Can you obtain any further clarification on which ones they are?

Thanks,
Heather

From: Laughner, Erik [Erik.Laughner@fda.hhs.gov]
Sent: Friday, August 06, 2010 12:35 PM
To: Knight Trent, Heather
Subject: FDA information Request STN 125377 (Ipilimumab)

Heather,

FDA references the following final study report CA184004 in BLA:

“An Exploratory Study to Determine Potential Predictive Markers of Response and/or Toxicity in Patients with Unresectable Stage III or IV Malignant Melanoma Randomized and Treated with Ipilimumab (MDX-010/BMS-734016) at Two Dose Levels”

I have received the following comment and information request:

ECGs waveforms submitted to the ECG warehouse for this study report are not acceptable. Several ECGs have been incorrectly annotated . Please ask the sponsor to have them re-annotated, re-read and re-submitted to the ECG warehouse as soon as possible.

Please confirm receipt of this message.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
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4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Food and Drug Administration
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Memorandum

Date: 08/06/10 *EKL 08/06/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information requests (CMC and QT-IRT)

The following 2 emails were sent on 08/06/10:

#1.

From: Laughner, Erik
Sent: Friday, August 06, 2010 12:36 PM
To: 'Knight Trent, Heather'
Subject: FDA information Request STN 125377 (Ipilimumab)

Heather,

FDA references the following final study report CA184004 in BLA:

“An Exploratory Study to Determine Potential Predictive Markers of Response and/or Toxicity in Patients with Unresectable Stage III or IV Malignant Melanoma Randomized and Treated with Ipilimumab (MDX-010/BMS-734016) at Two Dose Levels”

I have received the following comment and information request:

ECGs waveforms submitted to the ECG warehouse for this study report are not acceptable. Several ECGs have been incorrectly annotated. Please ask the sponsor to have them re-annotated, re-read and re-submitted to the ECG warehouse as soon as possible.

Please confirm receipt of this message.

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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<http://www.fda.gov/cder/Offices/OODP/about.htm>

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#2.

From: Laughner, Erik
Sent: Friday, August 06, 2010 1:58 PM
To: 'Peck, David'
Subject: FW: BMS Clarification Request BLA STN 125377 (Ipilimumab); Product/Facilities

David,

FDA is requesting Product Code/Catalog Number for raw materials and not batch number.

Erik

From: Peck, David [mailto:david.peck@bms.com]
Sent: Friday, August 06, 2010 11:55 AM
To: Laughner, Erik
Subject: BMS Clarification Request BLA STN 125377 (Ipilimumab); Product/Facilities

Hi Erik -

BMS requests clarification regarding FDA Request for Information dated August 2, 2010.

Product, Question #6

Provide specification/acceptance criteria, **batch number** and approved vendor information for all raw materials used in the manufacturing process including items such as (b) (4) components and (b) (4). In addition, identify the commercial suppliers for each excipient, including water for injection, used in the drug product formulation.

BMS assumes that FDA is requesting Product Code/Catalog Number for raw materials and not batch number. Please clarify.

Thank you,

Dave Peck
Associate Director
Global Regulatory Sciences - CMC
609-818-5881

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Public Health Service
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Memorandum

Date: 08/05/10 25² 08/05/10

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: BMS (STN 125377) TCON; regarding FDA 07/30/10 information requests.

FDA ATTENDEES:

Erik Laughner, M.S., Senior Regulatory Health Project Manager, DBOP
Kaushik Shastri, M.D., Medical Officer, DBOP
Kun He, Ph.D., Acting Statistical Team Leader, OTC/OB/DBV
Yuan Li-Shen, Ph.D. Statistical Reviewer, OTC/OB/DBV

BMS ATTENDEES:

BMS Participants	Title
Dominic Labriola, Ph.D.	Vice President, Global Biometric Sciences
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences
Todd Rider	Senior Manager, GBS Programming
Heather Knight-Trent, Pharm.D.	Director, Global Regulatory Science-Oncology

BACKGROUND:

BMS requested a tcon to discuss FDA's questions/comments 6,7,10, and 11 from the July 30, 2010 information request.

DISCUSSION:

Prior to discussing the July 30, 2010 information request, FDA communicated to BMS that the high-level study data from the -024 study would not be formally presented in the ODAC briefing document. FDA requested that the high-level data to provided the week of November 8th and no later than November 16th. FDA asked that BMS confirm this understanding is the letter that had previously been requested regarding content/format of -024 data. BMS acknowledged.

Question 6 from 07/30/10 Information Request: Please identify and correct any dataset variables across the datasets that have the same variable name but indicate different things.

BMS agreed to update the variables to indicate as-randomized arms for the -20 study. Secondary variables would also be flagged.

Question 7 from 07/30/10 Information Request: Please identify and correct across the datasets if different names are used to indicate the same treatment.

BMS agreed to update the variables to indicate as-treated arms for the -20 study. Indicator variables would also be added for the CSS and CSE.

Question 10 from 07/30/10 Information Request: The variable **subjid** in the raw datasets that were used in DOS.SAS contains values with a length of 5 while those values in the derived datasets contained values with a length of 7. Character variables with the same names should contain the same format of values across different datasets. You should revise the datasets so that the value of the variables across different datasets containing the same format. The revised datasets should also contain converted numeric data to the data tabulation datasets (i.e. raw data).

BMS agreed to update the variables SUBJIB in the data listing datasets of study -20 to be consistent with the variables in the derived datasets. FDA and BMS after some discussion agreed that no updates were needed for the data tabulation datasets.

Question 11 from 07/30/10 Information Request: In the demographic dataset for CSS and CSE, please include an indicator variable for treatment arms. For examples of these treatment arms please see the treatment category in Tables 4.4.1B for CSE (page 36) and Table 5.3 for CSS (page 47) in Module 2.5 Clinical Overview.

BMS agreed that indicator variables will be added to the CSS and CSE database. SAS programs to generate these would also be provided for FDA review.



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Memorandum

Date: 08/05/10 Σ SL 08/05/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information requests (nonclinical)

From: Laughner, Erik
Sent: Thursday, August 05, 2010 2:01 PM
To: 'Knight Trent, Heather'
Subject: FDA Information Request STN 125377 (Ipilimumab)
Importance: High

Hello Heather,

We have the following information requests for BLA STN 125377. Please review with your team and let me know your estimates for providing a timely response.



080510 IR
memo.doc (48 KB)

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
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Memorandum

Date: August 5, 2010
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125377 (Ipilimumab)

Nonclinical

1. Regulatory action for BLA 125377 will likely be contingent upon reaching agreement regarding a postmarketing requirement (PMR) for submission of the results of a nonclinical embryofetal study in a pharmacologically-relevant animal model. FDA tentatively expects that the planned/ongoing pre/postnatal developmental toxicity study (ePPND) in monkeys (the subject of supporting documents submitted to IND 9186 on March 26, 2010 and June 16, 2010) will address this PMR. To facilitate discussion of this PMR during the review period, please provide the following information:
 - a. An interim summary of the available results for each monkey exposed to ipilimumab or control vehicle (e.g. maternal toxicity if any, pregnancy outcomes). Propose dates for submission of this summary (approximately October 15, 2010) and for data cut-off (approximately one week prior to submission of the report). Propose revised language for the label sections 8.1 and 13.2 based on these results.
 - b. Submit safety reports to the IND [as per 21CFR312.32(c)(1)(i)(B)] within 15 days for each serious adverse event in this study, including loss of pregnancy occurring in any control or ipilimumab-treated animal. Telephone and facsimile transmission of these safety reports are not required. Please include in each safety report a current summary table of the SAEs for each group. FDA recognizes that this reporting may appear to overpredict risk due to the high background incidence of loss of pregnancy in cynomolgus monkeys, but considers this information important.
 - c. As part of the PMR, FDA requests submission of an interim report on pregnancy outcomes and neonatal parameters after approximately one third of the in-life results are available (i.e. after the first post-natal assessment results for approximately 7 offspring per dose group are available).
 - d. Propose dates for submission of the interim draft report with the data on the pregnancy outcome in one-third of the study animals, the audited draft report, and the final study report.
 - e. If the results of the ePPND toxicity study in monkeys do not show that the monkey is a pharmacologically-relevant species for evaluation of potential developmental toxicity, FDA may require additional testing in an available alternative model. BMS (IND #9186, supporting document submitted 6/16/2010) indicated that the surrogate anti-mouse CTLA4 antibody is not sufficiently characterized for this purpose. Please apprise FDA of the status of the transgenic mouse model (human CTLA-4 under the mouse CTLA-4 promoter; study # MDX-010-005-R), the availability of other transgenic models

(e.g. Peggs et al. 2009¹), and whether BMS considers that these models may be relevant for assessment of the potential developmental toxicity of ipilimumab.

2. Section 2.6.2 (Pharmacology Written Summary) briefly notes that **“CTLA-4 knockout mice suffer a fatal lymphoproliferative disorder, supporting the concept that CTLA-4 functions as a key negative regulator of T-cell responses”**, and cites three papers as support (Chambers et al. 1997; Tivol et al. 1995; Waterhouse et al. 1995). The summary notes similar findings in CTLA-4 deficient mice (Wing et al. 2008; Read et al. 2006). If Bristol-Myers Squibb does not consider these data relevant to pregnant women receiving ipilimumab, provide scientific justification to the BLA. Alternatively, propose language for sections 8.1 and 13 of the label regarding the developmental toxicity observed in CTLA-4 knockout mice.
3. Study #MDX-1106/010-001R was submitted to IND 9186 on August 12, 2009, but does not appear to have been submitted to the BLA or discussed in the nonclinical summaries. Either indicate where in the BLA this study is located, or provide it to the BLA.
4. Summary information regarding nonclinical experiments to assess antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) was submitted to IND 9186 (supporting document submitted April 26, 2010). Either indicate where in the BLA the study report(s) is located, or provide the study report to the BLA. The results of these particular ADCC and CDC studies do not appear to have been incorporated into the nonclinical summary of ADCC and CDC (i.e. section 2.6.3). At the May 26, 2010 meeting, the potential clinical relevance of the ADCC data was discussed. Provide to the BLA an updated overall evaluation of the ADCC potential of ipilimumab, based on all available relevant data, (b) (4)

5. Good laboratory practices [21CFR58.185(a)] specify that the study reports include information on the test and control articles' identity, code number, strength, purity, and composition. For the following studies, indicate where in the BLA this information is located, or provide the omitted information to the BLA: Studies #7114-100, #01-3460, #IM578., #IM933, and #DSO5067.

¹ Peggs KS, Quezada SA, Chambers CA, Korman AJ, and Allison JP. 2009. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. The Journal of Experimental Medicine. 205: 1717-1725.



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Memorandum

Date: 08/02/10 ECL 08/02/10
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information requests
(Product/Facilities)

From: Laughner, Erik
Sent: Monday, August 02, 2010 9:15 AM
To: 'Knight Trent, Heather'
Subject: FDA Information Request STN 125377 (Ipilimumab); Product/Facilities

Hello Heather,

We have the following information requests for BLA STN 125377. Please review with your team and let me know your estimates for providing a timely response.



080210 IR
memo.doc (81 KB)

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
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Memorandum

Date: August 2, 2010
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: FDA Request for Information; BLA STN 125377 (Ipilimumab)

Product

1. For Quality Module 3 hyper-links to all referenced Sections and Tables should be provided. Examples of the referenced sections and tables that are not linked are shown below:
 - From page 3.2.S.2.3.1.3. Materials of Biological Origin (ipilimumab, (b) (4) a referenced section 3.2.A.2. “Adventitious Agents Safety Evaluation” was not able to be accessed.
 - From page 3.2.S.2.3.4 Source, History and Generation of Cell Substrate ipilimumab, (b) (4) a referenced section, “The structure of ipilimumab is described in Section 3.2.S.1.2, “Structure” could not be accessed.
 - From 3.2.S.2.4.1 Process Controls for the (b) (4), a referenced Section 3.2.S.2.2.2, (b) (4) could not be accessed.
2. Provide batch genealogy which traces each drug product batch from the working cell bank vial thaw to the final drug product lot. This should include information on the date of manufacture of drug substance and drug product, the manufacturing process used and the type of study each lot was used for (e.g., in pre-clinical, clinical, stability etc).
3. Provide complete information on the consistency batches including genealogy as indicated above, batch analyses and whether the drug substance/drug product consistency lots were produced consecutively.
4. Because data is not provided to support classification of process parameters as critical versus non-critical, acceptance criteria for controlled operating and performance parameters listed in the submission for each manufacturing step need to be provided in section 3.2.S.2.2. Update the BLA with a detailed tabular

summary of all (b) (4) controlled process parameters (operating and performance) with in-process acceptance criteria for all steps in the manufacturing process including (b) (4) criteria (b) (4) and testing performed (b) (4).

5. Update section 3.2.S.2.5.2.3 to support the revised controlled operating and performance parameters.
6. Provide specification/acceptance criteria, batch number and approved vendor information for all raw materials used in the manufacturing process including items such as (b) (4) components and (b) (4). In addition, identify the commercial suppliers for each excipient, including water for injection, used in the drug product formulation.
7. Provide a list of all drug substance and drug product release and stability assays and indicate the facility (s) at which each test is performed.
8. Provide the assay validation report and data for the host cell protein assay. The following issues should also be addressed. The (b) (4) antibody used in this assay may not detect all HCP specific to ipilimumab process. Submit data that demonstrates that the anti-HCP antiserum is able to detect a majority of the potential HCP impurities expected to be present in the process. This data needs to include (b) (4) SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as (b) (4), compared to the range detected by western blot analysis (or another similarly sensitive assay) using the antiserum employed in the assay. It is the Agency's experience that analysis of HCP coverage by a (b) (4) SDS-PAGE gel method is not sufficiently sensitive for this purpose.
9. Provide assay validation data for the DNA assay and data on assay performance characteristics such as the limit of detection for the (b) (4) assays.
10. Provide the validation reports and data for all non-compendial assays used for drug substance and drug product release and stability testing.
11. The drug substance specifications indicate that alternative methods may be used for many of the assays. Provide clarification on the use of these alternative methods and indicate where in the submission the alternative methods are described and where the validation reports for the alternative methods are located.
12. Provide a tabular list of all assays with acceptance criteria that will be used to monitor drug substance and drug product stability post-licensure.
13. Provide a more detailed description of how the System Analysis and Program development (SAP) inventory management system is used to track product batches through the manufacturing process.

Facilities

1. Please provide a report summarizing your bioburden and endotoxin mapping studies.
2. Please provide a table with bioburden and endotoxin limits for each manufacturing step and data from all batches manufactured using the commercial manufacturing process. Please also include in this table the bioburden results for the (b) (4) steps.
3. Please provide qualification data for the endotoxin test using in process intermediates, buffers, and drug substance. A summary report providing the maximum valid dilution (MVD) and results from 3 lots where interference/enhancements were assessed should be included.
4. For the bioburden test, data from 3 lots of in-process intermediates supporting that the method is suitable for its intended use should be included. The (b) (4) procedure used for bioburden testing of in-process intermediate and drug substance, including sample volume, (b) (4) volume, and controls used should be described.
5. For product (b) (4) hold studies, please provide the protocol which describes the experimental details such as temperature, duration, type of (b) (4) volume, lots tested, method and sampling time-points, and the report with data from these studies. The report should also include results from growth promotion studies for (b) (4) media and (b) (4) buffer.
6. Please provide data from 3 commercial lots to demonstrate microbial control of in-process intermediates and drug substance for the established hold times.
7. Please provide the protocol and report including summary data from your shipping qualification study for drug substance.
8. For the drug substance, please provide experimental details of the studies used to assess integrity of the (b) (4).



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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: 07/30/10 *ESL 07/30/10*

From: Erik Laughner, RPM DBOP/OODP/CDER/FDA

Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA information requests
(clinical, statistical, pharmacogenomics)

From: Laughner, Erik
Sent: Friday, July 30, 2010 12:58 PM
To: 'Knight Trent, Heather'
Subject: FDA Information Request STN 125377 (Ipilimumab)
Importance: High

Hello Heather,

We have the following information requests for BLA STN 125377. Please review with your team and let me know your estimates for providing a timely response.



073010 IR
memo.pdf (23 KB)

Please confirm receipt.

Sincerely,

Erik

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: July 30, 2010

From: Erik Laughner, M.S., DBOP/OODP/CDER

Subject: FDA Request for Information; BLA STN 125377 (Ipilimumab)

Clinical/Statistical

1. Please revise the proposed package insert so that the adverse reactions describe experience from the entire study duration and not only during the induction period. Please also revise the Adverse Reactions tables accordingly.
2. Please revise the indication statement of the proposed package insert to reflect the population studied, i.e., patients that are HLA-A*0201-Positive.
3. Please provide the annotated package insert that annotates the precise location of the information (i.e. include the precise page number(s) or output table number(s) in a cited study report).
4. Please provide SAS programs for safety data included in the proposed package insert.
5. Please provide a data definition file in PDF format for the Data tabulation dataset for study MDX10-20.
6. Please identify and correct any dataset variables across the datasets that have the same variable name but indicate different things.
7. Please identify and correct across the datasets if different names are used to indicate the same treatment.

8. Please provide computer software or simulation programs that were used to calculate the number of events required for the ipilimumab plus gp100 and gp100 monotherapy arms (3:1 ratio). As stated in the protocol, 385 deaths were required to achieve a 90% power to detect a median survival time difference of 10.8 months vs. 8.6 months assuming 2-sided 0.05 significance level.
9. Among those patients who had disease progression, please summarize the number of patients who took post-induction anti-melanoma treatment and if possible, the timing of receiving such treatment.
10. The variable **subjid** in the raw datasets that were used in DOS.SAS contains values with a length of 5 while those values in the derived datasets contained values with a length of 7. Character variables with the same names should contain the same format of values across different datasets. You should revise the datasets so that the value of the variables across different datasets containing the same format. The revised datasets should also contain converted numeric data to the data tabulation datasets (i.e. raw data).
11. In the demographic dataset for CSS and CSE, please include an indicator variable for treatment arms. For examples of these treatment arms please see the treatment category in Tables 4.4.1B for CSE (page 36) and Table 5.3 for CSS (page 47) in Module 2.5 Clinical Overview.

Pharmacogenomics

12. Please submit individual genotype data for subjects who provided a DNA sample in CA184004, CA184007, CA184008, and CA184022. SAS data sets would be fine, a formal report is not needed.

Pharmacometrics

13. Please submit the dataset (analysis and external validation dataset), NONMEM control streams (base, covariate and final models) and the output listing for the population PK analysis (Module 5.3.3.5) by August 6th 2010.
14. Please submit the dataset, associated program codes and the output files for the exposure-response analysis for efficacy and safety (Module 5.3.3.5) by August 6th 2010.

We encourage you to refer to the following pharmacometric data and models submission guidelines.

(<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>):

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).



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

Memorandum

DATE of DECISION: July 30, 2010

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status

Sponsor: Bristol-Myers Squibb Company
Product: Ipilimumab
Indication: Treatment of advanced melanoma in patients who have received prior therapy

TO: BLA file STN 125377/0

The review status of this file submitted as a BLA application is designated to be:

Priority (6 Months) Standard (10 Months)

Patricia Keegan, M.D.: Patricia Keegan Date: 7-30-2010



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

Memorandum

Date: 07/27/10 *ES on 7/27/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: BMS (IND 9186 and STN 125377) TCON; regarding expanded access drug supply and timing/content of -024 OS study data for BLA.

FDA ATTENDEES:

Erik Laughner, RPM -CDER/OND/OODP/DBOP
Kaushik Shastri Clinical Reviewer - CDER/OND/OODP/DBOP
Patricia Keegan, Director - CDER/OND/OODP/DBOP

BMS ATTENDEES:

BMS Participants	Title
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory Sciences, Pharmacovigilance & Epidemiology
Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Margo Heath-Chiozzi, MD	Vice President, Global Regulatory Science- Oncology & Virology
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
Heather Knight-Trent, PharmD	Director, Global Regulatory Science- Oncology
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences

BACKGROUND: FDA requested a brief tcon with BMS to discuss the use of "Process C" material in the expanded access program (under IND 1986) and the timing/content of -024 trial overall survival (OS) data to support the current BLA application STN 125377.

DISCUSSION REGARDING THE EXPANDED ACCESS PROGRAM: BMS noted that since the May 26, 2010 CMC meeting to discuss "Process C", additional safety data were available and this was communicated to FDA per the July 14, 2010 information amendment to IND 9186. BMS confirmed that at this time, "Process C" was going to be used first for the expanded access program but could be used in the future in ongoing clinical studies. Both FDA and BMS agreed that in this small study, the immune related AE rate, especially of grade III/IV colitis was higher in the new material. BMS felt that the AE's were manageable. BMS agreed that the most recent IB update (08/10) would inform investigators of the perceived rate of higher AE in the "Process C" material. In

addition, BMS would provide updates to the sites thru their routine communications. FDA confirmed that the "Process C" material could be used in the expanded access program provided an updated Investigator's Brochure, which provides separate safety summary data for Processes B and C and a safety communication alerting physicians to the apparent increase in toxicity with Process C were performed as discussed.

DISCUSSION REGARDING PROVIDING TOP-LINE DATE FOR -024 STUDY DURING STN 125377 REVIEW: FDA noted that as previously discussed, high-level OS data for study -024 would be required prior to ODAC. This data should be presented as a survival K-M curve with the number of patients at risk along the x-axis and which clearly identifies the treatment arms. Hazard ratios/confidence intervals could be provided, although not required. FDA requested that the DMC conduct the analysis and provide this information to FDA; BMS agreed but stated that the information would need to be provided in a manner that would allow BMS to remain blinded to the results since such data could be considered material findings. FDA agreed that there would be no statistical penalty imposed on this study (which is under SPA).

FDA stated that BMS should provide a formal letter to the BLA file outlining this plan by August 10, 2010. The filing deadline for the BLA would be August 24, 2010. The letter should also outline any of BMS's concerns/caveats as this data relates to FDA review/ODAC presentation etc. FDA indicated that it would take into consideration BMS's sensitivity regarding making this top-line DMC data available to only a select number of people to ensure confidentiality. BMS acknowledged and noted that the DMC charter would likely have to be revised to allow this non pre-specified analysis. BMS also noted that for the EMEA application, the European authorities have not yet requested the -024 data for review of the study -010 data.



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

Memorandum

Date: 07/09/10 *ESL 07/09/10*
From: Erik Laughner, RPM DBOP/OODP/CDER/FDA
Subject: Bristol-Myers Squibb Company; BLA STN 125377; FDA statistical information requests

From: Laughner, Erik
Sent: Friday, July 09, 2010 2:04 PM
To: 'Knight Trent, Heather'
Subject: STN 125377; FDA Information Request; Statistical

Hello Heather,

The statistician has identified the following issues, please review and address:

1. Attached is the SAS program based on the provided SAS macro MSURP and analysis dataset OS. FDA uses this program to duplicate the results on Table 7.2A of the CSR, but the results do not match. One possible reason could be the data used to generate the CSR is not the same as the data submitted. Please clarify.
2. The variables used in the SAS program DOS.SAS do not exist in the datasets provided. For example, aeoutn, aetoxgrn, aeendtn, etc are not in raw dataset AE or in derived dataset AESAESTR. Please provide datasets that contain the variables used in the DOS.SAS. FDA considers the derived variables used in the SAS program DOS important for verification of the overall survival results.



msurp.sas (3 KB)

Please confirm receipt.

Sincerely,

Erik
Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

If you have received this message in error, do not use, disclose, reproduce, or distribute this message (including any attachments) and notify me immediately. Thank you.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL [125377/0]

BLA ACKNOWLEDGEMENT
July 8, 2010

Bristol-Myers Squibb Company
Attention: A. Heather Knight-Trent, Pharm D.
Director-Oncology
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Knight-Trent:

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: Ipilimumab

Date of Application: JUNE 25, 2010

Date of Receipt: JUNE 25, 2010

Our Submission Tracking Number (STN): BL 125377/0

Proposed Use: Pretreated Advanced Melanoma

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. If you have any questions, contact Erik S. Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

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



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

Memorandum

Date: July 6, 2010 *ECL 07/06/10*
From: Erik Laughner, M.S., DBOP/OODP/CDER
Subject: BLA STN 125377 Yervoy (ipilimumab); Planning Meeting (First Committee Meeting)

Regulatory Management
Erik Laughner

CDRH
Donna Roscoe
Maria Chan

Clinical
Kaushik Shastri
Pat Keegan (TL/Director)

Biostats
Yuan Li Shen
Kun He (TL)

Nonclinical
Andrew McDougal
Anne Pilaro (TL)

Clinical Pharmacology
Aakanksha Khandelwal
Christian Grimstein (Pharmacogenomics)

Product
Subramanian Muthukkumar
Barbara Rellahan (TL)

Facilities
Kalavati Suvarna- Drug Substance
Don Obenhuber- Drug Product

DBOP Safety Team
Jeff Summers- DDS
Grace Carmouze

OSE
Sue Kang

Discussion:

Planning meeting was held. Participants were present from all disciplines. The content/structure of eCTD BLA, timelines for review of applicant, needed consults, 21st Century GRMP review dates were discussed. Early issues/deficiencies identified were discussed by team.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 009186

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Krisztina Nemenyi, Ph.D.
Director, Global Regulatory Science Oncology
5 Research Parkway
Signature 91 Building/3SIG-509
Wallingford, CT 06492

Dear Dr. Nemenyi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Human Monoclonal Antibody (MDX-010, MDX-CTLA4) to CTLA4; [ipilimumab]."

We also refer to the meeting between representatives of your firm and the FDA on March 4, 2010. A copy of the official minutes is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me, at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Erik Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 4, 2010
TIME: 2:00-3:30 PM ET
APPLICATION: IND 009186
SPONSOR: Bristol Myers Squibb Company [BMS]
DRUG NAME: Ipilimumab [Human Monoclonal Antibody (MDX-010, MDX-CTLA4) (Bristol Myers) to CTLA4]
TYPE OF MEETING: Type B; Pre-BLA; Face-to-Face
MEETING CHAIR: Kaushikkumar Shastri
MEETING RECORDER: Erik Laughner

FDA ATTENDEES:

CDER

Richard Pazdur, M.D.	Director, OODP
Patricia Keegan, M.D.	Director, DBOP/OODP
Kaushikkumar Shastri, M.D.	Clinical Reviewer, DBOP/OODP
Yuan Li Shen, Dr. P.H.	Statistical Reviewer, DV5/OB
Mark Rothmann, Ph.D.	Statistical Team Leader, DV5/OB
Anne M. Pilaro, Ph.D.	Pharmacology/Toxicology Supervisor, DBOP/OODP
Andrew McDougal, Ph.D.	Toxicology Reviewer, DBOP/OODP
Erik Laughner, M.S.	Senior Regulatory Health Project Manager, DBOP/OODP
Karen Jones, B.S.	CPMS, DBOP/OODP
Lee Pai-Scherf, M.D.	Clinical Reviewer, DBOP/OODP
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCP5/OCP
Aakanksha Khandelwal, Ph.D.	Clinical Pharmacology Reviewer, DCP5/OCP
Issam Zineh, Ph.D.	Associate Director of Genomics, OCP
Christine Garnett, Ph.D.	Associate Director of Pharmacometric Operations, OCP
Christian Grimstein, Ph.D.	Genomics Reviewer, OCP
Jeff Summers, M.D.	Deputy Director of Safety, DBOP/OODP
Kathryn O'Connell, M.D., Ph.D.	Medical Officer, DRISK/OSE
Subramanian Muthukkumar, Ph.D.	Product Reviewer, DMA/OBP

CDRH

Donna Roscoe, Ph.D.	Science Reviewer, DIHD/OIVD
Thomas Gwise, Ph.D.	Statistician, CDRH
Robert Becker, M.D., Ph.D.	Chief Medical Officer, DIHD/OIVD

BMS ATTENDEES:

Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Axel Hoos, M.D., Ph.D.	Group Director, Oncology, Global Clinical Development
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Michael Giordano, M.D.	Vice President, Global Development and Medical Affairs
Eric Masson, PharmD	Director, Discovery Medicine and Clinical Pharmacology
Zhengqing Li, Ph.D.	Executive Director, Global Biometric Sciences
Tai-Tsang Chen, MS	Associate Director, Global Biometric Sciences
Joan Ryan, MD	Medical Director, Global Pharmacovigilance & Epidemiology
Helena Brett-Smith, MD	Executive Director, Global Clinical Development
Mathias Hukkelhoven, Ph.D	Senior Vice President, Global Regulatory Sciences and Pharmacovigilance
Margo Heath-Chiozzi, MD	Vice President, Global Regulatory Science- Oncology & Virology
Krisztina Nemenyi, Ph.D.	Director, Global Regulatory Science Oncology

1.0 MEETING OBJECTIVES:

To discuss the proposed contents/format of an eCTD BLA for an indication in advanced melanoma.

2.0 BACKGROUND

Relevant Past Regulatory History (Abbreviated)

During the previous April 25, 2008, pre-BLA meeting, BMS proposed to submit under 21 CFR 601.40 (Subpart E) a BLA primarily based on CDER study CA184008 which is briefly described below:

CA184008: open-label, single-arm (n=155), ipilimumab monotherapy (10 mg/kg; and maintenance) in subjects with previously treated advanced melanoma.

This study was reviewed under Special Protocol Assessment (SPA) for consideration of accelerated approval, 21 CFR 601.40 (Subpart E), for ipilimumab monotherapy in the second-line setting based on objective response rate as a surrogate endpoint. The prespecified agreement for overall response rate stated that "the lower boundary of the two-sided exact 95% confidence interval for the best overall response rate (BORR) will

be at least 10% when 23 or more responses are observed (i.e. BORR ≥ 15.3%). Such observation would be considered clinically important.”

At that time BMS proposed to verify clinical benefit of ipilimumab by demonstration of superiority in progression free survival (PFS) from the addition of ipilimumab to dacarbazine in the ongoing study CA184024 (blinded, randomized n=500 planned, Phase 3, dacarbazine with or without ipilimumab (10 mg/kg) in subjects with previously untreated or advanced melanoma).

In the FDA preliminary responses provided to BMS on April 23, 2008, FDA noted that trial CA184008 demonstrated a Best Overall Response Rate (BORR) of 5.8 % (95% CI 2.7, 10.7) and therefore failed to meet its primary endpoint as specified in the statistical analysis plan and strongly recommended that BMS wait for the overall survival (OS) results from the above ongoing Phase 3 study CA184024 to support a BLA.

At the meeting, BMS acknowledged and indicated that the primary endpoint in study CA184024 would likely be changed from PFS to overall survival. Mature survival data was anticipated to be available in 2010.

January 13, 2010 Teleconference

On December 1, 2009, BMS requested a Type C meeting to discuss the overall development plan for melanoma based on new preliminary survival data from CBER study MDX010-20. During the January 13, 2010, Type C teleconference, BMS presented study MDX010-20 which was a randomized, double-blind, multicenter CBER study conducted in HLA-A*0201-positive subjects who had Stage III or IV melanoma and who had relapsed/progressed after one or more of the following treatments: IL-2, DTIC, temozolomide, fotemustine, and/or carboplatin. Randomization was stratified for TNM status (M0, M1a, M1b vs. M1c) and prior treatment with IL-2; patients were randomized (3:1:1) to receive either 3mg/kg ipilimumab q3 wks and gp100 q3 wks, 3mg/kg ipilimumab monotherapy, or gp100 monotherapy, respectively. The protocol allowed for reinduction with the assigned treatment regimen for subjects with an initial response of stable disease (SD) or better after induction with subsequent disease progression after study week 12. BMS noted that 646 subjects either completed the study or died.

Results as summarized by BMS from the January 13, 2010, meeting briefing document are:

	Ipilimumab + gp100 (n=403)	Ipilimumab (n=137)	gp-100 (n=136)
Overall Survival			
# Deaths	306	100	119
Median (mos)	9.95	10.12	6.44
Hazard Ratio ¹	0.68	0.66	

(95% CI)	(0.55, 0.85)	(0.51, 0.87)	
Nominal p-value	0.0004	0.0026	
BORR	5.7% (23/403)	10.9% (15/137)	1.5% (2/136)
(95% CI)	(3.7, 8.4)	(6.3, 17.4)	(0.2, 5.2)
Progression-free survival			
Median (mos)	2.76	2.86	2.76
Hazard Ratio ¹	0.81	0.64	
(95% CI)	(0.66, 1.00)	(0.50, 0.83)	

BMS noted that the safety profile from MDX010-20 was consistent with that reported with ipilimumab in previously reported monotherapy studies.

During the teleconference, FDA agreed that that the OS data was of interest, but expressed concern with the gp100 control arm and the study size. FDA noted that as only HLA-A*0201-positive subjects were treated expansion of labeling to an unrestricted population would be dependent on the results of CA184024. The CA184024 OS data would be important to provide additional confirmatory evidence of efficacy. BMS indicated that CA184024 was still blinded and efficacy data was likely not going to be available until October 2010 at the earliest. (b) (4)

. In addition, BMS was asked to provide an all known, relevant data regarding effects on survival. BMS and FDA agreed that the scheduled March 4, pre-BLA meeting would continue to discuss the total planned data package.

Current Pre-BLA Meeting

On December 14, 2009, BMS requested a clinical pre-BLA meeting to obtain feedback and reach agreement with FDA on the registrational program for advanced melanoma. As noted in the current meeting briefing document, BMS intends to submit in the second quarter of 2010, a eCTD BLA for full approval based on survival data noted above from CBER study MDX010-20. Additional supportive efficacy data is proposed from studies of ipilimumab with dosing at both 3mg/kg and 10mg/gk. A priority review will be requested.

The following tables are taken from BMS's current briefing document and summarize the planned data package for efficacy:

Table 2A: Studies Providing Efficacy Data for Ipilimumab (3 mg/kg) in Subjects with Advanced Melanoma (Unresectable Stage III or IV)

<i>Ipilimumab dosing Dose schedule</i>	<i>Induction only and possible re- induction</i>	<i>Every 3 weeks</i>		<i>Every 4 weeks</i>
		<i>Induction and maintenance</i>		<i>Induction only</i>
<i>Study</i>	<i>MDX010-20</i>	<i>CA184022</i>	<i>CA184004</i>	<i>MDX010-08^c</i>
<i>Number randomized</i>	676	72	40	40 in ipi monotherapy 36 in ipi+DTIC
<i>Primary efficacy endpoint</i>	OS	BORR	BORR	BORR
<i>Other efficacy endpoints</i>	BORR, major durable response rate, duration of response, PFS, time to progression, QoL	OS, DCR, PFS, time to response, and duration of response	OS, DCR, PFS, time to response, and duration of response	OS, PFS, time to response, and duration of response
<i>Eligibility criteria</i>				
<i>Stage III (unresectable) / IV</i>	√	√	√	√
<i>Measurable disease</i>	√	√	√	√
<i>Previously untreated</i>	-	-	√	√
<i>Pre-treated^b</i>	√	√ ^a	√	√
<i>ECOG PS 0 or 1</i>	√	√	√	-
<i>Karnofsky PS</i>	-	-	-	≥60%
<i>Brain metastases</i>	-	-	-	-
<i>Ocular / Mucosal melanoma</i>	-	-	-	-
<i>Autoimmune Disease</i>	-	-	-	-
<i>Prior vaccines</i>	√	√	√	-
<i>Efficacy endpoints based on IRC</i>	-	√	-	-

^a Progressive disease, no response in 3 months, and/or intolerance after any therapy

^b Pre-treated subjects are defined as subjects with prior systemic anti-cancer therapy received for the stage of disease under study (excluding adjuvant therapy). For MDX010-08, pre-treated subjects are defined as subjects with prior systemic anti-cancer therapy (ie, no restriction on adjuvant therapy setting as this information is not collected in the CRF).

^c Subjects alive at the end of MDX010-08 were eligible for entry in MDX010-28 and survival data was collected in MDX010-28

Table 2B: Efficacy Studies of Ipilimumab (10 mg/kg) in Subjects with Advanced Melanoma (Unresectable Stage III or IV)

Ipilimumab dosing Dose schedule Study	Every 3 weeks					
	Induction and maintenance					
	CA184022	CA184008	CA184007	CA184004	MDX010-15 ^d	CA184042
Number randomized	72	155	57 in ipi+plac 58 in ipi+bude	42	23 (per-protocol)	28 (treated)
Primary efficacy endpoint	BORR	BORR	BORR	BORR	BORR	DCR
Other efficacy endpoints	OS, DCR, PFS, time to response, and duration of response	OS, DCR, PFS, time to response, and duration of response	OS, DCR, PFS, time to response, and duration of response	OS, DCR, PFS, time to response, and duration of response	DCR, PFS, and duration of response	BORR, PFS
Eligibility criteria						
Stage III (unresectable) / IV	√	√	√	√	√	√
Measurable disease	√	√	√	√	√	√
Previously untreated	-	-	√	√	√	-
Pretreated	√ ^a	√ ^b	√	√	√	√
ECOG PS 0 or 1	√	√	√	√	-	√
Karnofsky PS	-	-	-	-	≥ 70%	-
Brain metastases	-	-	√	-	√	√
Ocular / Mucosal melanoma	-	-	-	-	√	√
Autoimmune Disease	-	-	-	-	-	-
Prior vaccines	√	√	√	√	-	√
Efficacy endpoints based on IRC	√	√	√ ^c	-	-	-

^a Progressive disease, no response in 3 months, and/or intolerance after any therapy

^b Failed prior IL-2, dacarbazine, temozolomide, fotemustine, paclitaxel, and/or carboplatin

^c IRC assessment included retrospectively

^d Subjects alive at the end of MDX010-15 were eligible for entry in MDX010-28 and survival data was collected in MDX010-28; Information about other dose groups in MDX010-15 is collected in the CSR.

OS: Overall Survival, BORR: Best Overall Response Rate, DCR: Disease Control Rate, PFS: Progression-free Survival

For the BLA, BMS has proposed (b) (4) dosing of 3 mg/kg every 3 weeks for 4 doses

(b) (4)

From a number of Phase 1,2, and 3 studies, the proposed BLA will contain a safety database of approximately 4000 patients. In addition, due to the primary safety concerns with immune related adverse events (irAEs), BMS will provide a Risk Evaluation and Mitigation Strategies

(REMS) in the BLA for FDA review which will be composed of a Communication Plan and a Medication Guide.

Draft FDA responses were communicated to BMS on March 2, 2010. On March 3, 2010, BMS acknowledged FDA responses to questions, 2, 3, 4a-e, 5b, c, 6, 7, 8, 9, 10, 11 b-d, 12, 13, 14, 15, 16, 18-28. BMS requested further discussion on FDA responses on question 1, 4f-i, 5a,d, 11a, 17, and also clarified to FDA that the proposed indication was ipilimumab monotherapy for pretreated advanced melanoma indication [REDACTED] ^{(b) (4)} as noted in FDA's background section of the comments.

3.0 DISCUSSION

SPONSOR SUBMITTED PREAMBLE (*ITALIC*), QUESTIONS AND FDA RESPONSE:

On March 18, 2010, BMS provided as an official IND amendment, a summary of the March 4, 2010, meeting as well as a document "DESCRIPTION OF ANALYSIS DATA SETS PROPOSED FOR SUBMISSION" for FDA comment. FDA will provide any specific comments regarding the proposed datasets under a separate correspondence.

Role of MDX010-20 in BLA

In January 2010, BMS and FDA discussed the role of MDX010-20 in a BLA submission. BMS has provided further information as follows for the concerns raised by FDA (see Section 3):

- 1. The design features and characteristics of results of MDX010-20 allow for a robust assessment of evidence of effectiveness with a single trial according to FDA guidance.*
 - 2. In the absence of an approved therapy or standard-of-care for patients with pretreated advanced melanoma, the use of gp100 peptide vaccine was an adequate control for MDX010-20.*
 - 3. The available clinical literature and clinical data support the proposed indicated use in patients with pretreated advanced melanoma without restriction by HLA subtype.*
 - 4. There are potentially meaningful differences between the 2 anti-CTLA-4 molecules and their respective development programs.*
 - 5. Based on the slow event rate in CA184024, it is estimated that topline data will be available in December 2010.*
1. Can the data from MDX010-20, supported by the clinical development program for melanoma, form the basis for submission of a BLA for full approval in pretreated advanced melanoma without HLA restriction?

FDA March 2, 2010, Preliminary Response: No, the data from MDX010-20 can only potentially support approval of ipilimumab in patients with previously treated, advanced melanoma who have the HLA phenotype required for study entry. FDA will require the submission of the results of a definitive analysis for overall survival in study CA184024 to the license application prior to FDA's regulatory action on this application.

BMS will need to specify at least one FDA-approved companion diagnostic test that will permit identification of the indicated population (patients with HLA-A2*0201 phenotype); this test must be available at the time of the approval of ipilimumab. Currently the (b) (4) is FDA-cleared (not FDA approved) as an unclassified device. The performance characteristics for this test have not been evaluated for specifically phenotyping HLA-A2*0201. BMS may either arrange with the manufacturer of the (b) (4) Test to submit an application for FDA approval (class III, PMA), arrange for concurrent approval of other comparable device(s) to which a bridging study could be conducted using both screen-positive and screen negative samples from the trial, or make available a centralized testing service. FDA will provide further advice and guidance on BMS's chosen option.

Meeting Discussion: FDA re-emphasized the need to provide the top line survival data from study CA184024 to FDA for review; the summary results for survival will be needed in order for FDA to take final action on the BLA. FDA noted that results of secondary endpoints other than survival would not provide compelling supportive information. As BMS noted that the CA184024 data would likely not be available until months after the BLA was submitted, FDA stated that if the study has not reached the specified number of events target, the Agency would be willing to review the available data directly submitted to the FDA from the Data Monitoring Committee of the study CA184024. BMS acknowledged and agreed to permit the Data Monitoring Committee to release the results directly to the FDA. As BMS will remain blinded to the results of the study, FDA agreed that an alpha adjustment for this look exclusively by the FDA will not be required for the final analysis of the CA18024 results for survival.

FDA noted that the label for ipilimumab will require a boxed warning regarding the unique immune-related adverse reactions profile. BMS acknowledged and noted that they plan to include a proposal for the REMS program in the original application. BMS confirmed that the dosing recommendation for the upcoming BLA will be 3 mg/kg (b) (4)

FDA reiterated that as only HLA-A2*0201 patients were enrolled in the main efficacy study, the indication will be restricted to HLA-A2*0201 patients. FDA noted that BMS must specify the companion test for selection of HLA-A2*0201 patients for a melanoma indication and describe this approach in their application. This companion test should be cleared at the time of regulatory action on the BLA. BMS agreed to request a separate meeting with CDRH regarding the diagnostic test requirement.

FDA noted that this application will very likely be presented at the ODAC.

Proposed Dose

The proposed induction dosing of 3 mg/kg every 3 weeks for 4 doses (b) (4) (b) (4) is based on the Phase 3 study MDX010-20 supported by the Phase 2 studies CA184022, CA184004 and MDX010-08, pharmacokinetics (PK) modeling, and nonclinical data. MDX010-20 has demonstrated a statistically significant and clinically meaningful survival benefit at the 3 mg/kg induction dose and schedule. There was increasing biologic and clinical activity with increasing doses of ipilimumab (0.3, 3, and 10 mg/kg) based on the PK, pharmacodynamics (PD), BORR, and OS results in CA184022. For safety, the rate of high-grade (ie, Grade 3 - 4) irAEs was also elevated with increasing dose levels, with the highest rate at the 10 mg/kg dose level. irAEs at all dose levels were generally reversible and medically manageable. Drug-related deaths were similar between dose levels. As the benefit risk of 3 mg/kg is the best characterized to date, the recommended dose is 3 mg/kg, infused every 3 weeks for 4 doses (b) (4). The results of a randomized, controlled study comparing the OS of the combination of DTIC and ipilimumab (10 mg/kg) versus DTIC monotherapy in previously untreated subjects with advanced melanoma are currently pending. BMS intends to continue the current Phase 3 studies that are ongoing with 10 mg/kg every 3 weeks. Additional information is provided in Section 9.

2. Does the FDA agree that the data are sufficient to support the recommended dosing of 3 mg/kg every 3 weeks for 4 doses (b) (4)?

FDA March 2, 2010, Preliminary Response: FDA does not object to BMS proposing the dose and dosing schedule used in the study MDX010-20 to support the proposed BLA.

Meeting Discussion: BMS acknowledged FDA's preliminary comments. There was no further discussion during the meeting.

Safety Database

The clinical development program includes data from more than 4000 subjects in several cancer types, with an emphasis on studies investigating the effect of ipilimumab in melanoma (approximately 3700 subjects). Overall, data from 32 clinical studies contribute PK, PD, efficacy, and safety data supporting the use of ipilimumab in pretreated advanced melanoma:

- 6. 14 completed Phase 1, 2, and 3 monotherapy and combination studies in melanoma*
- 7. 6 completed Phase 1 and 2 monotherapy and combination studies in various cancer types other than melanoma*
- 8. Limited safety data will be available from 12 ongoing Phase 1, 2, and 3 studies:*
 - 6 studies in advanced melanoma*
 - 2 studies of adjuvant therapy for melanoma*
 - 4 studies in other cancer types (2 studies in prostate and 1 study each in lung and urothelial cancers)*

In addition, limited safety information will be available from 10 studies in various cancer types other than melanoma sponsored under separate INDs. More detailed information is contained in Section 6 of this background document.

3. Ipilimumab has a large clinical development program encompassing approximately 4000 subjects. Is the number of subjects in the safety database sufficient for filing and approval of ipilimumab?

FDA March 2, 2010, Preliminary Response: The size of the safety database is adequate for the proposed indication and duration of exposure.

Meeting Discussion: BMS acknowledged FDA's preliminary comments. There was no further discussion during the meeting.

Statistical Analysis Plans for Summary of Clinical Efficacy and Summary of Clinical Safety

The statistical analysis plan (SAP) for the summary of clinical efficacy (SCE) is provided in Appendix 3A. BMS does not plan to pool data from any studies. Data will be summarized by dosing regimen (ie, 3 mg/kg ipilimumab, 10 mg/kg ipilimumab) and prior treatment status (pretreated subjects, previously untreated subjects). Treatment groups will be presented side-by-side; however, heterogeneous groups will not be displayed in the same presentation.

The SAP for the summary of clinical safety (SCS) is provided in Appendix 3B. Heterogeneous study periods and doses will not be pooled or displayed in the same presentation. Safety data will be presented by study period (ie, induction, maintenance, reinduction):

9. *Induction period: Treatment groups from MDX010-20 will be presented in a side-by-side manner with pooled 3 mg/kg and pooled 10 mg/kg data; interim data from CA184042 will also be presented*
10. *Maintenance period: Pooled 3 mg/kg and pooled 10 mg/kg data will be presented in a side-by-side manner, along with interim data from CA184042*
11. *Reinduction period: Treatment groups from MDX010-20 will be presented in a side-by-side manner.*

4. Are the proposed analyses specified in the SAP for the Summary of Clinical Efficacy and Summary of Clinical Safety acceptable to the FDA? Does the FDA have any comments on the SAPs?

FDA March 2, 2010, Preliminary Response: See comments below.

Regarding the statistical analysis plan for the SCE:

- a. Studies CA184008 (a single arm trial), CA184004 and CA184022 (include multiple dose levels) are not controlled trials that isolate the effect of the ipilimumab. Study CA184007 (b) (4) (b) (4)) and study MDX010-08 (b) (4) (b) (4)) and CA184042 (single arm study in patients with brain metastasis) included only 10 mg/kg dose arm and were not designed to assess the effect of ipilimumab 3 mg/kg monotherapy. Therefore, FDA finds that studies CA184008, CA184004, CA184022, CA184007 and MDX010-08 CA184042 will provide very limited support of the efficacy claim for 3 mg/kg Ipilimumab.

Meeting Discussion: BMS acknowledged FDA's preliminary comments 4a-d. There was no further discussion during the meeting.

- b. BMS should provide individual study report in the submission. The pooled analyses proposed in the SCE will be considered as exploratory analyses.
- c. Overall survival data that is based on or includes the roll-over or follow-up studies (e.g. CA184025 or study MDX010-28) will be considered as exploratory.
- d. Please note that pooled phase 2 study data to assess the consistency of OS results based on the HLA subgroup (HLA-positive vs. HLA-negative) are considered exploratory.

Regarding the statistical analysis plan for the SCS:

- e. FDA expects to see: (1) individual study safety datasets for MDX010-20 (2) Integrated safety datasets for all completed studies in melanoma subjects using 3 mg dose (3) Integrated safety datasets for all completed studies in melanoma subjects using 10 mg dose, which could possibly be used in the overdose section of the PI.

Meeting Discussion: BMS acknowledged FDA's preliminary comment e. There was no further discussion during the meeting.

- f. Please clarify the proposed safety analyses population "All treated Subjects". Specifically, clarify if "All subjects who received at least one dose of study medication" mean Ipilimumab in all instances (with the exception for the gp100 only safety comparison group in Study MDX010-20).

All analyses of safety (deaths, SAEs and all the various AE tables proposed in the submission, including but not limited to common AEs, AE's leading to study discontinuation and AEs of special interest and all the subgroup analyses) from the datasets identified in e. should be presented for the entire study duration as well as according to the phases of study. In addition to Tables 3.2a you should add a table that includes the entire study duration for all the studies. The listings of deaths and SAEs should also be provided for the safety population (i.e. those who received at least one dose of Ipilimumab). Analysis of safety parameters of interest by grouped PTs (using SMQs) should be provided for the above identified datasets individually. (b) (4)

Meeting Discussion: BMS clarified and confirmed that by 'all subjects who received at least one study drug', they meant all subjects who received at least one dose of ipilimumab in all instances.

BMS agreed to include in the safety summaries all reported adverse reactions occurring throughout the entire study duration in addition to providing adverse reaction data restricted to the various treatment phases (e.g., induction, maintenance, re-induction) of the studies for all the completed studies for melanoma at both 3 mg/kg for consideration for inclusion in label and 10 mg/kg for describing the overdose experience. BMS will include in the safety datasets with appropriate flags for the study treatment phase.

FDA urged BMS to carefully consider FDA's advice regarding the clarity of presentation of the safety data, to facilitate a possible priority review timeframe and adequate preparation for an ODAC discussion of this application.

BMS stated that they did not include study MDX010-08 in the pooled 3 mg/kg integrated safety analysis population because of differences in study design (08 was limited to treatment-naïve patients and also had DTIC in the treatment

regimen, thus it did not isolate the toxicity of ipilimumab) from the indication being sought.

- g. The resolution time for all adverse events occurring during any time in the study should be presented and available in the safety datasets. To provide adequate description of adverse events of interest such as irAE, besides providing the resolution time by categorizing the time as indicated on page 190, you should provide the summary of the results using continuous variables. This summary should not be confined to only induction phase but should be provided for the entire study duration as well as for each study period.

Meeting Discussion: BMS clarified that all treated subjects did indeed receive at least one dose of ipilimumab.

- h. For the ongoing studies, BMS should provide a summary of the exposure, SAEs and deaths occurring within 3 months of last dose.

Meeting Discussion: BMS stated that they had used a cut-off of 70 days in their clinical protocols (~ 5 half-lives) for prospective data collection and that summary of exposure for the blinded studies would be difficult. FDA acknowledged presentation of exposure data is challenging with blinded studies. FDA agreed that BMS could only provide summary of SAEs and deaths occurring within 70 days from last dose. Regarding difficulties in estimating exposure, FDA advised BMS to do their best.

- i. The reporting of adverse events in the individual study reports must match the SCS.

Meeting Discussion: FDA re-stated that given that priority review will be requested, the application should be of the highest quality. Safety data in the study reports should match with those in the SCS. It is expected that the SCS and CSR datasets include MedDRA preferred terms from a single harmonized version of MedDRA. In addition, BMS should provide a single CSR which incorporates all addendum/ erratas into the final CSR for each study.

BMS should note that summary tables and data tables in all clinical study reports that are included in the application in support of safety and efficacy of ipilimumab should match the information provided in the integrated safety datasets noted in FDA response 4e.

Regarding SAS programs:

- j. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be

included. If the SAS programs use any macro programs, please provide all necessary macro programs.

Meeting Discussion: BMS acknowledged FDA's preliminary comment j. There was no further discussion during the meeting.

- k. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every value proposed to be included in the label.

Meeting Discussion: BMS acknowledged FDA's preliminary comment k. There was no further discussion during the meeting.

- l. The SAS transport files should be created by a procedure which allows the file to be easily read by JMP software.

Meeting Discussion: BMS acknowledged FDA's preliminary comment l. There was no further discussion during the meeting.

Characterization of the Effects of Ipilimumab on the QT Interval

BMS submitted a cardiac safety assessment report and proposal on 03 October 2006, which is described in more detail in Section 8. FDA previously commented that this proposal was acceptable (email correspondence from FDA to BMS on 09 November 2006). BMS plans on submitting all available electrocardiogram (ECG) data from Days -1, 1, and 64 from CA184004. Available ECG data from baseline and Day 85 (3 weeks post last dose) from MDX010-21 will also be submitted.

5. Does the FDA agree that the completed and ongoing evaluations outlined above are sufficient to characterize the effects of ipilimumab on the QT interval?

FDA March 2, 2010, Preliminary Response: Whether the data as outlined are sufficient to fully characterize the effects of ipilimumab on the QT interval will be an FDA review issue for the BLA submission. In general, the proposed data appear sufficient to exclude a clinically important effect on QT interval for this monoclonal antibody. Available ECG data at week 24 from CA184004 should also be submitted.

In addition, the following should be components of the analysis of the ECG data:

- a. Measures of Central Tendency: mean, baseline-adjusted, and placebo- and baseline-adjusted HR, RR, QT, QTcF, PR, and QRS for each assessment timepoint, including two-sided 90% confidence intervals, as well as mean maximum and baseline-adjusted values for each parameter.

Meeting Discussion: FDA clarified that 5a-d are standard comments and not specific to the ipilimumab application. BMS should provide in the BLA a rationale why it is not possible to obtain placebo controlled data in this population and that in reference to 5d, data should be provided across the program in melanoma, not just for study CA184-004.

- b. Categorical Analysis: number and percentage of individuals with QT/QTc values > 450 ms, > 480 ms, > 500 ms, number and percentage of individuals with changes from baseline > 30 and > 60 ms.

Meeting Discussion: See discussion under 5a.

- c. Number and percentage of individuals with abnormal ECG findings.

Meeting Discussion: See discussion under 5a.

- d. Number and percentage of individuals with adverse events that could be associated with prolongation of cardiac repolarization or proarrhythmia, i.e. palpitations, dizziness, syncope, cardiac arrhythmias, sudden death.

Meeting Discussion: See discussion under 5a.

Risk Management

The primary safety concerns observed with ipilimumab are irAEs of the GI tract, liver, skin, endocrine system, and nervous system that include inflammatory colitis, intestinal perforation, inflammatory hepatitis, rash, hypophysitis, and neurologic syndromes. Most irAEs occur within the first 12 weeks of ipilimumab treatment, and this period is particularly important for monitoring for signs and symptoms such as diarrhea, rash, fatigue, or elevated liver function tests that may indicate an irAE.

In the clinical studies and expanded access programs, most irAEs were reversible provided that they were identified early and intervention generally followed the recommended management guidelines. The irAE management guidelines implemented in the clinical studies and expanded access programs were developed in collaboration with experts and study investigators based on the accumulated clinical experience. Because of the immune-related nature of these AEs, the management guidelines are specific to the mechanism of action of these reactions and differ from the management of similar symptoms of non-irAEs. Effective patient and physician education on the early recognition and appropriate irAE assessment and management using the guidelines is, therefore, key to minimizing the consequences of irAEs.

In general, for patients with low grade irAEs that persist despite symptomatic treatment and for patients with high grade irAEs, the basic treatment principle is to stop ipilimumab and institute corticosteroid therapy. In some cases, patients with high grade irAEs refractory to corticosteroid therapy have responded to a second immunosuppressive agent, such as infliximab or mycophenolic acid.

BMS will implement a risk minimization program focused on effective education of patients and a broad range of health care providers using a multi-pronged strategy that includes communication distributed through a variety of media, beginning with education of physicians participating in the expanded access programs. To manage the risks of irAEs, a REMS is proposed, which includes a Communication Plan and Medication Guide. The goal of the ipilimumab proposed REMS is to minimize the occurrence of serious irAEs and mitigate the impact of irAEs that do occur.

The REMS design and implementation strategy will be specifically designed to provide effective educational elements. Preliminary REMS plans and the current treatment management guidelines are provided in Appendix 4. The management guidelines are being reviewed with external experts. High-level strategies of the proposed REMS program include:

- 1. Timely, redundant, and effective educational efforts using a variety of REMS and voluntary educational tools and media, consistent with adult education methods; for example, tools such as checklists have been demonstrated in hospital operating room settings to improve clinical outcomes*
- 2. Collaboratively designing educational program content and tools with stakeholders to assure they are useful in clinical practice*
- 3. Frequent measurements of program implementation markers that supplement the REMS assessment to help assure REMS and non-REMS communications are effectively disseminated to targeted audiences and achieve the desired objective*
- 4. Continuous analysis of program metrics to identify the need for further improvements/refinements in program implementation, education, and overall performance*

Communication Plan materials and the Medication Guide will be submitted to the Review Division and Office of Safety Evaluation (OSE) for review. It is BMS' plan to have Communication Plan materials and the Medication Guide reviewed and available for public dissemination at the time of product approval.

- 6. Does FDA agree with BMS' proposal to provide a REMS and can FDA provide guidance on an appropriate process to obtain agreement on the REMS?*

FDA March 2, 2010, Preliminary Response: FDA has no objection to BMS proposing to provide a draft proposal for REMS. An applicant may voluntarily submit a proposed REMS without having been required to do so by FDA. Any proposal that includes a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use as described under 505-1(e) of the Food and Drug Administration Amendments Act (FDAAA) should be submitted as a proposed Risk Evaluation and Mitigation Strategy (REMS) in the original application (i.e. at the time of initial submission). Please note that a complete review of the new drug application will be necessary to determine if a REMS is needed to ensure that the benefits of the drug outweigh the risks and what components will be essential to assure safe use. The proposal is not a REMS unless and until the FDA determines that it is required and approves it.

FDA suggests that BMS review as an example the REMS for Actemra (tocilizumab) found at the following website:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125276REMS.pdf

Please see the attached proposed REMS template “Appendix A” below at the end of FDA’s preliminary comments.

Meeting Discussion: BMS acknowledged FDA’s preliminary comments. There was no further discussion during the meeting.

CLINICAL PHARMACOLOGY

The PK of ipilimumab has been primarily studied in subjects with advanced melanoma. PK parameters were derived using non-compartmental methods using extensive PK sampling data from subjects treated with ipilimumab during induction at 3 and 10 mg/kg. In addition, sparse sampling was obtained from nearly 500 subjects treated in Phase 2 with ipilimumab monotherapy at doses of 0.3, 3.0, and 10 mg/kg; however, PK was not measured in the Phase 3 study. The same drug product, ipilimumab Process B, as described in Section 5, was used in the Phase 2 studies and MDX010-20. These PK data will form the basis of the population pharmacokinetic (PPK) analysis and exposure-response relationship for safety and efficacy (best overall response [BOR] and OS). Several biomarkers were also collected in Phase 2. These analyses will also be presented in the Summary of Clinical Pharmacology Studies. Additional information is provided in Appendix 5.

As per International Conference on Harmonization (ICH) Guidance S6, no studies were conducted to evaluate the metabolism, metabolic pathways, and excretion of ipilimumab in humans. Because ipilimumab is a protein and does not undergo metabolism by the cytochrome

P450 enzymes, no formal PK drug interaction studies were conducted with ipilimumab. However, as requested by FDA, a drug-drug interaction study with chemotherapy (carboplatin/paclitaxel and DTIC) was initiated and is ongoing, but results from this study will not be included in the BLA.

7. Does the FDA have any comments on the PPK analysis plan and exposure response analysis to support the intended dose?

FDA March 2, 2010, Preliminary Response: The population PK analysis approach is reasonable. The following are the general expectations for submitting pharmacometric data and models:

- a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Meeting Discussion: BMS acknowledged FDA's preliminary comments 7a-d. There was no further discussion during the meeting.

- b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- c. A model development decision tree and/or table which gives an overview of modeling steps.
- d. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

8. Does the FDA agree that the clinical pharmacology studies listed herein are sufficient to support the filing and review of the BLA?

FDA March 2, 2010, Preliminary Response: Yes.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

Immunogenicity

Although ipilimumab is a fully human IgG1 protein, it still has the potential to induce the formation of antibodies to itself (human anti-human antibodies [HAHAs]). The development of HAHAs and neutralizing antibodies were assessed, as well as any impact on PK and safety. An enzyme-linked immunosorbent assay (ELISA; HAHA ELISA A) was used to identify anti-ipilimumab antibodies early in the development program. An electrochemiluminescent (ECL) immunoassay in serum confirmed by immunodepletion of the drug and analysis for neutralization was used to evaluate immunogenicity in the Phase 2 studies (CA184004, CA184007, CA184008 and CA184022). A similar assay was used for study MDX010-20 but was validated in a different matrix (plasma). Immunogenicity serum samples were collected in these studies at baseline, Day -1 and prior to all subsequent ipilimumab doses (trough drug concentration). Plans were to collect immunogenicity samples at least 5-half lives after the last dose of ipilimumab (prior to Week 24 dose and between 70 to 85 days after the last dose). However, the majority of subjects did not provide this latter sample due to disease progression prior to the planned collection. Approximately 2.1% (11/531) of subjects developed HAHA after receiving ipilimumab in the Phase 2 studies, but none were found to be positive in MDX010-20. None of the positive HAHA in Phase 2 were neutralizing. Moreover, the development of HAHA did not have a significant effect ipilimumab clearance. These analyses will be presented in the Summary of Clinical Pharmacology Studies.

9. Does the FDA have any comment on the planned assessment and presentation of immunogenicity data in the BLA?

FDA March 2, 2010, Preliminary Response: FDA has the following comments:

- a. When presenting immunogenicity data, the dataset should contain individual titers and highlight those which were found to be above the cut-off value for each study. This data should be organized by trial number and sampling time.

Meeting Discussion: BMS acknowledged FDA's preliminary comments 9a-c. There was no further discussion during the meeting.

- b. Provide a single summary table ("Clinical Immunogenicity Summary") listing each study and indicating the number and proportion of patients positive for HAHA response and those who developed neutralizing antibodies (if none, as indicated in the preBLA meeting package, then please state so in the table). Include the following information: study number, population, duration of study, dose, dosing frequency, pre-existing binding antibodies, development of binding antibodies, neutralizing antibodies, and total number of subjects tested. Provide totals for each column at the bottom of the table as appropriate.

- c. The meeting package indicates that several immunogenicity assays have been used to assess HAHA responses. The BLA should include information on the qualification and validation of all assays used for HAHA assessment. This should include data demonstrating that the assays are specific, sensitive and reproducible. It is noted that while you intended to collect immunogenicity samples at least 5-half lives after the last dose of ipilimumab, the majority of the subjects did not provide this latter sample due to disease progression prior to the planned collection point. In order to be meaningful, HAHA assays need to be capable of sensitively detecting ADA responses in the presence of drug levels that are present in the patient sample. Information on assay performance therefore should include information on the sensitivity of the assays to product interference at levels present in the samples tested.

Nonclinical

A comprehensive nonclinical program was designed to conform to expectations outlined in ICH and FDA guidance documents. Additional details on the nonclinical program are provided in Appendix 6.

Ipilimumab was evaluated in various in vitro assays, in vivo pharmacodynamic models of T-cell function (T cell-dependent antibody production), and in animal models of disease (inhibition of the growth of tumors implanted in mice).

All pharmacokinetic studies were conducted in cynomolgus monkeys after IV dosing. These included single-dose and repeat-dose pharmacokinetic studies, and evaluation of exposure in repeat-dose toxicology studies of up to 6 months duration. In accordance with ICH Guidance S6, no tissue distribution, mass balance, or metabolism studies with ipilimumab were conducted in animals.

The scope of the toxicologic evaluation for ipilimumab supports its proposed clinical use for pretreated advanced melanoma. The pivotal toxicology studies supporting the safety of ipilimumab were of adequate design and scope and were conducted in compliance with good laboratory practice (GLP) regulations. Genotoxicity and carcinogenicity studies for ipilimumab were not conducted in accordance with ICH Guidance S6. FDA agreed in correspondence dated 05 May 2006 and 11 July 2006 that no formal reproductive or developmental studies would be required for the BLA for advanced melanoma. Potential reproductive risks will be addressed with appropriate wording in the US Prescribing Information (USPI).

10. Does the FDA agree that the nonclinical studies described are sufficient to support the filing and review of the BLA?

FDA March 2, 2010, Preliminary Response: Overall, the design and the scope of the completed nonclinical toxicology studies appear appropriate to support the filing of the BLA submission for ipilimumab. FDA's position regarding the nonclinical reproductive and developmental toxicity (DART) testing has not changed since the 2006 correspondence. FDA concurs that no DART testing is needed to support clinical trials or a BLA for treatment of patients with late stage or advanced cancer. However, FDA cannot provide a definitive response regarding the review of these studies at this time; the adequacy of the nonclinical package will be a review issue when the licensing application is received.

In the BLA, please include a summary assessment of safety pharmacology based on the available nonclinical data. Please also include a summary assessment of potential adverse effects of ipilimumab on developmental and reproductive toxicity (DART), based on the available nonclinical (e.g. reproductive organ weight and histopathology) and clinical data (i.e. panhypopituitarism). For additional information, please consult ICH guidance S9 Nonclinical evaluation for anticancer pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085389.0df>), ICH guidance S6, and the ICH guidance S6(A1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf>).

Meeting Discussion: BMS acknowledged FDA's preliminary comments. There was no further discussion during the meeting.

Administrative Topics

The administrative aspects of the BLA are described in Section 11, Appendix 7 (Draft Table of Contents), and Appendix 8 (Proposal for Submission of the Electronic CTD).

11. The BLA will be submitted in eCTD format as specified in Appendix 8 (Proposal for Submission of the Electronic CTD) and Appendix 7 (Draft Table of Contents). Is the proposed format and content of the BLA acceptable to the FDA?

FDA March 2, 2010, Preliminary Response: FDA has the following comments:

- a. Only study reports of studies contributing to the analysis of safety or efficacy of ipilimumab in **malignant melanoma** should be included in the application (see comments under question 4). Study listings for ongoing studies are not required.

Meeting Discussion: FDA clarified that completed melanoma studies should include case report forms and narrative summaries for all SAEs including deaths within 70 days of last dose and for any patient who discontinues treatment due to toxicity. For any ongoing studies, narrative summaries for all SAEs including deaths within 70 days of last dose and for any patient who discontinues treatment due to toxicity should be provided both in melanoma and non-melanoma indications. CRFs and financial disclosures are not needed for ongoing studies.

- b. All study reports should be final. There should not be separate erratas and addendums to the clinical study report.

Meeting Discussion: BMS acknowledged FDA's preliminary comments 11b-d. There was no further discussion during the meeting.

- c. The safety tables within the study reports must match the datasets provided.
- d. Hypertext links should be provided between data definition document and blank annotated CRF.

12. BMS proposes to not include a Master Investigator List in the BLA. Does FDA agree?

FDA March 2, 2010, Preliminary Response: No. A master investigator list should be included. Please note that financial disclosure information must also be provided for each investigator in the trial.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

13. Does the FDA agree with the proposed data cutoffs for the BLA?

FDA March 2, 2010, Preliminary Response: The cutoff date for study MDX010-020 is acceptable. Please see comments under question 4.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

14. Do the proposed plans for providing Case Report Forms in the BLA remain acceptable to the FDA?

FDA March 2, 2010, Preliminary Response: Case report forms should be provided for all deaths occurring within 90 days of last study medications, all serious adverse vents and all study discontinuations for reasons other than disease progression. Please also see comments under 11a.

Meeting Discussion: See discussion under 11a.

15. Are the proposed plans for providing datasets in the BLA acceptable to the FDA?

FDA March 2, 2010, Preliminary Response: FDA requests that BMS provide analysis datasets in the CDISC ADaM format rather than in a proprietary BMS format; further, please note that the permissible variable should not be considered optional. If ADaM is not provided, please provide justification as to why the datasets in the proprietary BMS format will give the same functional performance as ADaM.

Since CDISC SDTM v1.1 as you proposed to be used for the raw CRF datasets submission does not include tumor/response specific domain, please submit a mock-up table for the definition of tumor/response data.

For study MDX010-020, please separate the overall survival data and response data in the following manner to include additional information:

- a. For time-to-event type endpoints, please provide for each subject the censoring status, the time-to-event, the date of the event, and which event type occurred (when an event occurs), the reasons for censoring if censored, and the data-cutoff date. Information for individual component of the primary endpoint should also be provided. The variables used for sensitivity analyses for the primary and key secondary efficacy endpoints should be included. The important time variables, usually used for deriving variables for sensitivity analyses, such as the last disease assessment time, last disease assessment time before > 1 missing assessment, last assessment time prior to non-protocol specified anti-cancer therapy and last contact time, etc., should be included.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

- b. For response analysis datasets, in addition to provide one response per patient data (i.e. Place investigator and independent reviewers' assessed BORR as two separated variables in the same datasets), please provide a one record per visit per patient ID dataset using separated variable for target, non-target response, new tumor and other criteria for the response as well as the overall response.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

Regarding safety datasets please see FDA's comments in response to BMS' question 4.

16. Does the FDA agree with the proposed plan (as described here and in Appendix 8) for inclusion of subject narratives in the BLA?

FDA March 2, 2010, Preliminary Response: No, safety narratives should be provided for all the deaths within 90 days of the last dose instead of the proposed (b) (4) from the last dose as well as for related SAEs, and AEs leading to study drug discontinuation.

Meeting Discussion: See discussion under 11a.

17. Per the regulations, the Safety Update will be submitted after submission of the BLA. Is the proposal for the submission Safety Update acceptable to the FDA?

FDA March 2, 2010, Preliminary Response: The safety update should be provided at 90 days instead of the proposed (b) (4). This should be limited to information on previously unreported deaths, serious adverse events or adverse events resulting in discontinuation of study drug and for updates on previously reports of deaths, serious adverse events or adverse events resulting in discontinuation of study drug.

Meeting Discussion: See discussion under 11a

ADDITIONAL FDA COMMENTS:

Clinical Pharmacology

For the BLA submission:

18. Pharmacokinetic study reports should also include an evaluation of the effects of covariates such as age, weight, gender, race, etc. on the pharmacokinetics of ipilimumab.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

19. Present the PK data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate for individual PK parameters. Include the data file(s) used to generate the results.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

20. Provide a table listing of patients with renal or hepatic impairment, 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), LFT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

21. For each pharmacokinetic study, provide raw data sets in .xpt format (SAS transport files) accompanied by a data definition file. Any concentrations and/or subjects that have been excluded from the analyses should be flagged and maintained in the dataset.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

Nonclinical

22. Regarding the nonclinical pharmacokinetic study in monkeys (study # DS07165, discussed at the 6/03/2009 Type C meeting), please indicate the date and IND submission serial number for the specific IND application to which the study report was submitted.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

23. Regarding the list of nonclinical references (volume 1 pp 237-242) provided in the meeting package, references #4 and #25 appear to be the same report, and references #5 and #21 appear to be the same report. Please submit all relevant nonclinical study reports in the BLA. For efficiency of review of the BLA, please use a single citation for each particular study report, and provide cross-reference (i.e. hyperlinks to appropriate section and report) in the eCTD BLA submission.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

Facilities

24. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. Please provide the preliminary manufacturing schedule for both the drug substance and drug product and manufacture facility information should be included as soon as possible in order to facilitate the planning of the pre-license inspections.. This information should be updated in the BLA submission. Manufacture facility information should be included in the BLA as background information for the pre-license inspections.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

25. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- a. Monitoring of bioburden and endotoxin levels at critical manufacturing steps using validated bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).

Meeting Discussion: BMS acknowledged FDA’s preliminary comments 25a-f. There was no further discussion during the meeting.

- b. Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- c. Column resin [REDACTED] (b)(4) validation (3.2.S.2.5).
- d. Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- e. Data summaries of shipping validation studies (3.2.S.2.5).
- f. Drug substance bioburden and endotoxin release specifications. The bioburden limit should be [REDACTED] (b)(4) for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).

- 26. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the [REDACTED] (b)(4) processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”. Test methods and validation data summaries for the container closure integrity test and preservative effectiveness test (if applicable) should be submitted in Section 3.2.P.2.5 of the submission.

Meeting Discussion: BMS acknowledged FDA’s preliminary comment. There was no further discussion during the meeting.

- 27. Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:

- a. [REDACTED] (b)(4)

Meeting Discussion: BMS acknowledged FDA’s preliminary comments 27a-f. There was no further discussion during the meeting.

- b. [REDACTED] (b)(4)

- c. In-process controls and hold times,

- d. Three successful consecutive (b) (4) runs, including summary environmental monitoring data obtained during the runs,
 - e. A description of the routine environmental monitoring program, and;
 - f. (b) (4), if applicable.
28. FDA recommends that the container closure integrity test be performed in lieu of the sterility test for stability samples at initial time and every 12 months (annually) until expiry.

Meeting Discussion: BMS acknowledged FDA's preliminary comment. There was no further discussion during the meeting.

ADDITIONAL DISCUSSION DURING THE MEETING

- BMS indicated that they were planning to submit the data in CDISC format.
- FDA advised BMS that the REMS should be submitted with the BLA to the review division and not OSE. The REMS should be purged of all promotional language.
- BMS indicated that they will be requesting a pediatric waiver (Orphan status).
- FDA requested that for study MDX010-20, BMS provide the information per study site on the number of subjects, number of protocol deviations, adverse events and efficacy per site in advance of formal submission of the BLA. Such information will assist FDA in selection of clinical sites for inspection during review of the BLA. This data must be contained in the BLA in order to be filed.
- BMS indicated that they do not plan to have a pre-BLA CMC meeting as process B material would be used (b) (4). FDA acknowledged and suggested that BMS provide a list of drug manufacturing sites, with the latest GMP inspection and campaign dates in advance of the BLA if possible (such data must be contained in the BLA in order to be filed).
- BMS indicated that they plan to reopen the expanded access protocol at 3 mg/kg dose without HLA restriction. A formal IND amendment of the protocol would be provided to the IND.
- FDA advised BMS that the proposed tradename (b) (4), was reviewed under the IND and found to be unacceptable. A formal letter would be provided by FDA's OSE. FDA advised that BMS consider submitting a first choice and second choice tradename for consideration in the BLA.
- FDA advised BMS that the updated EOP2 General Comments would be provided after the meeting.

- FDA advised BMS that an applicant orientation meeting may occur as early as two weeks after BLA submission. BMS would present the BLA to FDA with an emphasis on the clinical data.

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 009186

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Heather Knight-Trent, PharmD
Director, Global Regulatory Oncology
5 Research Parkway
Signature 91 Building/3SIG-509
Wallingford, CT 06492

Dear Dr. Knight-Trent:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Human Monoclonal Antibody (MDX-010, MDX-CTLA4) to CTLA4; [ipilimumab]."

We also refer to the teleconference between representatives of your firm and the FDA on January 13, 2010. A copy of the official minutes is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me, at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Erik Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 13, 2010
TIME: 9:00-9:30 AM ET
APPLICATION: IND 9186
SPONSOR: Bristol Myers Squibb Company [BMS]
DRUG NAME: Ipilimumab [Human Monoclonal Antibody (MDX-010, MDX-CTLA4) (Bristol Myers) to CTLA4]
TYPE OF MEETING: Teleconference
MEETING CHAIR: Kaushikkumar Shastri
MEETING RECORDER: Erik Laughner

FDA ATTENDEES:

CDER

Patricia Keegan, M.D.	Director, DBOP/OODP
Kaushikkumar Shastri, M.D.	Clinical Reviewer, DBOP/OODP
Yuan Li Shen, Ph.D.	Statistical Reviewer, DV5/OB
Mark Rothmann, Ph.D.	Statistical Team Leader, DV5/OB
Anne M. Pilaro, Ph.D.	Pharmacology/Toxicology Supervisor, DBOP/OODP
Andrew McDougal, Ph.D.	Toxicology Reviewer, DBOP/OODP
Dubravka Kuftrin, Ph.D.	Toxicology Reviewer, DBOP/OODP
Mary Jane Hinrichs, Ph.D.	Toxicology Reviewer, DBOP/OODP
Erik Laughner, M.S.	Senior Regulatory Health Project Manager, DBOP/OODP
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCP5/OCP
Aakanksha Khandelwal, Ph.D.	Clinical Pharmacology Reviewer, DCP5/OCP

CBER

Lydia Martynec, M.D.	Clinical Reviewer, OCTGT/CBER
Bindu George, M.D.	Medical Team Leader, OCTGT/CBER
Syed Husain, Ph.D.	Research Chemist, OCTGT/CBER

BMS ATTENDEES:

Renzo Canetta, M.D.	Vice President, Oncology, Global Clinical Development
Axel Hoos, M.D.	Group Director, Oncology, Global Clinical Development
Rachel Humphrey, M.D.	Vice President, Ipilimumab Global Development
Eric Masson, PharmD	Director, Discovery Medicine and Clinical Pharmacology
Zhengqing Li, Ph.D.	Executive Director, Global Biometric Sciences
Tai-Tsang Chen, Ph.D.	Associate Director, Global Biometric Sciences
Heather Knight-Trent, PharmD	Director, Global Regulatory Science Oncology
Margo Heath-Chiozzi, M.D.	Vice President, Global Regulatory Science- Oncology & Virology

1.0 MEETING OBJECTIVES:

To briefly discuss the overall development plan for melanoma based on new preliminary survival data from CBER study MDX010-20.

2.0 BACKGROUND

On December 1, 2009, BMS requested a Type C teleconference with FDA to discuss whether recent overall survival (OS) data from a CBER IND study could be used to support a CDER BLA submission for advanced melanoma. MDX010-20 was a randomized, double-blind, multicenter CBER study conducted in HLA-A*0201-positive subjects who had Stage III or IV melanoma and who had relapsed/progressed after one or more of the following treatments: IL-2, DTIC, temozolomide, fotemustine, and/or carboplatin. Randomization was stratified for TNM status (M0, M1a, M1b vs. M1c) and prior treatment with IL-2; patients were randomized (3:1:1) to receive either 3mg/kg ipilimumab q3 wks and gp100 q3 wks, 3mg/kg ipilimumab monotherapy, or gp100 monotherapy, respectively. The protocol allowed for reinduction with the assigned treatment regimen for subjects with an initial response of stable disease (SD) or better after induction with subsequent disease progression after study week 12. BMS notes that 646 subjects either completed the study or died. Reported results from the meeting briefing document are summarized below:

	Ipilimumab + gp100 (n=403)	Ipilimumab (n=137)	gp-100 (n=136)
Overall Survival			
# Deaths	306	100	119
Median (mos)	9.95	10.12	6.44
Hazard Ratio ¹ (95% CI)	0.68 (0.55, 0.85)	0.66 (0.51, 0.87)	
Nominal p-value	0.0004	0.0026	
BORR (95% CI)	5.7% (23/403) (3.7, 8.4)	10.9% (15/137) (6.3, 17.4)	1.5% (2/136) (0.2, 5.2)
Progression-free survival			
Median (mos)	2.76	2.86	2.76
Hazard Ratio ¹ (95% CI)	0.81 (0.66, 1.00)	0.64 (0.50, 0.83)	

¹HR comparison vs. gp100 arm

BMS notes that the safety profile from MDX010-20 was consistent with that reported with ipilimumab in previously reported monotherapy studies. In particular, immune-related adverse events (irAEs) were reported in MDX010-20.

BMS considers CBER study MDX010-20 to be a well-designed, randomized controlled study and intends to file a BLA with this data along with supportive safety data from single arm Phase 2 studies (CA184008, CA184007, and CA184004) and a single dose-ranging monotherapy study (Studies CA184022) utilizing a regimen of 10 mg/kg ipilimumab q4 wks. If FDA concurs, a clinical pre-BLA meeting has been scheduled for March 4, 2010 to discuss the registrational plan in more detail.

Draft FDA responses were communicated to BMS on January 12, 2010.

3.0 DISCUSSION

SPONSOR SUBMITTED PREAMBLE (*ITALIC*), QUESTIONS AND FDA RESPONSE:

In line with the summary of the program provided in this briefing document, and the unmet medical need in this condition, BMS intends to submit a BLA based on the Phase 3 study MDX010-205 and the Phase 2 studies CA184022,1 as well as CA184008,2 CA184007,3 and CA184004,4 for the indication of advanced melanoma. BMS considers MDX010-20 a well-designed, randomized controlled study with an appropriate patient population, primary endpoint, and comparator/control to support registration of ipilimumab in advanced melanoma.

As there are no approved therapies for advanced melanoma that have demonstrated improved survival, unmet medical need remains high. Ipilimumab has demonstrated a clinically meaningful survival benefit with a statistically significant reduction for death of 34% (ipilimumab monotherapy compared with gp100) in a setting where none of the available therapies have demonstrated a survival benefit for patients with advanced melanoma.

The ipilimumab dose in MDX010-20 was 3 mg/kg q3 weeks, while the majority of the Phase 2 program studied 10 mg/kg q3 weeks. The MDX010-20 protocol planned no maintenance dosing, and it allowed for reinduction of the original regimen for subjects with stable disease (SD) or better after induction who progressed after Week 12. Ipilimumab monotherapy in MDX010-20 demonstrated a survival benefit with a hazard ratio of 0.66 (95% CI: 0.51, 0.87) compared with the gp100 peptide vaccine.

*The ipilimumab clinical development program has been conducted without regard to HLA subtype, with the exception of MDX010-20. Because the gp100 peptide vaccine is specific for individuals with the A*0201 HLA subtype, subjects randomized to MDX010 20 were restricted to*

*the HLA A*0201 subtype. The association between HLA-A*0201 status and both clinical response and irAEs was an exploratory biomarker analysis in the four Phase 2 studies. Based on the data from the Phase 2 studies, there was no apparent association between HLA-A*0201 status and clinical benefit (response and stable disease) or occurrence of irAEs.*

The majority of drug-related adverse events in subjects receiving ipilimumab were inflammatory in nature, reflecting the mechanism of action of the drug (ie, these were mainly irAEs). With few exceptions, the irAEs were generally manageable and reversible. Detailed toxicity management guidelines were developed based on the experience of irAEs in the ipilimumab clinical program and are provided in the investigator brochure. Use of these guidelines has been shown to be effective in reducing the occurrence of severe complications related to irAEs.

The BMS integrated safety database is anticipated to include data from subjects treated in the melanoma clinical program. In addition to the integrated safety data from BMS, there is anticipated to be limited safety data from a global compassionate use program (ie, single patient and treatment protocol) in more than 1200 subjects and multiple US National Cancer Institute (NCI) sponsored studies in approximately 175 subjects. The NCI studies involve many different schedules, doses, and combination regimens.

1. Can the data from MDX010-20, supported by the Phase 2 studies for melanoma (ie, CA184022, CA184008, CA184007 and CA184004), form the basis for submission of a BLA for full approval in advanced melanoma?

FDA PRELIMINARY RESPONSE PROVIDED ON JANUARY 12, 2010: While of interest, the results from this single study (MDX010-20) must be considered in light of the trial design of MDX010-20 and available data from other studies designed to characterize the impact on overall survival. Specifically, the “control” arm for MDX010-20 utilized an investigational product; in order to interpret the results of this study, BMS must provide data which demonstrate that gp-100 administration does not impair survival. If such data are derived from clinical experience, BMS must establish that the clinical experience is robust (from trials capable of detecting such impairment through use of internal controls) and representative of all known experience with gp100. In addition, an application must provide all known, relevant data regarding effects on survival. The survival data from the Phase 2 studies cannot be interpreted, due to the lack of an internal control. Therefore, a regulatory action would be contingent on evidence that effects of ipilimumab on survival observed in MDX010-20 are replicated in by the high-level results of Study, CA184024.

DISCUSSION DURING THE TELECONFERENCE: BMS acknowledged FDA's concerns regarding the use of gp100 as a control arm, however, re-emphasized the magnitude of the effect (OS) observed in the context that no other available drugs for advanced melanoma were available with the observed treatment effect as seen in the combination arm of this study. BMS felt this was solely attributable to ipilimumab and not gp100. BMS noted that literature regarding gp100 single-arm trials, alone or in combination use had been reviewed including information from Dr. Rosenberg at NCI and a recent ASCO 2009 report of prospective randomized Phase 3 trial in advanced melanoma comparing IL-2 monotherapy vs. IL-2 and gp100. BMS concluded from this data that gp100 did not appear to have a negative effect on survival and inquired whether FDA had any additional knowledge of this concern. FDA stated that it would not be possible for FDA to divulge privileged information. BMS would have to provide a summary of all information available from published literature and any information they might have collected from their own studies with gp100. The summary from the literature should include the search strategies used to obtain the information. BMS agreed to provide this information for FDA review in the briefing package of the pre-BLA meeting.

FDA noted that while the OS data are of interest, MDX10-20 was not a very large trial and there was concern that with only one study, BMS was simply observing a "false positive" outcome result. FDA further stated that the study was randomized 3:1:1 (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]. BMS acknowledged this concern, but pointed out that MDX10-020 demonstrated a large magnitude of effect on OS with high significance on two separate comparisons made within the study; ipilimumab and ipilimumab +gp100. BMS agreed that the Phase 2 study was not designed to definitively test for survival, but countered that through-out these studies, there was a dose-effect and a consistent observation of a larger than expected proportion of long-term survivors with ipilimumab treatment.

FDA re-emphasized that the CA184024 high-level OS data would be very important to provide additional confirmatory evidence of efficacy, especially in the context of the unique and substantial safety profile of the drug. BMS indicated that the specified number of events (deaths) in the -024 study had not yet been reached, thus the study was still blinded. Study -024 did not contain provisions for prespecified interim efficacy analyses and based on current projections, efficacy data was likely not going to be available until October 2010 at the earliest. This was a best guess based on predictive modeling. BMS also clarified that all efficacy endpoints (OS, PFS, etc) for the study

would be analyzed at the time of the final analysis. FDA stated that OS or PFS data from the -024 study would likely be needed to ensure confirmation of ipilimumab efficacy for BLA approval. BMS offered to provide FDA a blinded survival curve in the upcoming pre-BLA meeting package. FDA acknowledged.

2. Given the large experience in non-HLA restricted studies, does FDA agree to the indication of advanced melanoma without HLA restriction based on the survival data in MDX010-20, supported by the survival data in the Phase 2 studies?

FDA PRELIMINARY RESPONSE PROVIDED ON JANUARY 12, 2010: No.

Evidence of an effect on overall survival is limited to MDX010-20 which restricted enrollment based on HLA. Expansion of labeling to an unrestricted population would be dependent on the results of CA184024.

Please provide detailed information on the method(s) used to identify patients with HLA*0201 phenotype for determination of eligibility for enrollment in MDX010-20. Please indicate BMS's plans for development of an assay for identification of patients based on HLA phenotype.

DISCUSSION DURING THE TELECONFERENCE: BMS acknowledged FDA's comments and noted that a single HLA test kit made by (b) (4) had been used for all relevant patient samples. This information would be provided in the planned upcoming pre-BLA meeting package. FDA noted that details on sample handling should also be provided and indicated that CDRH may be consulted to review the kit.

3. CDER is responsible for the review of the ipilimumab compound; therefore, BMS seeks confirmation that CDER will be the lead review center for a joint review of the BLA by CDER and CBER.

FDA PRELIMINARY RESPONSE PROVIDED ON JANUARY 12, 2010: CDER would be the primary review center for an application based on MDX010-20. The data summarized in the meeting briefing document do not support a conclusion that the addition of gp100 to ipilimumab provides incremental benefit as compared to ipilimumab alone.

DISCUSSION DURING THE TELECONFERENCE: BMS acknowledged FDA's comments. There was no further discussion.

ADDITIONAL DISCUSSION:

(b) (4)

BMS and FDA agreed that the scheduled pre-BLA meeting would continue to discuss the total planned data package and FDA noted that Dr. Pazdur was likely to participate.

ACTION ITEMS:

- BMS agreed to provide the gp100 vaccine data from literature and the search term used in the pre-BLA meeting package.
- BMS confirmed that HLA assay information, sample handling, and analysis information would be provided for FDA review in the pre-BLA meeting package.
- BMS confirmed that updated event rate data for currently blinded study CA184024 would be provided in the pre-BLA meeting package.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-9186	GI-1	BRISTOL MYERS SQUIBB CO	Ipilimumab [Human Monoclonal Antibody (MDX-010, MDX-CTLA4) (Bristol Myers) to CTLA4], Interleukin-2 (Chiron), and Chemotherapy

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

/s/

ERIK S LAUGHNER
02/16/2010